Near-infrared spectroscopy for functional studies of brain activity in human infants: promise, prospects, and challenges

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Abstract. A recent workshop brought together a mix of researchers with expertise in optical physics, cerebral hemodynamics, cognitive neuroscience, and developmental psychology to review the potential utility of near-IR spectroscopy (NIRS) for studies of brain activity underlying cognitive processing in human infants. We summarize the key findings that emerged from this workshop and outline the pros and cons of NIRS for studying the brain correlates of perceptual, cognitive, and language development in human infants. [DOI: 10.1117/1.1854672]

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In the past 40 yr, researchers studying human infants have developed a variety of clever behavioral methods, revealing remarkable capacities that belie the apparent incompetence of the immature neonate. Rather than a bundle of reflexes, infants in the first postnatal year have been shown to possess sophisticated sensory and perceptual skills, memory and cognitive abilities, and language competencies.[1–3] However, these capacities show substantial improvement from birth to puberty, due in part to maturation of the brain and in part to the richness of the environment, within which infants and children are exposed to a wealth of information to be learned. Despite the knowledge gained by behavioral methods, the brain of the human infant defies direct scrutiny for obvious reasons: invasive studies of the human brain are limited to clinical cases or to postmortem analyses. Thus, indirect methods have been exploited to make inferences about brain activity while infants are exposed to stimulation or are engaged in a particular task. These methods include recordings from scalp electrodes [electroencephalography (EEG) and event-related potentials (ERPs)], changes in cerebral hemodynamics correlated with neural activity [functional magnetic resonance imaging using blood oxygenation level differences (fMRI BOLD)], and the topic of a recent workshop in Boston (February 5–7, 2004, for which support was provided by the J. S. McDonnell Foundation under Grant No. 21002017): noninvasive, near-IR spectroscopy (NIRS) of the brain using emitters and detectors attached to the scalp.

An obvious first question when considering NIRS as a method for assessing infant brain function is what advantages it offers over EEG/ERP and fMRI BOLD. EEG/ERP has the advantage of being a measure of neural activity, whereas both fMRI BOLD[4] and NIRS[5] are measures of cerebral hemodynamic responses correlated with neural activity. However, EEG/ERP has relatively poor spatial localization, even with high-density electrode arrays, unless one has a precise model of the infant skull to enable cortical source localization.[6] Structural MRI can provide highly detailed images of brain anatomy and fMRI BOLD can localize brain activity with great spatial precision, but it requires extremely rigid stabilization of the head and exposes infants to both high magnetic fields and rapid RF gradients, raising safety concerns. Thus, although fMRI studies with human infants are beginning to be feasible,[7] it is unlikely that structural MRI will become routine for measuring infant brain/skull anatomy (for EEG/ERP), or for measuring fMRI BOLD. Finally, MRI places the infant in a high-intensity acoustic environment (due to RF pulses) that interferes with the presentation of auditory/language stimuli.

Although NIRS was developed over 25 yr ago,[8] it was not applied to awake, full-term human infants until the mid-1990s.[9] Three recent reports provide evidence that NIRS can be used to gather information about the hemodynamic correlates of neural activity in infants, ranging from neonates to 12-month-olds, using tasks that assess visual,[10] memory,[11] and language[12] abilities. These are exciting findings, but they are tempered by a number of critical methodological issues that must be grappled with to ensure that NIRS becomes a technique that is robust and reliable for use with human infants.

First, like EEG/ERP, NIRS requires attachment of a set of probes (near-IR emitters and detectors) on the scalp, but in contrast to MRI, it does not expose infants to high magnetic fields or RF pulses. But near-IR light must conform to safety standards, and these standards are at present somewhat unclear for the infant brain. Thus, while there is general agreement that near-IR light in the range of 0.3 to 5.0 mW is ''safe,'' there have been no studies of neural tissue damage in infant brain. Moreover, using current standards based on animal studies requires the infancy researcher to take into account overall laser power, the number of emitters, and the characteristics of the fiber optics.

Second, an intrinsic advantage of NIRS over fMRI BOLD is that the latter provides only a measure of deoxy-Hb, whereas the former can use two (or more) near-IR wavelengths to provide separate measures of oxy-Hb and deoxy-Hb. These two measures are potentially advantageous in sepa-

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rating signals due to increased flow from signals due to increased oxygen comsumption (an issue of considerable concern in studies of fMRI/BOLD). The independence of these two measures is a function of the wavelengths that are used and the characteristics of the underlying tissues (neural and nonneural). Despite the availability of two hemodynamic signals, one must carefully choose the two wavelengths and the separation of emitters and detectors. While it is clear in adult brain that wavelengths of 690 to 760 and 830 nm are optimal (best SNR with least crosstalk), these wavelengths may not be optimal for infant brain. Moreover, the distance between emitters and detectors for adult brain is typically 3.0 cm, and it has been assumed that this interprobe distance should be scaled to the smaller head size of infants (e.g., 1.7 to 2.0 cm) to sample similar superficial regions of cortex. But there are no comparative data on this question of optimal interprobe distance for the infant brain. The thinner skull, the finer and less dense hair, and different vasculature of the infant may enable adult interprobe distances to sample signals from deeper brain regions than in adults. At minimum, both oxy-Hb and deoxy-Hb should be reported in all studies conducted with infants.

Third, while in principle NIRS does not require the severe head-movement constraint of MRI, any slippage of the probes on the scalp, or variations in the intensity of the near-IR light at the point of contact with the scalp, will lead to spurious signals at one or more detectors. Four solutions to these movement artifacts have been suggested. The first is to design probes and probe-holders that reduce gross movement artifacts. Great progress has been made in the past year by a number of labs. Second, define automatic algorithms to reject signals that fall outside the range of hemodynamic responses. Although this has been implemented, both in real time and in postprocessing, uncertainty remains concerning the precise form of the hemodynamic response function in infant brain. Thus, while many responses can be accepted and artifacts rejected algorithmically, others will require further detailed study to refine the algorithms for use with infants. The third solution is to use statistical techniques (e.g., regression and cross-correlation) to eliminate signals with shared variance. However, while such techniques can potentially filter motion artifacts and systemic hemodynamic signals arising from the cardiac and respiratory cycles, they must be carefully implemented so as not to filter out the hemodynamic response due to neural activation. The fourth is to ignore the hemodynamic response and seek data on the optical correlates of the neural response. This has the advantage of shifting from a slow hemodynamic response in the 2- to 10-s range to a neural response in the 10- to 200-ms range, thereby reducing contamination by slow signals and enabling event-related designs. Although there is evidence that these so-called ''fast'' responses are present in the adult brain,[13,14] their SNR is extremely small, necessitating hundreds of stimulus events. Thus, most infancy researchers are focusing on the slower and more robust hemodynamic response.

Fourth, the typical design of a NIRS study involves a 15- to 30-s block of stimulation followed by a 30- to 45-s period of no stimulation (the variable rest period is used to decorrelate the timing of stimulus onset with spontaneous hemodynamic oscillations). Such a design, while maximizing the amplitude of the hemodynamic response, is problematic for infant studies for two reasons. First, the longer the duration of a stimulus, the more likely an infant is to make spontaneous movements, to become disinterested in the stimulus, or to undergo a change in state of arousal/attention. All three of these factors add variance to the response that, in principle, can be reduced by signal averaging. However, the overall duration of an infant's state of ''cooperation'' is perhaps 10 to 20 min, thereby severely limiting the number of stimulus epochs that can be obtained from an infant for signal averaging. Second, blocked stimulus presentations increase the likelihood that nonneural vascular responses will contaminate the signal. There are systemic vascular changes that fall within the same frequency-response range as, and have larger amplitudes than, the neurally induced hemodynamic responses that are the signal of interest. For the same reason already mentioned, signal averaging is not completely effective in reducing these nonneural vascular changes. Several potential solutions to these problems have been suggested: (1) obtain a separate (e.g., pulse oximeter) measure of systemic vascular changes to regress out the nonneural hemodynamic responses, (2) use statistical techniques (e.g., principal components analysis) to subtract the nonneural signals and leave the residuals, or (3) use an event-related rather than a blocked design to reduce the likelihood of artifacts correlated with stimulus presentation.

The fifth and final issue is coregistration. How can we localize the measured NIRS signals with respect to specific brain sites? The obvious solution is to first attach the probes, measure precisely their position on the skull with reliable external landmarks, and then use these same landmarks (minus the probes) with structural MRI to determine the relation between probe positions and brain sites. This can certainly be done with adults, but as mentioned earlier, there are ethical and technical reasons why MRI is not readily used with infants (at least those who are otherwise healthy and not being scanned for clinical reasons). One alternative is to use an atlas of the ''average'' infant brain based on a composite of MRI images at different ages (i.e., a Talairach-like system), although this certainly introduces considerable variation given individual differences in brain structure. Another alternative is to gather high-resolution ultrasound images in an attempt to locate major anatomical landmarks (e.g., sulci), especially since ultrasound is considered safer than MRI. Finally, one can conduct coregistration with a nonanatomical technique, such as EEG/ERP, although this comparison focuses on the correlation between hemodynamics and neural activity, rather than hemodynamics and brain anatomy.

In summary, NIRS is rapidly becoming a viable and potentially robust technique for studies of functional brain activity in human infants. Probe designs are now suitable for use with infants and data collection appears to be reliable even under conditions of modest head/body movement. Spatial localization of signals will never achieve the precision of fMRI BOLD, but in concert with EEG/ERP techniques, NIRS is emerging as a third noninvasive window into the infant brain.

References

1. J. Mehler and E. Dupoux, *What Infants Know*, Basil Blackwell, Cambridge, MA (1994).
2. P. W. Jusczyk, *The Discovery of Spoken Language*, MIT Press, Cambridge, MA (1997).
3. P. J. Kellman and M. E. Arterberry, *The Cradle of Knowledge: Development of Perception in Infancy*, MIT Press, Cambridge, MA (1998).

4. N. K. Logothetis, J. Pauls, M. Augath, T. Trinath, and A. Oeltermann, ''Neurophysiological investigation of the basis of the fMRI signal,'' *Nature (London)* **412**, 150–157 (2001).
5. H. Obrig and A. Villringer, ''Beyond the visible—imaging the human brain with light,'' *J. Cereb. Blood Flow Metab.* **23**, 1–18 (2003).
6. T. DeBoer, L. Scott, and C. A. Nelson, ''Event-related potentials in developmental populations,'' in *Event-Related Potentials: A Methods Handbook*, T. Handy, Ed., pp. 263–297, MIT Press, Cambridge, MA (2004).
7. G. Dehaene-Lambertz, S. Dehaene, and L. Hertz-Pannier, ''Functional neuroimaging of speech perception in infants,'' *Science* **298**, 2013–2015 (2002).
8. F. F. Jöbsis, ''Noninvasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters,'' *Science* **198**, 1264–1267 (1977).
9. J. Meek, ''Basic principles of optical imaging and application to the study of infant development,'' *Developmental Science* **5**, 371–380 (2002).
10. G. Taga, K. Asakawa, A. Maki, Y. Konishi, and H. Koizumi, ''Brain imaging in awake infants by near-infrared optical topography,'' *Proc. Natl. Acad. Sci.* **100**, 10722–10727 (2003).
11. A. A. Baird, J. Kagan, T. Gaudette, K. Walz, N. Hershlag, and D. Boas, ''Frontal lobe activation during object permanence: data from near infrared spectroscopy,'' *Neuroimage* **16**, 1120–1126 (2002).
12. M. Peña, A. Maki, D. Kovacic, G. Dehaene-Lambertz, H. Koizumi, F. Bouquet, and J. Mehler, ''Sounds and silence: an optical topography study of language recognition at birth,'' *Proc. Natl. Acad. Sci.* **100**, 11702–11705 (2003).
13. G. Gratton and M. Fabiani, ''The event-related optical signal: a new tool for studying brain function,'' *Int. J. Psychophysiol.* **42**, 109–121 (2000).
14. M. A. Franceschini and D. A. Boas, ''Noninvasive measurement of neuronal activity with near-infrared optical imaging,'' *Neuroimage* **21**, 372–386 (2004).