Multimodal Integration of fMRI, EEG, and NIRS

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Abstract: Multimodal integration in the field of human brain mapping has evolved from structural-functional co-registrations toward functional-functional combinations. This paper briefly reviews fMRI-EEG, fMRI-NIRS, EEG-NIRS, and fMRI-EEG-NIRS combinations.
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1. Functional neuroimaging and multimodal integration

After years of incubation [1], noninvasive functional imaging of the human brain came of age in the 1990s [2] with discovery and utilization of the intrinsic BOLD (blood oxygen level dependent) signal of fMRI (functional magnetic resonance imaging) [3-5]; the establishment in 1993 of two journals, *NeuroImage* and *Human Brain Mapping*; and the inaugural 1995 meeting in Paris of the Organization of Human Brain Mapping. The field flourished in the 2000s in an upward trend that shows no sign of abating, e.g., as indexed by PubMed. Queries for each year from 2000 to 2010 indicate that fMRI-related publications increased steadily by about 1660 per year. In the same period, EEG/ERP (electroencephalography and event-related potential) publications increased about 370 per year; those for MEG/ERF (magnetoencephalography and event-related field) increased about 22 per year; and brain NIRS (near-infrared spectroscopy) [6] publications increased about 15 per year.

Thus, fMRI techniques substantially dominate human brain mapping (following the lead of PET—positron emission tomography—in the 1980s). In addition, (except for PET) fMRI and functional neuroimaging are nearly synonymous terms in the cognitive neuroscience literature [7]. Nevertheless—following the brain's own tendency to integrate multiple sensory modalities (visual, auditory, somatosensory, etc.)—*multimodal integration* of different neuroimaging techniques has been a recurring theme in the field. Initially, the emphasis was integration with structural imaging—in particular, structural MRI (sMRI)—as a common, anatomical backdrop for mapping the results of each functional modality [8]. Subsequently, methodologists have worked to improve *spatiotemporal* resolution by combining two or more functional techniques [9], most typically, fMRI (a hemodynamic modality with approximately uniform ~3 mm spatial resolution, but low temporal resolution, on the order of several seconds) with MEG or EEG (which reflect neuroelectric activity with ~1 ms temporal resolution, but ambiguous and variable spatial resolution: at best a few mm, at worst a few cm). A related aim of multimodal functional integration has been to investigate the phenomenon of neuroelectric-hemodynamic coupling, i.e., *neurovascular coupling*, the complex mechanism which is the basis for fMRI neuroimaging [10].

The modalities fMRI, EEG, MEG, and NIRS may be paired in six ways. (i) MEG and EEG have a common biophysical basis [11] (despite extreme differences of instrumentation), and concurrent MEG-EEG recordings are routine [12]. However, (ii) concurrent fMRI-MEG measurements are prevented for physical reasons; and (iii) reports of concurrent MEG-NIRS recordings [13] have not reached a critical mass. The remaining three combinations—(iv) fMRI-EEG, (v) fMRI-NIRS, and (vi) EEG-NIRS—support concurrent measurements, and have significant literatures, which we review with an eye towards the prospect of fMRI-EEG-NIRS integration.

2. fMRI-EEG

Technical issues with concurrent fMRI-EEG recordings (principally, RF pulse, gradient switching, and ballistocardiogram artifacts) have been largely resolved; commercial solutions are available; and a recent book has been devoted to the topic [14]. On the frontier are analysis methods for extracting new information from the concurrent data. On one hand, *model-driven fusion* algorithms fit parameters of biophysically detailed models conjointly to fMRI-EEG data, producing Bayesian inferences about unobserved underlying neuronal activity [15].

At the opposite extreme, *data-driven fusion* algorithms like joint or parallel ICA (independent component analysis) uncover statistically independent sources of conjoint fMRI-EEG features [16] *without* neuroelectric-hemodynamic coupling models. In between are methods which employ *functional models* of the hemodynamic response [17].

3. fMRI-NIRS

The fMRI BOLD signal derives from magnetic susceptibility effects of deoxy-hemoglobin, which serves as an intrinsic paramagnetic contrast agent [3], whereas NIRS (based on photon absorption and scattering) is sensitive to changes in the micromolar concentrations of both deoxy- and oxy-hemoglobin [6]. Consequently, simultaneous fMRI- NIRS recordings [18] have been employed principally to disentangle different vascular and metabolic components of the hemodynamic response to electrophysiological activity, as reviewed in [19]. As expected theoretically, the BOLD signal correlates very highly with the NIRS measure of deoxy-hemoglobin, and correlates less with oxy- and total hemoglobin [20-22]. Also, high resolution NIRS tomographic mapping studies have revealed good correspondence with fMRI findings [23, 24]. Concurrent measures have been used to investigate the BOLD post-stimulus undershoot [25], and to assess the contribution of oxygen extraction fraction to the nonlinearity of the BOLD response [26]. More recently, fMRI-NIRS has been used to quantify the cerebral metabolic rate of oxygen without hypercapnia [27, 28], and to assess when NIRS may be substituted appropriately for fMRI [29].

4. EEG-NIRS

EEG and NIRS measurements depend on different physical properties (conductivities; absorption and scattering coefficients) of the same head tissues such as scalp, skull, cerebrospinal fluid, gray matter, and white matter; so that forward models are needed to estimate neuroelectric sources or cerebral hemodynamic states in a common anatomical space (e.g., derived from sMRI) using suitable inverse methods. As with fMRI-EEG, a principal interest of EEG-NIRS is to study neuroelectric-hemodynamic coupling, e.g., related to the alpha rhythm [30, 31], or in epilepsy [32]. In addition, noninvasive detection of an ERP-like fast optical signal (FOS) due to changes of scattering properties in neural tissue [33] has been a topic of considerable interest, and also controversy [34,35] due to its low theoretical and experimental signal to noise ratio. However, a recent report used simultaneous ERP and NIRS measurements to demonstrate robust fast temporal correlations between EEG-derived ICA components and NIRS-derived ICA components [36]—thus showing that concurrent EEG may facilitate FOS detection.

5. Prospects for fMRI-EEG-NIRS

A recent paper demonstrated the scientific and potential clinical usefulness of nonlinear Volterra kernel estimation of neurovascular coupling for both fMRI-EEG and EEG-NIRS in epilepsy [32]—an approach we also have been developing for analysis of concurrent fMRI-EEG [37]. The authors of [30] likewise used both fMRI-EEG and EEG-NIRS fruitfully in parallel. Thus, taken together with considerations reviewed above, three-fold simultaneous fMRI-EEG-NIRS measurements may prove valuable from multiple points of view. Higher order multimodal relationships become possible, e.g., cerebral metabolic rate of oxygen estimated with fMRI-NIRS [27] could be related to EEG. Another suggestion is that head model parameters for EEG-NIRS might be "calibrated" with fMRI in a joint fMRI-EEG-NIRS session—thereby improving subsequent standalone EEG-NIRS inverse solutions.

6. References

[1] M.E. Raichle, "Functional neuroimaging: a historical and physiological perspective" in *Functional neuroimaging of cognition*, R. Cabeza, A. Kingstone eds. (MIT, 2001), pp. 3-26.

[2] W.W. Orrison, Jr., J.D. Lewine, J.A. Sanders, M.F. Hartshorne, *Functional brain imaging* (Mosby, 1995).

[3] S. Ogawa, T.M. Lee, A.R. Kay, D.W. Tank, "Brain magnetic resonance imaging with contrast dependent on blood oxygenation," PNAS USA **87**, 9868-9872 (1990).

[4] K.K. Kwong, J.W. Belliveau, D.A. Chesler, I.E. Goldberg, R.M. Weisskoff, B.P. Poncelet, et al., "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation," PNAS USA **89**, 5675-5679.

[5] S. Ogawa, D.W. Tank, R. Menon, J.M. Ellermann, S.G. Kim, H. Merkle, K. Ugurbil, "Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging," PNAS USA **89**, 5951-5955 (1992).

[6] M. Wolf, M. Ferrari, V. Quaresima, "Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications," J Biomed Optics **12**, 062104 (2007).

[7] R. Cabeza, A. Kingstone eds. *Functional neuroimaging of cognition, 2nd edition* (MIT, 2005).

[8] R.W. Thatcher, M. Hallett, T. Zeffiro, E.R. John, M. Huerta, eds. *Functional neuroimaging: technical foundations* (Academic, 1994).

[9] A.M. Dale, E. Halgren, "Spatiotemporal mapping of brain activity by integration of multiple brain modalities," Curr Opin Neurobiol **11**,

202-208 (2001).
[10] X. Wan, J. Riera, K. Iwata, M. Takahashi, T. Wakabayashi, R. Kawashima, "The neural basis of the hemodynamic response nonlinearity in human primary visual cortex: implications for neurovascular coupling mechanism," Neuroimage **32**, 616-625 (2006).
[11] J. Malmivuo, R. Plonsey. *Bioelectromagnetism* (Oxford, 1995).
[12] S. Baillet, L. Garnero, G. Marin, J-P. Hugonin, "Combined MEG and EEG source imaging by minimization of mutual information," IEEE Trans Biomed Eng **46**, 522-534 (1999).
[13] B.M. Mackert, G. Wübbeler, S. Leistner, K. Uludag, H. Obrig, A. Villringer, et al., "Neurovascular coupling analyzed non-invasively in the human brain," Neuroreport **15**, 63-66 (2004).
[14] M. Ullsperger, S. Debener. *Simultaneous EEG and fMRI: recording, analysis, and application* (Oxford, 2010).
[15] P.A. Valdes-Sosa, J.M. Sanchez-Bornot, R.C. Sotero, Y. Iturria-Medina, Y. Aleman-Gomez, J. Bosch-Bayard, et al., "Model driven EEG/fMRI fusion of brain oscillations," Human Brain Mapp 30, 2701-2721 (2009).
[16] T. Eichele, V.D. Calhoun, S. Debener, "Mining EEG-fMRI using independent component analysis," Int J Psychophysiol **73**, 53-61 (2009).
[17] J.C. de Munck, S.I. Gonçalves, L. Huijboom, J.P.A. Kuijer, P.J.W. Pouwels, R.M. Heethaar, et al., "The hemodynamic response of the alpha rhythm: an EEG/fMRI study," Neuroimage **35**, 1142-1151 (2007).
[18] A. Kleinschmidt, H. Obrig, M. Requardt, K.D. Merboldt, U. Dirnagl, A. Villringer, J. Frahm, "Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy," J Cereb Blood Flow Metab **16**, 817-826 (1996).
[19] J. Steinbrink, A. Villringer, F. Kempf, D. Haux, S. Boden, H. Obrig, "Illuminating the BOLD signal: combined fMRI-fNIRS studies," Magn Reson Imaging **24**, 495-505 (2006).
[20] V. Toronov, A. Webb, J.H. Choi, M. Wolf, A. Michalos, E. Gratton, D. Hueber, "Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging," Med Phys **28**, 521-527 (2001).
[21] B.J. MacIntosh, L.M. Klassen, R.S. Menon, "Transient hemodynamics during a breath hold challenge in a two part functional imaging study with simultaneous near-infrared spectroscopy in adult humans," Neuroimage **20**, 1246-1252 (2003).
[22] T.J. Huppert, R.D. Hoge, S.G. Diamond, M.A. Franceschini, D.A. Boas, "A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans," Neuroimage **29**, 368-382 (2006).
[23] C. Habermehl, S. Holtze, J. Steinbrink, S.P. Koch, H. Obrig, J. Mehnert, C.H. Schmitz, "Somatosensory activation of two fingers can be discriminated with ultrahigh-density diffuse optical tomography," Neuroimage **59**, 3201-3211 (2012).
[24] B.W. Zeff, B.R. White, H. Dehghani, B.L. Schlaggar, J.P. Culver, "Retinotopic mapping of adult human visual cortex with high-density diffuse optical tomography," PNAS USA **104**, 12169-12174 (2007).
[25] M.L. Schroeter, T. Kupka, T. Mildner, K. Uludağ, D.Y. von Cramon, "Investigating the post-stimulus undershoot of the BOLD signal—a simultaneous fMRI and fNIRS study," Neuroimage **30**, 349-358 (2006).
[26] H. Toyoda, K. Kashikura, T. Okada, S. Nakashita, M. Honda, Y. Yonekura, et al., "Source of nonlinearity of the BOLD response revealed by simultaneous fMRI and NIRS," Neuroimage **39**, 997-1013 (2008).
[27] S. Tak, J. Jang, K. Lee, J.C. Ye, "Quantification of CMRO(2) without hypercapnia using simultaneous near-infrared spectroscopy and fMRI measurements," Phys Med Biol **55**, 3249-3269 (2010).
[28] S. Tak, S.J. Yoon, J. Jang, K. Yoo, Y. Jeong, J.C. Ye, "Quantitative analysis of hemodynamic metabolic changes in subcortical vascular dementia using simultaneous near-infrared spectroscopy and fMRI measurements," Neuroimage **55**, 176-84 (2011).
[29] X. Cui, S. Bray, D.M. Bryant, G.H. Glover, A.L. Reiss, "A quantitative comparison of NIRS and fMRI across multiple cognitive tasks," Neuroimage **54**, 2808-2821 (2011).
[30] M. Moosmann, P. Ritter, I. Krastel, A. Brink, S. Thees, F. Blankenburg, et al., "Correlates of alpha rhythm in functional magnetic resonance imaging and near infrared spectroscopy," Neuroimage **20**, 145-158 (2003).
[31] S.P. Koch, S. Koendgen, R. Bourayou, J. Steinbrink, H. Obrig, "Individual alpha-frequency correlates with amplitude of visual evoked potential and hemodynamic response," Neuroimage **41**, 233-242 (2008).
[32] P. Pouliot, J. Tremblay, M. Robert, P. Vannasing, F. Lepore, M. Lassonde, et al, "Nonlinear hemodynamic responses in human epilepsy: a multimodal analysis with fNIRS-EEG and fMRI-EEG," J Neurosci Methods (Epub 2011 Nov 25).
[33] G. Gratton, M. Fabiani, P.M. Corballis, D.C. Hood, M.R. Goodman-Wood, J. Hirsch, et al., "Fast and localized event-related optical signals (EROS) in the human occipital cortex: comparisons with the visual evoked potential and fMRI," Neuroimage **6**, 168-180 (1997).
[34] J. Steinbrink, F.C. Kempf, A. Villringer, H. Obrig, "The fast optical signal—robust or elusive when non-invasively measured in the human adult?" Neuroimage **26**, 996-1008 (2005).
[35] A.V. Medvedev, J. Kainerstorfer, S.V. Borisov, R.L. Barbour, J. VanMeter, "Event-related fast optical signal in a rapid object recognition task: improving detect ion by the independent component analysis," Brain Res **1236**, 145-158 (2008).
[36] A.V. Medvedev, J.M. Kainerstorfer, S.V. Borisov, A.H. Gandjbakhche, J. VanMeter, "'Seeing' electroencephalogram through the skull: imaging prefrontal cortex with fast optical signal," J Biomed Optics **15**, 061702 (2010).
[37] M.E. Pflieger, "Efficient identification of oblique Volterra systems," Proceedings of NFSI-IJBEM 2011 (May 13-16, Banff, CD-ROM).