fNIRS and the Interactive Brain
Utilizing functional Near-Infrared Spectroscopy for Neuroimaging Research
The urgency of this widespread and unmet medical need alongside recent advances in neuroscience, however, has inspired the hopeful vision that a comprehensive understanding of the brain is a realistic goal. This vision has recently been focused into an action plan in the United States referred to as the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative. The initiative was launched on April 2, 2013 by U.S. President Barack Obama who announced a Grand Challenge to “accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought” (The White House, 2013). Subsequently, the National Institutes of Health (NIH) formulated a 10-year plan to achieve the primary objective of accelerating the development of technology for acquiring fundamental insights about how the nervous system functions in health and disease. A starting point for the BRAIN initiative is focused on the neural circuits in the brain including characterization of the component cells, synaptic connections, and dynamic ensembles of activity associated with behavior. This overarching objective spans multiple scales of investigation ranging from the molecular and cellular processes that govern short-range neural circuits to long-range processes that govern complex behaviors observed by neuroimaging of humans.

Imaging the human brain in action

A primary objective targeted for this initiative encompasses both the improvement of existing technologies and the development of entirely new technologies that interrogate and model relationships between brain mechanisms and behaviors. Existing technologies for brain mapping, predominantly using magnetic resonance imaging (MRI) and electromagnetic techniques such as magnetoencephalography (MEG) and electroencephalography (EEG), are foundational for the investigation of the human brain under normal and pathological conditions. These technologies have contributed extensively to a major branch of neuroscience focused on the correlation of functional brain activity with cognition and behavior. In particular, the explosive growth in brain imaging technologies has led to an operational understanding of specialized neural processes associated with complex cognitive behaviors such as human language, memory, decision-making, vision and auditory processes, emotions, learning and social interactions.

In general, the neural and physiological components that underlie these systems are 1) localized to specific brain regions and short-range neural circuits that receive and transmit information, and 2) are interconnected by long-range pathways between the participating brain regions. Thus, two principles of brain organization emerge. The first is the principle of segregation where specific regions of brain are dedicated to specific tasks and processing, and the second is the principle of integration where co-active regions in the brain are interconnected under specific task demands. For example, in the case of the human language system, a region located in the left superior temporal gyrus, often referred to as Wernicke’s area, is specialized for receptive functions of language (understanding and interpreting spoken words). Additionally, a region located in the left inferior frontal gyrus, often referred to as Broca’s Area, is specialized for productive language functions (production of speech). These two complexes of specialized brain regions are interconnected by well-known pathways, including the arcuate fasciculus and the arcuate uncinate, that transmit information relevant to the processes of understanding language and producing speech. Other brain areas that are widely recognized as essential for memory and emotion become functionally connected to the language system during specific tasks. The dynamic relationships among these interacting areas during language-related operations have been extensively studied using contemporary neuroimaging techniques.

Technological advances

Primarily due to the constraints of studying brain processes using magnetic resonance imaging (MRI) technologies, mainstream neuroimaging has been limited to studies of single individuals. Natural interpersonal interaction between two individuals is not possible in a scanner environment. However, communication in real time involves verbal and non-verbal exchanges including eye-to-eye contact, dynamic facial expressions, and responsive gestures. These implicit communication cues do not occur in a scanning environment including only one individual, although interactive social behavior involving dynamic communications between two individuals is a fundamental aspect of human socialization. Largely due to these technological limitations, little is known about the underlying neural circuits that regulate and modulate natural interpersonal interactions and communication. Consequently, the neurophysiological mechanisms of psychiatric conditions with potentially profound deficits related to social interactions (e.g., autism spectrum disorders, schizophrenia, anxiety, and depression) remain undefined. The development of new technologies for brain imaging during communication between two individuals in ecologically valid conditions presents a particularly impactful opportunity to address the needs of large clinical populations for which the information gleaned through traditional neuroimaging is insufficient (Schilbach et al., 2013).
A foundational new role for near-infrared spectroscopy (NIRS)

An emerging neuroimaging technology, functional near-infrared spectroscopy (fNIRS), uses optodes secured in a cap worn on the head and is suitable for simultaneous use on multiple subjects in natural situations without intolerance to head movement. Like MRI, NIRS enables the observation of working neural systems in individual subjects without toxicity due to ionization. This technology takes advantage of the physiological principle that active neural tissue recruits oxygenated blood in greater proportions than non-active neural tissue. The paramagnetic effects of deoxyhemoglobin (deOxyHb) are reduced within the local micro vasculature during this recruitment process. The signal amplification in MRI referred to as the blood oxygen level-dependent (BOLD) signal (Ogawa et al., 1990) is due to the reduced proportion of deOxyHb and the resultant decrease in paramagnetic effects. The BOLD signal is also detected by NIRS using spectral absorption (Jöbsis, 1977) which differentiates oxyhemoglobin, OxyHb, and deOxyHb signals. Pulsed lasers (using the Shimadzu NIRS systems) emit 3 wavelengths of light and detectors measure the changes in oxygenated hemoglobin (OxyHb) and deoxygenated hemoglobin (deOxyHb) concentrations. For each channel, the absorption of near-infrared light at 780, 805, and 830nm is measured and converted to corresponding concentration changes for deOxyHb, total Hb (HbT), and OxyHb (Matcher & Cooper, 1994) respectively according to the modified Beer-Lambert Law (Fig. 1).

Shimadzu Corporation (Kyoto, Japan) is a leading manufacturer of fNIRS systems. Figure 2 shows a Shimadzu LABNIRS configuration specialized for hyperscanning in which signals are acquired simultaneously for two individuals who are engaged in an interactive task. This particular system enables the acquisition of real-time NIRS signals and eye-tracking acquisitions using SMI glasses with scene and pupil cameras synchronized to the neural signals. In this example, each cap includes 42 channels divided into two hemispheres for each subject. Cap configurations are flexible and can be modified according to experimental aims. Acquisition rates for NIRS signals range from 10 to 33 ms with spatial resolution of approximately 3 cm. This temporal resolution is well-suited for measures of connectivity between active brain regions within and across brains, but compared to fMRI, relatively compromised with respect to spatial resolution.

Both fMRI and fNIRS signals reflect changes in brain blood flow and blood oxygenation, which are coupled to underlying neuronal activity. The latter has been well established as recently demonstrated by Eggebrecht and colleagues (Eggebrecht et al., 2012) during visual stimulation in healthy volunteers. The high positive correlation between fMRI BOLD with deOxyHb and OxyHb is now well-established (Sato et al., 2013; Scholkmann et al., 2014).

“Raw” fNIRS signals obtained during a finger thumb tapping task for a single subject, single run and single optode illustrate the acquisition of both OxyHb and deOxyHb signals in response to a task-related time series (Figure 3). Note the anti-correlation between the OxyHb and deOxyHb signals, consistent with theoretical expectations. Due to the known correspondence with neural (rather than cardiovascular) events, the deOxyHb signal is expected to be most closely related to fMRI BOLD signal (Franceschini et al., 2006).
Cap design for optimal brain coverage

Optode placements for corresponding hemispheres on two subjects are illustrated in Fig 4. Table 1 includes an example of the anatomical locations for each channel (single subject), as represented in standard anatomical coordinates using the current Montreal Neurological Institute system (ICBM152, Mazziota et al., 2001). Since NIRS does not provide structural information, as in the case of MRI, standard brain atlases are employed to relate channel locations to known anatomical structures.

Optodes are positioned in similar head locations on both subjects to obtain cortical signals from nearly corresponding brain regions. The probes are positioned on each participant’s head, aligned to the midline defined as the arc running from the nasion through Cz to the inion. The position of the probes is based on the 10-20 international coordinate system (Jasper, 1958), which provides an accurate relationship with the cortical anatomy (Koessler et al., 2009). A 3D magnetic digitizer such as the PATRIOT Polhemus (Colchester, VT) is frequently used to identify the optode locations and, therefore, the channel positions for each subject, which are normalized by shape and size of the subject’s skull (Singh et al., 2003). Three-dimensional coordinates of anatomical landmarks on the head are recorded in addition to locations of the individual optodes (Okamoto et al., 2004). These coordinates are used to estimate the position of each channel as defined by an emitter-detector optode pair using standard software packages such as NIRS-SPM (http://www.fil.ion.ucl.ac.uk/spm/), a MATLAB-based application.

<table>
<thead>
<tr>
<th>Channel</th>
<th>x</th>
<th>y</th>
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<td>4</td>
<td>63</td>
<td>-18</td>
<td>48</td>
<td>0.30</td>
</tr>
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Table 1 Example of MNI coordinates for channel locations

Channel Centroid Locations: MNI Coords

The new neuroscience of two or more

Recent investigations of interpersonal interactions between two or more persons have demonstrated the efficacy of NIRS technology, which now leads the way toward a new neuroscience of natural cross-person communication (Babiloni & Astolfi, 2014; Scholkmann et al., 2013). Breakthroughs in technology, computational algorithms, and experimental paradigms promise a quantum leap in future advances for developing a theoretical framework of the social brain, and for treating the many psychiatric and neurological conditions in which social functioning is often compromised. An emerging basis for a new neuroscience originates with advanced computational approaches to observe cross-brain synchrony associated with specific functions. For example, coherence between frontal cortical signals during cooperation on a computer task has been measured using wavelet analysis and showed greater coherence between subjects who were competing on the same task, suggesting a neurophysiological substrate sensitive to interpersonal cues that are specific for cooperation (Cui et al., 2013). A similar frontopolar finding using simultaneous recordings of individuals in groups of four was reported during a cooperative word game (Nozawa et al., 2016). The emergence of leaders and followers has been studied in groups using simultaneous NIRS recordings of left frontal and parietal brain areas. Findings revealed that the emergence of a group leader was associated with increased neural synchronization between the leader and the follower relative to synchronization between followers (Jiang et al., 2015). These findings suggest that neural mechanisms for leadership may be understood in the future using hyperscanning methodologies and NIRS. Increased neural synchronization observed between left hemisphere signals across brains during face-to-face communication, and point the way toward the investigation of live facial cues as a fundamental component of natural interpersonal interaction (Jiang et al., 2012). Synchrony between premotor areas of two brains participating in an imitation task of finger tapping was greater than a control task in which the task was performed by self-pacing (Holper et al., 2012). Eye-to-Eye contact also increases coherence between brains (Hirsch et al., 2017). Additional examples include cooperative button pressing (Funane et al., 2011) and the n-back task (Dommer et al., 2012). Together, these findings contribute to the growing documentation that cross-brain effects are specific to neural regions, and that coherence is increased under varied conditions of interpersonal engagement. These foundational findings are early entry points that document the potential significance of a new hyperscanning technology based on NIRS, and the forward trajectory is moving at a very fast pace.

Fig. 4 Channel distributions for both cerebral hemispheres applied for two subjects
What happens when two brains talk to each other?

In our early studies of simultaneous cross-brain interactions during face-to-face communication between pairs of healthy adults, dyads alternated between talking and listening about pictures of objects in 15 second epochs. These epochs were structured and determined the turns between speaking and listening. Neural activity from signals acquired under monologue/dialogue and face-to-face/occluded conditions was compared for pairs of subjects. Run times of three minutes were partitioned into twelve 15 second epochs. The hypothesis was that regions of brain associated with talking and listening would increase within-brain and cross-brain synchrony during dialogue compared to monologue. For each epoch a single picture of an object was presented on a monitor and was viewed by each subject. Tasks were run under face-to-face conditions and occluded-face conditions (in which subjects had no view of their partner).

**Structured Monologue Task:** In the first instance, subject 1 identifies the picture object and provides a spoken narrative that relates to the object. Subject 2 listens, but does not respond. The next epoch is cued by the presentation of a new picture. Subject 2 names the object and provides a spoken narrative about it while subject 1 listens. This exchange of talking and listening continues for 3 min and is illustrated in Fig. 5.

**Structured Dialogue Task:** The structured dialogue task is identical to the structured monologue task except that the speaker includes a response to the narrative of the previous speaker. The expectation is that the dialogue condition will reveal upregulation of language systems during the face-to-face condition due to variations in the intensity of the dynamic interactions.

Analyses aimed at understanding conventional task-related, single-brain functional connectivity effects confirm the neural salience of dialogue in face-to-face interaction. A measure of functional connectivity between remote regions of brain shows that synchrony during a dialogue compared to monologue is increased. In particular, a psychophysiological interaction, PPI (Friston et al., 1997) analysis where fusiform Gyrus, a face-sensitive region of brain (Kanwisher et al., 1997) is selected as a seed confirms that dialogue during face-to-face gaze increases the strength of neural covariations between Wernicke and Broca’s Area (Fig 7). Findings confirm expectations of the canonical language system with increased connectivity between Broca’s and Wernicke’s Areas during face-to-face dialogue.

**Coherence Across Brains during dialogue>monologue:** Cross-brain coherence (using wavelet comparisons) to investigate brain-to-brain interactions.

The internal (within-brain) functional connectivity findings predict that these regions will also resonate across brains during face-to-face conditions. Cross-brain coherence (Fig 8A) for dialogue (red) and monologue (blue) conditions is plotted against wavelet kernels from the decomposed signals acquired at each channel. All possible pairs of brain regions across the two brains were considered in an unbiased manner. Significant differences between brain-to-brain coherence were found between the dialogue and monologue conditions only for the Broca-Wernicke pair of regions for kernel ranges centered around 6.34 secs (x-axis). Cross-brain coherence between putative functions of language production (Broca’s Area) and language reception (Wernicke’s Area) is consistent with these findings and with expectations based on current understanding of these areas (Fig 8B) (Jiang et al., 2012).
Functional NIRS is a rapidly growing neuroimaging technology that has doubled the number of publications every 3.5 years over the past 20 years (Boas et al., 2014), and the current trajectory is exponential. The major development areas include instrumentation, analysis methods, and optimization of experimental procedures for applications in mainstream areas of conventional neuroscience including neuro-development, perception and cognition, motor control, and psychiatric and neurological disorders and treatments. Recent applications for neurofeedback (Lapborisuth, et al, 2017) and adult cognitive neuroscience of conflict (Noah, et al, 2017) illustrate these new directories. However, the primary advantages of fNIRS are related to signal acquisitions in natural environments not constrained by the limitations of a high magnetic field and uncomfortable imaging conditions that restrict head motion and communication. These advantages position fNIRS as a potential leading technology for a new frontier in neuroscience that aims to understand the neural correlates of social behavior and cross-brain interpersonal interactions (Pinti et al., 2015; Noah et al., 2015; Hirsch et al, 2017). Most of the pieces are in place for the realization of this major advance. The key development priorities toward this specific end goal include: 1) computational algorithms focused on signal components that represent the neural contributions of the signal separate from systemic and other non-neural components (Kirilina et al., 2012; Zhang et al., 2016); 2) full head coverage of optodes to acquire the dynamic activity of underlying long-range neural circuits; and 3) multimodal systems that synchronize combined acquisitions of EEG, fNIRS, and eye-tracking measurements (for example) for a comprehensive report of long-range brain mechanisms. The co-occurrence of the BRAIN initiative and the emergence of fNIRS as a mainstream neurotechnology catalyzes the impactful potential to probe untapped neural systems specialized for interpersonal interactions between two or more individuals.

Where do we go from here?

These studies illustrate potential future directions to investigate the dynamic relationships between interacting human brains using fNIRS and hyperscanning techniques. Additionally, the language hyperscanning studies document that well-known functional neural anatomy such as the components of the language system are observable using fNIRS, and that the additional features of cross-brain coherence and synchrony between two individuals can be investigated as novel probes to characterize uncharted questions that underlie the neural events of social interaction. These studies also confirm the advantages of technology that populates the surface of the head with full head coverage (Zhang, et al, 2016; Zhang, et al, 2017; Dravida, et al, 2017). Since neural systems depend upon signal cooperation between multiple areas (the integration principle) the most successful NIRS technology will depend upon sampling brain function over the entire brain. Potential benefits include a landmark breakthrough in methodology and technology leading to principles of neural organization engaged during interpersonal and reciprocal interactions. Future studies may apply these new techniques to further understand the neural underpinnings of disorders of communication as well as how the neural underpinnings of social disability in developmental disorders deviate from typical development.

Fig. 8 Coherence analysis of cross-brain synchronization. A. Coherence is plotted for the deOxyHb fNIRS signals for Wernicke’s and Broca’s Areas (WA and BA) during monologue (blue line) and dialogue (red line) conditions, indicating a significantly higher synchrony during dialogue than monologue (p < 0.005), and was observed only for the face-to-face condition. Findings were bilaterally significant across pairs of subjects and unbiased with respect to regions of interest. B. These coherence findings are specific to Broca’s and Wernicke’s areas (group data). (Hirsch, J., Noah, A., Zhang, X., Yahil, S., Lapborisuth, P., & Biriotti, M. (2014, October). Neural specialization for interpersonal communication within dorsolateral prefrontal cortex: A NIRS investigation. Presentation at the Annual Meeting of the Society for Neuroscience, Chicago, Illinois, USA.)
References


