

EEG signals and fMRI activation overlap to some extent. It is the scientific question that determines which method will be appropriate.

## References

- 1 Scherg, M. and Berg, P. (1996) New concepts of brain source imaging and localization. *Electroencephalogr. Clin. Neurophysiol. Suppl.* 46, 127–137
- 2 Grent-t-Jong, T. and Woldorff, M.G. (2007) Timing and sequence of brain activity in top-down control of visual-spatial attention. *PLoS Biol.* 5, e12
- 3 Bledowski, C. *et al.* (2006) Mental chronometry of working memory retrieval: a combined functional magnetic resonance imaging and event-related potentials approach. *J. Neurosci.* 26, 821–829
- 4 Schicke, T. *et al.* (2006) Tight covariation of BOLD signal changes and slow ERPs in the parietal cortex in a parametric spatial imagery task with haptic acquisition. *Eur. J. Neurosci.* 23, 1910–1918
- 5 Debener, S. *et al.* (2006) Single-trial EEG-fMRI reveals the dynamics of cognitive function. *Trends Cogn. Sci.* 10, 558–563
- 6 Hyvärinen, A. *et al.* (2001) *Independent Component Analysis*. John Wiley & Sons
- 7 Vanni, S. *et al.* (2004) Sequence of pattern onset responses in the human visual areas: an fMRI constrained VEP source analysis. *Neuroimage* 21, 801–817

1364-6613/\$ – see front matter © 2007 Elsevier Ltd. All rights reserved.  
doi:10.1016/j.tics.2007.09.006

## Letters Response

# Towards single-trial analysis in cognitive brain research

**Stefan Debener, Markus Ullsperger, Markus Siegel and Andreas K. Engel**

Medical Research Council Institute of Hearing Research, Royal South Hants Hospital, Brintons Terrace, Southampton SO14 0YG, UK

Bledowski and coworkers advocate functional magnetic resonance imaging (fMRI)-constrained source analysis of event-related potentials (ERPs), that is, trial-averaged electroencephalogram (EEG) responses, over the single-trial based EEG-fMRI integration technique we recently proposed [1]. The authors focus on three arguments.

First, they argue that our EEG-informed fMRI analysis approach might misidentify cortical generators of EEG activity by not taking into account physically plausible locations of ERP sources. We agree that if the goal is to identify the neural sources of ERPs, spatial constraints are valuable and should be used in the analysis. Independent component analysis (ICA) does not explicitly include this information, but it is readily gleaned by a comparison of the location(s) identified by fMRI with the dipole source analysis of the independent component(s). Indeed, we have previously shown a close correspondence between the dipole source location of the selected independent component and the single-trial EEG-fMRI integration result [1]. Therefore, although the ICA-based trial-by-trial approach can easily incorporate ERP source analysis, the reverse is not feasible. We consider it an advantage of our analysis that it is, in principle, not limited to the identification of common generators of EEG and fMRI. By contrast, the method can deliberately be used to identify functionally defined neural networks that are correlated with temporally well-localized EEG features, using the spatial resolution of fMRI [2].

Second, Bledowski and colleagues argue that the EEG-informed fMRI analysis approach assumes a linear correlation between fMRI and EEG features. Although a linear model is a natural starting point for this analysis scheme,

the proposed method is, in fact, not limited to a linear correlation. The method can be generalized to any non-linear relationship simply by constructing corresponding non-linear fMRI regressors from the single-trial EEG features of interest [3].

Third, Bledowski *et al.* argue that the trial-by-trial approach suffers from the assumptions inherent in ICA. In particular, they state that current ICA algorithms require knowledge about the number of sources contributing to the mixed data. The infomax ICA algorithm we use is among the most widely applied algorithms [4] and does not in practice require this knowledge. However, the authors might be referring to the underlying problem, which is the selection of those independent components that can be reliably identified. We have successfully used different strategies to tackle this issue [5,6] and, consistent with others, have found ICA to be of great value – in particular for the direct integration of EEG and fMRI [1,2,7,8]. By contrast, the ‘number of sources’ problem applies to the fMRI-constrained ERP analysis approach because fMRI does not unambiguously identify the number of possible ERP dipole sources. It is worth recapitulating that fMRI could be blind to some EEG phenomena and vice versa. Hence, none of the currently available EEG-fMRI integration approaches unambiguously tells how many sources are relevant.

To advance EEG-fMRI integration, we need to further our understanding of how these signals relate to each other. However, the fMRI-constrained ERP source-analysis approach does not have much potential in addressing the fundamental question of EEG-fMRI coupling. The sole consideration of trial-averaged data in each modality neglects the amount of information that can be extracted from fluctuations across trials. By contrast, the trial-by-trial approach can help to identify which fractions of EEG

Corresponding author: Debener, S. (s.debener@soton.ac.uk).  
Available online 9 November 2007.

and fMRI signals are related to each other and which are not. Importantly, single-trial EEG [1] and fMRI signals [9,10] have predictive power with regard to trial-by-trial fluctuations of behaviour. In fact, a rapidly growing body of evidence shows that temporal fluctuations of neuronal activity are not merely noise, but instead are functionally relevant signals [11]. Thus, the analysis of simultaneous EEG–fMRI signals on a trial-by-trial level is likely to provide key information for a deeper understanding of the brain–behaviour relationship.

#### References

- 1 Debener, S. *et al.* (2005) Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *J. Neurosci.* 25, 11730–11737
- 2 Feige, B. *et al.* (2005) Cortical and subcortical correlates of electroencephalographic alpha rhythm modulation. *J. Neurophysiol.* 93, 2864–2872
- 3 Büchel, C. *et al.* (1998) Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. *Neuroimage* 8, 140–148
- 4 Makeig, S. *et al.* (2004) Mining event-related brain dynamics. *Trends Cogn. Sci.* 8, 204–210
- 5 Debener, S. *et al.* (2005) What is novel in the novelty oddball paradigm? Functional significance of the novelty P3 event-related potential as revealed by independent component analysis. *Brain Res. Cogn. Brain Res.* 22, 309–321
- 6 Debener, S. *et al.* (2007) Improved quality of auditory event-related potentials recorded simultaneously with 3-T fMRI: Removal of the ballistocardiogram artefact. *Neuroimage* 34, 590–600
- 7 Eichele, T. *et al.* (2005) Assessing the spatiotemporal evolution of neuronal activation with single-trial event-related potentials and functional MRI. *Proc. Natl. Acad. Sci. U. S. A.* 102, 17798–17803
- 8 Mantini, D. *et al.* (2007) Electrophysiological signatures of resting state networks in the human brain. *Proc. Natl. Acad. Sci. U. S. A.* 104, 13170–13175
- 9 Weissman, D.H. *et al.* (2006) The neural bases of momentary lapses in attention. *Nat. Neurosci.* 9, 971–978
- 10 Fox, M.D. *et al.* (2007) Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron* 56, 171–184
- 11 Fox, M.D. *et al.* (2006) Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat. Neurosci.* 9, 23–25

1364-6613/\$ – see front matter © 2007 Elsevier Ltd. All rights reserved.  
doi:10.1016/j.tics.2007.09.005

## Elsevier.com – linking scientists to new research and thinking

Designed for scientists' information needs, Elsevier.com is powered by the latest technology with customer-focused navigation and an intuitive architecture for an improved user experience and greater productivity.

The easy-to-use navigational tools and structure connect scientists with vital information – all from one entry point. Users can perform rapid and precise searches with our advanced search functionality, using the FAST technology of Scirus.com, the free science search engine. Users can define their searches by any number of criteria to pinpoint information and resources. Search by a specific author or editor, book publication date, subject area – life sciences, health sciences, physical sciences and social sciences – or by product type. Elsevier's portfolio includes more than 1800 Elsevier journals, 2200 new books every year and a range of innovative electronic products. In addition, tailored content for authors, editors and librarians provides timely news and updates on new products and services.

Elsevier is proud to be a partner with the scientific and medical community. Find out more about our mission and values at Elsevier.com. Discover how we support the scientific, technical and medical communities worldwide through partnerships with libraries and other publishers, and grant awards from The Elsevier Foundation.

As a world-leading publisher of scientific, technical and health information, Elsevier is dedicated to linking researchers and professionals to the best thinking in their fields. We offer the widest and deepest coverage in a range of media types to enhance cross-pollination of information, breakthroughs in research and discovery, and the sharing and preservation of knowledge.

**Elsevier. Building insights. Breaking boundaries.**  
**www.elsevier.com**