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The use of near-infrared spectroscopy in the study of typical and atypical development

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Abstract

The use of functional Near Infrared Spectroscopy (fNIRS) has grown exponentially over the past decade, particularly among investigators interested in early brain development. The use of this neuroimaging technique has begun to shed light on the development of a variety of sensory, perceptual, linguistic, and social-cognitive functions. Rather than cast a wide net, in this paper we first discuss typical development, focusing on joint attention, face processing, language, and sensorimotor development. We then turn our attention to infants and children whose development has been compromised or who are at risk for atypical development. We conclude our review by critiquing some of the methodological issues that have plagued the extant literature as well as offer suggestions for future research.

Introduction

The use of functional near-infrared spectroscopy (fNIRS) as a neuroimaging tool has emerged slowly over the last twenty years; indeed, much of the *developmental* literature has accumulated over the past 5 years. Many of these developmental studies have begun to examine complex perceptual, social, and cognitive functions in the developing brain, including attention, language acquisition, and speech and face perception. This relatively new technology has the potential to shed light on the functional development of the brain in awake, behaving infants and children.

Functional near-infrared spectroscopy measures changes in concentrations of oxygenated, deoxygenated, and total hemoglobin (OxyHb, DeoxyHb, and TotHb) in brain hemodynamics by measuring the absorption of near-infrared light projected through the scalp (Gervain, et al., 2011; Minagawa-Kawai, et al., 2008; Strangman, et al., 2002). Therefore, as with fMRI, fNIRS provides an indirect measure of neural activity based on changes in blood oxygenation due to metabolic processes within the cortex. Unlike fMRI, however, fNIRS is more impervious to movement artifact because the light emitters and detectors, or optodes, can be fitted in a cap worn by the participant. This opens the possibility of studying, in vivo, functional neural activity while individuals interact with their environment.

The resilience of fNIRS to movement artifact makes it an ideal tool for studying early brain development (primarily due to the advantageous features of thin skull, shallower sulci, and less dense hair) and in study designs or populations where movement may be unavoidable during testing, e. g. action execution tasks or children with ADHD. Finally, fNIRS has greater spatial resolution when compared to event-related potential (ERP) or EEG techniques making it an ideal technique for addressing questions of regional specificity (Gervain et al., 2011; Minagawa-Kawai, et al., 2008). Despite these advantages, however, it

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should be noted that a major limitation of this tool is its dependence on light penetration and reflection, therefore, fNIRS can only examine the cortical surface within 2 – 3cm of the scalp (2–3 mm of cortex); thus, deep structures and circuits (e. g., hippocampus or amygdala) or even those that lie deep in a sulcus, may not lend themselves to fNIRS investigations.

Even in its infancy, the use of fNIRS has expanded our understanding of cortical function at birth as well as in changes of regional activity as a result of emerging behaviors. The majority of this research has focused on the development of perceptual discrimination within auditory and visual systems or language processing (see Aslin, 2012; Crista, et al., 2013; Dieler, et al., 2012; Lloyd-Fox, et al., 2010; Minagawa-Kawai, et al., 2008; Minagawa-Kawai, et al., 2011; Rossi, et al., 2012) largely using designs in which the infants are able to sleep through the assessment. Findings from these studies have demonstrated the applicability of fNIRS for infant research, but more importantly that the neonate brain shares some of the specialized functional characteristics of a mature brain.

Some inroads have been made to study neural activity associated with complex social and cognitive abilities in awake infants, including cognitive control, face perception, object processing, and sensorimotor development (Table 1; for a continuously updated database of developmental study using fNIRS, see Crista, et al., 2013). In this review we will selectively draw from fNIRS research that has contributed to our emerging understanding of functional brain development in the context of core deficits identified in developmental disorders; specifically joint attention, face processing, language perception, and sensorimotor development. After discussing the literature on typical development, we turn our attention to the emerging literature on atypical development.

Use of fNIRS in the Study of Typical Development

The use of fNIRS in studies of typically developing infants and children is of critical importance for laying the foundation for interpreting the results of studies in atypically developing populations. The studies of socio-cognitive development in infants we review below are in domains that represent some of the core deficits or have been implicated in the emergence of developmental disorders such as attention deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD). The evidence from these and future studies of typically developing infants will help identify the neural changes associated with the acquisition of newly emerging socio-cognitive behaviors and will help researchers better understand the mechanisms that place an individual at risk for developmental disorders.

It is important to note that the use of fNIRS has only recently gained popularity for its use in research with infants and children and many of these early studies collected data from a limited number of optodes. Furthermore, standardization of optode arrangement within a probe set and optode or probe set positioning has not been established – and is often variable between different studies from the same lab. For the purposes of this review we will identify optode locations with respect to their approximate scalp location from the international 10–20 system and, where appropriate, refer to the underlying brain structure measured.

Finally, not surprisingly many studies suffer from methodological limitations; perhaps because of how relatively new this imaging technique is (in the context of development). Rather than critique each study, we instead include a section at the end of our review that summarizes some of the major concerns that need to be addressed in future studies.

Development of Joint Attention—Joint attention is a fundamental social skill that supports shared interactions between individuals and their environment. Impairments in the ability to engage in joint attention is one of the earliest indicators of autism spectrum

disorder (ASD; Charman, 2003). In order to achieve joint attention, an infant must attend to and interpret the meaning of another individual's goal. In adults, successful engagement in joint attention recruits: attentional control systems (such as the medial prefrontal cortex; mPFC); regions involved in understanding the actions of others, specifically the posterior superior temporal sulcus (pSTS); and regions involved in attributing mental states such as right lateralized activity in the temporal-parietal junction (rTPJ; for a review, see Saxe, 2006; Saxe, et al., 2004).

Converging evidence demonstrates the recruitment of mPFC and pSTS in infants engaging in social interactions. In an ingenious series of studies, Lloyd-Fox and colleagues (2009) placed fNIRS sensors bilaterally over scalp locations that were presumably sitting over the pSTS and temporal lobes (just above the F7/8-T5/6 line) of 5-month-old infants while they observed social video clips of a woman performing left and right eye movements, mouth opening and closing, or hand games (e.g. "peek-a-boo") compared to nonsocial dynamic videos of mechanical toys or static images of vehicles. The authors found that the greatest increase in OxyHb concentrations occurred in optodes placed over the pSTS (T5 and T6) to the social stimuli. These data suggest that at 5 months (and possibly earlier; see Grossmann, et al., 2008 below) there is already regional specificity for the observation of social stimuli.

Grossmann and colleagues (2008) replicated these findings, demonstrating differential activation of the pSTS region (T5 and T6) in 4-month-old infants viewing a video of an animated face shifting their gaze towards the infant compared to the face shifting their gaze away from the infant. In addition to the posterior activations, they also identified activity in the mPFC, from optodes placed over Fp1 and Fp2, which demonstrated differential responses to the different gaze shift conditions. These effects were dominant over the right hemisphere; however, more recent evidence from this lab has demonstrated broad activation from the left dorsal mPFC (data were averaged across multiple channels surrounding AF3) to joint attention between the infant and an animated adult (Grossmann, et al., 2010). Taken together, these data demonstrate that 4- to 5-month-old infants activate similar regions as in adults (inferred from fMRI) associated with representing mental states of others (Saxe, 2006; Saxe, et al., 2004).

Face Perception—Faces are an incredibly rich source of information about our social world. At birth infants prefer face-like stimuli although it is unclear if they prefer faces qua faces or rather the physical complexity of the stimulus (see Righi & Nelson, 2012 for recent review). Still, there is an abundance of evidence that within the first months of life, there is an early predisposition towards face-like stimuli. This undoubtedly sets up the developmental events that follow, in which infants gradually become experts at perceiving and recognizing faces. Moreover, disrupted facial processing is a core deficit in ASD (Sasson, 2006). Unfortunately the primary region identified in face perception, the fusiform gyrus, is positioned deeper in the cortex than can be easily detected by fNIRS (Otsuka, et al., 2007), but other regions, specifically the STS and anterior part of the orbitofrontal cortex (aOFC), contribute to facial processing and these regions have been the focus of a number of developmental studies examining face processing.

Disrupting the normal configuration of the human face by inverting the image or by rearranging the internal features makes facial recognition difficult and a number of behavioral and electrophysiological studies have demonstrated this to be true for infants, children, and adults (Bhatt, et al., 2005; de Haan, et al., 2002; Taylor et al., 2004). To test the sensitivity of fNIRS to assay this facial inversion effect (from which one typically infers a representation of the face), Otsuka et al. (2007) measured the effect of face inversion in 5- to 8-month-old infants. Their results showed a significant increase in OxyHb and TotalHb to upright faces in the right hemisphere but not to inverted faces in either hemisphere; an effect

replicated recently by Fox, et al. (under review). Similarly, Honda and colleagues (2010) observed similar right hemisphere dominance for processing canonical versus scrambled faces in both 7- to 8-month old infants and adults. Both of these studies averaged activity across a broad number of optodes placed over the temporal scalp, placed between T3/T4 and T5/T6, and were not able to identify a specific region of activity associated with the effect. It is likely that these findings reflect general activation for processing social stimuli (e.g. face versus non-face). However, the identification of sensitivity in the right hemisphere to canonical faces over scrambled or inverted faces demonstrates the ability of fNIRS to detect activity associated with face processing

Emotional faces convey a great deal of information about the internal states of others. Through ERP studies we know that by 7 months, infants can distinguish between positive (happy) and negative (anger or fear) emotions (Leppanen, et al., 2007; Nelson & de Haan, 1996), however, much less is know about the hemodynamic responses associated with emotional face processing in infancy. Nakato and colleagues (2011) presented 6.5-month-olds with pictures of a woman expressing a happy or an angry face. The authors found that happy facial expressions activated the left temporal cortex while angry faces activated the right temporal cortex in these infants. While these results are consistent with an fMRI study in adults that found similar lateralization effects for positive and negative emotions, that study focused on the role of the somatosensory cortex in emotion face recognition (Adolphs, et al., 2000). Because Nakato et al averaged across optodes placed over the posterior temporal cortex (centered on T5 and T6), it is unclear what about the valence of the emotions was being processed.

Finally, the aOFC may also play a role in the processing of emotional faces. In a unique experimental design, Minagawa-Kawai et al. (2009) recorded videos of mothers producing a smile and of their 12-month-old infants producing a smile. They then measured hemodynamic changes in the aOFC (optodes centered on Fpz) of the mothers observing their own infant or an unfamiliar infant smiling and similarly while the infant observed their mother or a stranger producing a smile. They observed an increase in OxyHb along the midline of the aOFC in both mothers and their infants to observations of the familiar face and no change while observing the unfamiliar face. In the adult brain, the OFC is responsible for regulating emotional arousal and the results of this study suggest that some of the functional role of the OFC may already be evident by the end of the first year.

Language Acquisition—There is a large body of research using fNIRS to examine the functional neural dynamics of early language processing in typically developing infants. Here we highlight a few of the studies that have identified important developmental changes in language processing that relate to our discussion of atypical development below (for more in depth reviews, see Dieler, et al., 2012; Minagawa-Kawai, et al., 2011).

At birth, infants are able to distinguish between speech and non-speech stimuli, with the neural sources of such processing lying within the left hemisphere (Bortfeld, et al., 2009; Pena, et al., 2003). The results of Pena and colleagues demonstrate that, at birth, infants' brains share some of the specialized functional characteristics of a mature brain and are not as undifferentiated as previously believed. While these specialized structures are present at birth, it is clear that a significant level of learning still needs to take place. Using fNIRS, research examining discrete properties of speech perception, including prosody and phonetics, have identified changes in the activity of brain structures that correspond to developmental changes in infants' language acquisition.

Over the first year of life infants' ability to discriminate between phonemes of nonnative languages declines and becomes tuned to the limited range of phonetics in their native

language. Minagawa-Kawai and colleagues (2007) studied phonemic processing in a large (N=127 across all ages) cross sectional sample of infants between 3 and 28 months. Four optode pairs were placed over the temporal cortex with the lowest channel corresponding to T3 or T4. The authors found that there was a shift from bilateral processing of phonemes in infants younger than 12 months to greater left lateralized activity in infants older than 12 months of age, similar to greater left activity during phonemic processing in adults (Jacquemot, et al., 2003). This study benefited from two strengths: first, its large sample sizes for each age group and second, analyses were conducted at the individual channel level. As a result, the authors were able to show that, in addition to the lateralization of phonemic processing, the activity in the left auditory cortex became more focused with age. This lateralization of phonemic processing appears to occur around the same time in development as the loss of broader discriminatory abilities, suggesting that the decline in ability is directly related to changes in neural organization.

The processing of prosodic components of speech (intonation or loudness of the speaker) is important for aiding infants in parsing continuous utterances into words. The ability to use prosody to identify word boundaries emerges in the second half of the first year. In a series of studies, Homae and colleagues (2006; Homae, et al., 2007) examined the neural changes associated with this shift in prosodic processing using normal intonated speech or "flattened" speech with all intonation removed. In adults, there is greater activation of right frontal and temporoparietal scalp regions to flattened speech (Meyer, et al. 2004); however, in 3-month-old infants, the opposite effect, right temporoparietal activation (anterior to P4) to normal speech, was found (Homae et al., 2006). In a follow-up study with 10-month-old infants, using the same stimuli and probe placement, Homae et al. (2007) found more adult-like activation to flattened speech compared to normal speech. Taken together, these data suggest that, like phonemic processing, there is reorganization of speech processing regions that coincide with the emergence of new speech discrimination abilities.

Sensorimotor Development—One domain in which there is very little research in either typical or atypical development and yet is ideal for fNIRS, is action observation, execution, and understanding (Bolling, et al., 2012; Koenraadt, et al., 2012). The neural mechanisms underlying these behaviors have recently gained popularity for their potential connection to the human mirror neuron system (MNS). The human MNS is comprised of the sensorimotor cortex, inferior frontal gyrus (IFG), and inferior parietal lobe (IPL; Buccino, et al., 2001). The regions within the human MNS show similar activation while an individual performs an action and while they observe another performing that action. Because of the congruence of activation for the observation and execution of actions, the MNS facilitates action understanding by giving the observer an embodied understanding of the actor's goal. Many have hypothesized a link between action understanding and the development of more complex social cognition, such as joint attention, imitation, theory of mind, and empathy (for a review see: Vanderwert, et al., 2013). Moreover, in populations that show clear behavioral deficits in these domains, such as ASD and schizophrenia, there is evidence to suggest a disruption of functioning in these regions.

The use of fNIRS presents a unique opportunity to measure the early development of the MNS because of the proximity to the scalp of the three regions. In some of the most convincing evidence to date, Lloyd-Fox et al. (2011) presented 5-month-old infants with videos of a woman moving her eyes, opening and closing her mouth, and making a fist with her right hand. The biological movement conditions were contrasted with a baseline condition of moving toys. Changes in OxyHb and DeoxyHb were measured over frontal (Fp1/2), prefrontal (F7/8), and temporal regions (T3/4 and T5/6). The increases in OxyHb were observed for the hand and eye conditions were in bilateral scalp locations

approximately over the IFG. The results of this study represent the earliest demonstration that observation of biological motion activates motor regions in human infants.

A few other studies have examined the perception of biological motion in young infants with mixed results. The differences may be a result of very different stimuli. Grossmann et al. (2013) presented 4-month-old infants with four videos of an individual performing dance moves. In two of the videos, there was a human performing a natural dance or robotic movements. In the other two videos a Lego™ man was animated to match the two dances performed by the human. Source-detector pairs were placed over frontal (posterior to F5/6) and temporal (superior to T3/4) brain regions. Contrary to the results reported by Lloyd-Fox et al. (2011), there was no clear increase in OxyHb in channels over the IFG region to the observation of human actions. The major differences in the stimuli may explain this discrepancy; specifically, Lloyd-Fox et al. used actions within the repertoire of the infant (i.e. opening and closing their hand) as opposed to the complex dance moves used in the study by Grossmann and colleagues. These two studies represent first attempts to measure MNS activation to biological motion with fNIRS in infants; however, no study has measured activity in these regions during action execution. It is unclear if the observed increases in OxyHb reported by these studies also respond to action execution, which is a critical feature of the MNS. The functional activity of the sensorimotor cortex, IFG, and IPL represent important regions for fNIRS researchers to focus future efforts.

Summary—The limited body of research using fNIRS has already begun to contribute to our understanding of typical brain development. As can be seen from the evidence presented thus far, over the first year of life the infant brain already shows differentiated activation in regions known to be activated in the adult brain. Additionally, because of its ability to measure functional brain activity in very young infants, fNIRS has identified developmental changes in the brain associated with significant changes in infants' behavior. Deepening our understanding of typical brain development in these, and other domains, will help us identify critical periods in which developmental trajectories may be perturbed or offer us measures for early detection of developmental disorders.

Use of fNIRS in the Study of Atypical Development

As is evident from the preceding sections as well as other reviews on fNIRS (Aslin, 2012; Gervain, et al., 2011; Minagawa-Kawai, et al., 2008), this technology is a relatively new addition to the armamentarium of "neural assays" that permit one to study early brain development. Given that the method is still in a rapid phase of development, it is not surprising that this tool has been used relatively little in the study of atypical development or children at risk for atypical development. Specifically, because the corpus of knowledge of typical development is limited, it is difficult to identify what an atypical hemodynamic response would look like or how to interpret such a response. Nevertheless, some inroads have been made in this regard, which serves as the final section of this paper.

This work generally falls into a few different domains: studies of executive function deficits, including ADHD; epilepsy; speech and language delays/disorders; preterm birth/early brain injury; and autism. Because of our interest in focusing on the *functional* use of fNIRS, we will not review the literature on epilepsy and preterm birth/brain injury (where the focus has primarily been on using fNIRS to describe metabolic differences rather than functional differences). Additionally, because many of these developmental disorders emerge during childhood, the majority of research has focused on children meeting criteria for a developmental disorder; however, a few studies have focused on infant siblings of older children diagnosed with an autism spectrum disorder. We highlight these studies in the final section for their potential to identify early neural markers for a developing disorder.

Attention Deficit Hyperactivity Disorder (ADHD)—There is now an extensive literature using PET, SPECT, and fMRI that demonstrates dysfunction of regions in the prefrontal cortex in individuals with ADHD (it should also be noted that striatal circuitry, and connections between the striatum and the prefrontal cortex, have also been strongly implicated in ADHD, but the striatum and its connections to other brain regions lie out of the reach of fNIRS). In a rather demanding test of attentional focus, Weber, Lutschg, and Fahnenstich (2005) had 10-year-old boys with and without ADHD perform the Trail-making test (see below). Two optodes were placed over the child's forehead in positions between Fp1/F3 and Fp2/F4, putataively over regions corresponding to the superior and middle frontal gyri of the dorsalateral prefrontal cortex. In trail making, the numbers 1–90 are randomly distributed on a page and children must connect the numbers in ascending order (1–2–3, etc.). They were made to repeat this test 4 times, with breaks in between. The authors reported that during the first session (what the authors refer to as a test of short-attention), the boys with ADHD (but not the controls) showed a significant increase in cerebral blood volume over both left and right hemispheres and in OxyHb over the right hemisphere but no changes in DeoxyHb during the first test set. During the extended attention task (all 4 sessions), an increase in OxyHb and cerebral blood volume was observed in both groups, although only the controls showed a DeoxyHb response on the left side.

In addition to difficulty with sustained attention, children with ADHD have marked deficits in attentional control. A number of fNIRS studies have examined prefrontal cortex activity while children with ADHD and controls complete a color-word matching Stroop task (Jourdan Moser, et al., 2009; Negoro, et al., 2010; Xiao, et al., 2012), which requires individuals to cope with the incongruence of a color-word printed in a different color (e.g "Red" printed in blue ink); and a Go-NoGo task (Inoue, et al., 2012; Xiao, et al.), which requires the inhibition of a prepotent response. The results of these studies have identified disrupted prefrontal cortical activity in the boys with ADHD, however their findings are inconsistent and difficult to interpret.

In the first study of boys with and without ADHD performing the Stroop task, Jourdan Moser and colleagues (2009) measured prefrontal hemodynamic activity from optodes centered over F3, F4, FC3, and FC4. They found an increase in DeoxyHb in the channel corresponding to FC4, suggesting there was greater oxygen consumption by the right dorsolateral prefrontal cortex when subjects with ADHD had to cope with incongruent color-word pairs when compared to the controls.

In a similar study of 10-year-olds performing a Stroop task, Negoro and colleagues (2010) measured activity over 24 channels covering an 8 × 8 cm area centered on the midline of the forehead and spanning a much larger area of the prefrontal cortex than the study by Jourdan Moser et al. (2009). They found that control children had a significant increase in OxyHb in two channels located over the right and one channel over the left dorsolateral prefrontal cortex during incongruent color-word trials, whereas children with ADHD did not. The authors did not measure DeoxyHb during the task, making comparisons between their results and the results of Jourdan Moser et al difficult, however both studies report disrupted activity in children with ADHD in similar regions.

While the Stroop task requires individuals to inhibit competing responses, the Go-NoGo task requires the inhibition of a prepotent response; the ability to stop a repetitive action. Inoue and colleagues (2012) measured prefrontal activity in optodes placed across the foreheads of 9-year-old children performing a 2-minute block of Go trials (press a button every time a mole with sunglasses appears) and a 2-minute block of NoGo trials (don't press when a mole without sunglasses appears). The results found similar hemodynamic responses in both

groups during Go trials, but during the NoGo block, in which the participants had to inhibit their response on 50% of the trials, control children had a greater increase in OxyHb across the prefrontal cortex compared to children with ADHD, suggesting that the children with ADHD were not activating the prefrontal cortex to the same degree. For the analyses, the hemodynamic response was averaged across the 2-minute block and across all optodes, so fine grained interpretation of their data is not possible.

Recently, Xiao and colleagues (2012) tested a group of 10-year-old boys with and without ADHD on both a Go-NoGo and Stroop task. They measured concentration of OxyHb in optodes placed across the forehead in a similar placement as Inoue et al. (2012) but analyzed activity over the hemispheres separately. Consistent with the results of Inuoe et al., the authors found a significant decrease in OxyHb in children with ADHD during the NoGo block compared to controls, however, this effect was specific to the right hemisphere. There were no significant effects in OxyHb between groups for the Stroop task.

Autism—Although still small in number compared to studies of typical development, the use of fNIRS has begun to receive some attention by investigators interested in autism spectrum disorders and infants at risk for an ASD. Not surprisingly, given that two core features of autism include deficits in social communication and language, the work that has been done has focused on face processing and speech/language processing. Regarding the latter, Mingawa-Kawai and colleagues (2009) examined the functional lateralization of prosodic and phonemic processing. As mentioned above, prosodic processing becomes left lateralized after 12 months of age, and phonemic processing becomes right lateralized around 10 months, however, individuals with ASD may have atypical hemispheric specialization that may impair their ability to process language effectively (Lindell & Hudry, in press). Children with and without an ASD diagnosis listened to alternating blocks of words that contrasted either phonemically or in their prosody while hemodynamic responses were recorded from optodes placed over the auditory cortex (T3/4). Consistent with the developmental literature, the typically developing children had greater TotHb in the left hemisphere for phonemic contrasts and greater TotHb in the right hemisphere for prosodic contrasts. In comparison, the children with ASD only had a right lateralized effect for prosodic contrasts. These data suggest that phonemic processing may be disrupted in autism spectrum disorders by a lack of hemispheric specialization.

Funabiki and colleagues (2012) adopted a very complex experimental design that involved 4 different classes of auditory stimuli and two different test conditions. The auditory stimuli consisted of pure tones, vowels spoken by a female voice, a meaningless syllable sequence, and finally, stories containing 30 words read by a female voice. In one run, children were asked to listen carefully; in another they were asked not to listen and to essentially ignore what was being played (thus, the juxtaposition of “attend” vs. “ignore” conditions). Sixteen year olds with an autism spectrum disorder and 14-year-old controls served as study participants. The authors reported that both groups showed increases in OxyHb over the auditory cortex (channels slightly anterior to T3/4) during the “attend” condition but not the “ignore” condition. Differences in OxyHb showed a laterality switch between attention conditions in the ASD group but not in the controls over the prefrontal cortex (channels just above Fp1/2) specific to the story stimuli. The authors concluded that during intentional listening, the auditory cortex of individuals with ASD responds in a typical fashion; less clear is how to interpret the findings over the prefrontal cortex.

With regard to face processing, Kita et al. (2011) presented 10-year-old boys with and without an ASD with computer-generated morphed images of three different faces: the child’s own face, an age-matched familiar face (a friend of the participant), and an unfamiliar face; these images were stitched together to create a movie whereby over

successive frames the three faces would change from one to another. Optodes were placed across the forehead centered along the Fp1-Fp2 line over regions corresponding to the prefrontal cortex. The authors reported that in general, across both groups, the OxyHb response was greater over the right vs. left IFG. However, they also observed that within the ASD group, activation declined as a function of autism severity. This led the authors to conclude that the right IFG may play a key role in the face processing deficits that are sometimes observed among individuals with autism.

Infants at risk for autism—It is well established that the earlier in life children with autism receive treatment, the better their outcome. The challenge in early intervention, however, lies in early identification. This has led a number of investigators to study populations of children who are at elevated risk for developing an autism spectrum disorder. One such population are infants with an older sibling with autism - so-called “infant sibs. ” In contrast to the general population where the prevalence of autism is approximately 1:88, among infants with an older sibling with autism the prevalence falls to 1:5 (Ozonoff et al., 2011). Thus far two labs have focused on this population. Lloyd-Fox et al. (2013) studied 4- to 6-month-old infants at risk for an ASD (by virtue of having an older sibling with the disorder) and at low risk for an ASD (no family history). Infants were presented with movies of female actors’ faces, in which the eyes moved left or right, or the actors performed games like peek-a-boo; control stimuli consisted of still images of vehicles (e. g., cars, helicopters). On some trials auditory stimuli were presented. These stimuli consisted of either vocalizations of two different speakers (e. g., cough, yawn), or environmental sounds (e. g., running water, squeaky toys). Broadly speaking, then, the infants were exposed to two classes of events: social vs. non-social. This is an important manipulation, given the other studies reporting that infant sibs respond differently than controls to social stimuli but not non-social stimuli. Lloyd-Fox et al. reported that the infants at risk for autism showed a diminished response to the visual social stimuli over the left posterior temporal cortex (anterior to P3). The fact that the groups only differed in their response to social stimuli is consistent with studies of children and adults with autism, and in this case, may therefore represent an endophenotype or biomarker for autism risk.

Adopting a similar approach, Fox et al. (2013) presented 7-month-old high and low-risk infants with short movie clips of their mother or a stranger smiling or posing a neutral expression. This design permitted the investigators to disentangle differential responses to face type (familiar, novel), emotion (happy, neutral) and group (high vs. low risk). Group differences were observed in both OxyHb and DeoxyHb over a variety of prefrontal (AF3/4) and right temporal (T6) scalp locations. Face type and Emotion type effects were observed over both overlapping and unique optodes; often the interactions were driven by differing hemodynamic responses between the groups (e.g. increase in OxyHb in one group versus a decrease in DoxyHb in the other). What is unclear from the findings of these two studies is whether these hemodynamic response differences reflect anatomical (i.e. larger cortices), compensatory, or specialization differences. Similar to the conclusions drawn by Lloyd-Fox and colleagues (2013), Fox et al. speculated that these findings again point to an endophenotype of autism. It remains to be seen across both laboratories whether these early risk signs are predictive of autism or rather, reflect a signature of risk for autism.

Summary—On the whole, the literature on atypical development or risk for atypical development represents an encouraging next step in the evolution of this methodology. However, it is important to bring attention to a number of conceptual and methodological issues that come with the study of atypical development. First, one cannot emphasize enough the need for careful phenotyping of the populations in question. Without such information it may prove very difficult to understand why one group (e.g., children with ADHD) differs from another (those without ADHD). This, of course, is a problem that

plagues the field of developmental psychopathology and is not unique to fNIRS, although fNIRS investigators should give careful consideration to this issue. For example, in ERP studies of infants at high risk for developing autism, investigators have been able to distinguish those infants who do versus do not develop an ASD. By holding genetic background constant, it becomes possible to draw inferences about whether observed metabolic changes are attributable to autism per se or reflect a risk factor for developing autism.

Second, viewed from afar, most studies reviewed in this section can draw only the simplest conclusions: that one group differs from another. Although this level of description is important, it fails to address the deeper issue of what precisely differs in brain development that leads one child to develop a disorder and not another. For example, observing differences in OxyHb over the right temporal scalp to faces in a clinical vs. non-clinical population tells us little as to *why* such differences exist: for example, are these differences in underlying circuitry, blood flow, etc? Are these differences present at birth or have they developed over time?

Third, many of the studies reviewed in this section involve small sample sizes. Given how little we know about variability in the hemodynamic response to various task conditions or stimulus manipulations in typical development, we don't know if what is being observed in a clinical population represents a true (pathological) difference or is simply within normal limits. Moreover, in some disorders there is considerable variability among affected individuals, and biased sampling (whether intentional or not) can potentially mislead investigators into thinking that group differences reflect dysfunction in the underlying neural circuitry while they may simply reflect individual variability within the general population.

Conclusions

Functional near-infrared spectroscopy has already demonstrated its usefulness in studies of both typical and increasingly, atypical development. The ongoing research into understanding the hemodynamic changes that occur in the sensory systems in the infant brain (for a review, see Aslin, 2012) as well as more complex structures associated with socio-cognitive functioning has already changed the way we think of the infant brain at birth. But there are improvements that still need to be made.

In addition to the issues highlighted in the previous section for improving research in atypical development, there are domains in which research in typical and atypical development would directly benefit. First, across studies there is tremendous variability in optode placement and number of optodes used. The solution to this variability has often been to average over a large cluster of optodes, rather than identifying localized activity measured by a single optode pair. When this approach is used the interpretability of results suffers. Increasing the number of optodes and recording the precise location of each optode will improve our certainty of the underlying brain region activated. Moreover, recording from optodes covering the entire scalp will further our understanding of how complex stimuli, such as face processing or mirror neuron systems that recruit distal regions of cortex that operate in tandem in the mature brain, emerge and are processed developmentally. Standardization of the number, placement, and nomenclature of NIRS channels will greatly improve the interpretability of individual results as well as our ability to make comparisons across studies.

Second, inherent to research with infants is the difficulty of obtaining multiple trials and/or multiple conditions within an infant. As is the case with ERPs, increasing the number of trials improves the signal to noise ratio of the brain response. The experiments presented by Lloyd-Fox et al (2009) highlight the importance of both increasing the number optodes and

the number of trials. In one experiment, infants observed 10 trials of videos of socially engaging games (i.e. peek-a-boo) and activation was observed in single channels placed bilaterally over the pSTS. In a second experiment, the researchers included a second, non-social video condition, and showed infants 5 trials of the social and 5 trials of the non-social stimuli. Activation to the social videos was now observed in the original 2 channels and 7 additional channels. In this study, if the researchers had had fewer trials and placed fewer channels, their conclusions would have been dramatically different.

Finally, the studies reviewed above highlight the ability of fNIRS to record functional brain activity in very young infants and children making fNIRS an ideal technique for developmental research. The evidence from cross-sectional studies has identified a number of changes within the brain that occur around the time that behavioral studies describe behavioral changes (e.g. Minagawa-Kawai, et al., 2007). What cannot be concluded from these studies is whether the reorganization occurs because of behavioral changes or vice versa. Longitudinal designs are needed to address questions of these sorts. To date, only one study has measured fNIRS in a longitudinal sample (Baird, et al., 2002) finding increased activity in the anterior OFC associated with the onset of object permanence.

The emergence of near-infrared spectroscopy (NIRS) as a new technique for measuring functional brain activity in vivo has contributed to exciting advances in our understanding of typical brain development. Research utilizing fNIRS has changed the way we conceptualize the functional properties of the neonate brain. At birth, the brain is organized into specialized regions demonstrating responses to stimuli consistent with their functional role in a mature brain, such as regions associated with complex perceptual, social, and cognitive functions, including attention, language acquisition, and speech and face perception. Moreover, the developmental literature is establishing a rich foundation for our understanding of typical brain development that will inevitably help identify critical periods for identification of and intervention in atypical development.

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Table 1

Studies of typically developing awake infants using fNIRS to study social and cognitive development.

Author	Year	Participant Age[1]	Channels	Brain Region	International 10–20 Location	Probe Analysis	Main Finding
Joint Attention							
Grossmann, et al.	2008	4	6 10 × 2	Frontal Temporal	Along Fp1-Fp2 line Between T5/6 and F7/8	Channel	↑OxyHb in right fronto-polar cortex & Sup Post temporal cortex to gaze direction
Grossmann & Johnson	2010	5	12 × 2	Frontal	Between Fp1/2 and F3/4 From T3 to T4	ROI_S	↑OxyHb in left dorsal prefrontal region to joint attention condition
Grossmann, et al.	2010	5	12 × 2	Frontal	Between Fp1/2 and F3/4 From T3 to T4	Channel	↑OxyHb in left dorsal prefrontal to own name and ↑OxyHb in an adjacent channel to eye contact
Lloyd-Fox, et al. (Exp. 1)	2009	5	10 × 2	Temporal	Between T3/4 and C3/4 From T5/6 to F7/8	Channel	Exp1: ↑OxyHb in bilateral channels at T5/6 to social stimuli compared to static baseline Exp2: ↑OxyHb in same channels as Exp1 to dynamic social compared to dynamic nonsocial stimuli
Face Perception							
Carlsson, et al.	2008	7	1 1	Occipital Frontal	PO4 FC8	Channel	↑OxyHb in right fronto-temporal region to mother's face compared to unfamiliar face
Honda, et al.	2010	7	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	↑OxyHb in bilateral parietal regions to canonical vs scrambled face stimuli
Kobayashi, et al.	2012	5 to 8	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	No response for face size differences
Kobayashi, et al.	2012	7 – 8	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	↑OxyHb in left parietal region to upright Arcimboldo faces
Minagawa-Kawai, et al.	2009	9 – 13	4	Frontal	Square pad centered just above Fpz	Channel	↑OxyHb in OFC to mother vs. stranger face
Nakato, et al.	2009	5 & 8	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	↑OxyHb & TotHb in right parietal for frontal faces in 5- & 8-month olds, but only for profile faces in 8-mo-olds
Nakato, et al.	2011	7 – 8	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	↑OxyHb & TotHb in bilateral parietal for mother and only right parietal for stranger
Nakato, et al.	2011	6 – 7	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	↑OxyHb & TotHb in left parietal lobe for happy and right parietal lobe for angry faces
Otsuka, et al.	2007	5 – 8	12 × 2	Temporal	Square pad centered on C5/6.	ROI_A	↑OxyHb & TotHb in right temporal lobe to upright vs. inverted faces
Yamashita, et al.	2012	8	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	↑OxyHb & TotHb in bilateral temporal lobes to averted gaze compared to direct gaze
Language							

Author	Year	Participant Age[1]	Channels	Brain Region	International 10–20 Location	Probe Analysis	Main Finding
Bortfeld, et al.	2009	6 – 9	2 × 2	Temporal	Directly Ant & Post to T3/4	ROI_A	↑OxyHb in left temporal cortex to speech sounds
Bortfeld, et al.	2007	6 – 9	2 2	Temporal Occipital	Directly Ant & Post to T3/4	ROI_A	↑OxyHb to audiovisual stimuli in left temporal and bilateral occipital cortex, but only occipital for visual stimuli
Grossmann, et al.	2010	4 & 7	12 × 2	Temporal	Square pad centered on FC5/6.	Channel	↑OxyHb in right Sup temporal cortex to emotional prosodic voice vs non-voice sounds at 7mos, but not 4mos
Lloyd-Fox, et al.	2012	4 – 7	38	Temporal	From T5/6 to F7/8 centered on T3/4	Channel	↑ in voice selectivity between 4 & 7mos in bilateral temporal cortex
Minagawa-Kawai, et al.	2007	3 – 28	4 × 2	Temporal	Square pad centered on T3/4	Channel	Emergence of phonemic differentiation at 6–7mo bilaterally and becoming left dominant after 12mos
Minagawa-Kawai, et al.	2011	4	12 × 2	Temporal	Chevron pad centered on C5/6	Channel	↑OxyHb in left temporal cortex to language vs non-language (i.e. monkey vocalizations)
Naoi, et al.	2012	4 – 13	4 × 2 22	Temporal Frontal	Square pad centered on FC5/6; Between Fp1/2 and F3/4 from F7 to F8	Channel	↑OxyHb in bilateral temporal cortex to infant directed speech & ↑OxyHb to mother vs stranger voice emerging at 7mos ↑OxyHb in Sup frontal cortex to infant directed speech from mother vs stranger
Petitto, et al.	2012	2 – 16	12 × 2	Temporal	Square pad centered on C5/6	ROI_S	↑OxyHb in left Sup temporal gyrus to phonetic vs tone stimuli across all ages, but ↑OxyHb in left Inf frontal gyrus in older (12mo) compared to younger (4mo) for phonetic vs tone stimuli
Sato, et al.	2009	4 & 10	12 × 2	Temporal	Chevron pad centered on C5/6	ROI_S	↑OxyHb in bilateral Sup temporal cortex to pitch changes in 4-mo-olds, but only in left in 10-mo-olds
Wagner, et al.	2011	7	12 × 2	Temporal	Chevron pad centered on T5/6		↓DeoxyHb in bilateral anterior temporal regions to ABB vs ABC grammars in 7-mo-olds compared to ↓DeoxyHb to ABC vs ABB grammars in 9-mo-olds.
Action Observation							
Grossmann, et al.	2013	4	12 × 2	Temporal	Square pad centered on C5/6.	ROI_S	↑OxyHb in premotor cortex to robot actions & in Sup temporal lobe to congruent actions (i.e. human actions from a human performer)
Ichikawa, et al.	2010	7 – 8	12 × 2	Temporal	Square pad centered on T5/6.	ROI_A	↑OxyHb in right temporal lobe to upright face PLD vs inverted face PLD
Lloyd-Fox, et al.	2011	5	45	Frontal Temporal	Centered on Fpz From F7/8 to T5/6 centered on T3/4	Channel	↑OxyHb in Inf frontal cortex to eye and hand movements & ↑OxyHb in Ant Sup temporal region to mouth actions
Shimada, et al.	2006	6 – 7	7	Sensorimotor	Approximately C3	Channel	↑OxyHb in sensorimotor cortex to observation & execution of live actions vs TV

Author	Year	Participant Age[1]	Channels	Brain Region	International 10–20 Location	Probe Analysis	Main Finding
Object Permanence							
Baird, et al.	2002	5 to 12 monthly	4	Frontal	Square pad centered at Fz	ROI_A	↓OxyHb & TotHb pre object permanence shifts to ↑OxyHb & TotHb post object permanence

[1] Age is presented in months.

ROI_A = average of all channels within probe set; ROI_S = subset of channels combined for region of interest; OxyHb = Oxygenated Hemoglobin; DeoxyHb = Deoxygenated Hemoglobin; TotHb = Total Hemoglobin; Ant = anterior; Post = posterior; Sup = superior; Inf = inferior