fNIRS Studies on Hemispheric Asymmetry in Atypical Neural Function in Developmental Disorders

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Functional lateralization is highly replicable trait of human neural system. Many previous studies have indicated the possibility that people with attention-deficits/hyperactivity-disorder (ADHD) and autism spectrum disorder (ASD) show hemispheric asymmetry in atypical neural function. However, despite the abundance of relevant studies, there is still ongoing controversy over this issue. In the present mini-review, we provide an overview of the hemispheric asymmetry in atypical neural function observed in fNIRS studies on people with these conditions. Atypical neural function is defined as group-difference in the task-related concentration change of oxygenated hemoglobin. The existing fNIRS studies give support to the right-lateralized atypicality in children with ADHD. At the same time, we did not find clear leftward-lateralization in atypical activation in people with ASD. On the basis of these, we discuss the current states and limitation of the existing studies.

Keywords: fNIRS, hemispheric asymmetry, ADHD, ASD, prefrontal cortex, lateralization

LATERALIZATION IN ATYPICAL NEURAL FUNCTION IN DEVELOPMENTAL DISORDERS

Functional near-infrared spectroscopy (fNIRS) was introduced into the scientific community as a neuroimaging tool ~20 years ago (Hoshi and Tamura, 1993; Kato et al., 1993). Despite having relatively poor spatial and temporal resolution compared to fMRI and EEG/MEG respectively, fNIRS is associated with certain advantages over other non-invasive techniques for measuring neural function. For instance, fNIRS poses a low physical and psychological burden on participants. Additionally, fNIRS is less vulnerable to artifacts generated by bodily motion. These features are particularly advantageous for measuring neural function in individuals with pathological conditions (Doi et al., 2013; Koike et al., 2013; Adorni et al., 2016).

Besides them, fNIRS has some unique characteristics compared to the other non-invasive measurements of neural function. First, in contrast to EEG, which measures the electrical activity (primary signal) pooled across wide neural regions, fNIRS measures hemodynamic response (secondary signal) with relatively high spatial resolution. Second, the concentrations of oxygenated-/deoxygenated hemoglobin (oxyHb/deoxyHb) measured by fNIRS reflect aspects of hemodynamic response that are different from the indicators used in other neuroimaging techniques (Minagawa-Kawai et al., 2009a). Relative increase of oxyHb concomitant with slight decrease of deoxyHb is supposed to reflect the influx of oxyHb to the blood vessels adjacent to activated cortical region to meet the demands of energy consumption by neurons in the region (Minagawa-Kawai et al., 2009a; Doi et al., 2013). In contrast to this, the BOLD signal measured in fMRI technique is considered to mainly reflect the decrease of deoxyHb (Song et al., 2006), although
the physiological basis of BOLD signal remains elusive at this point. Therefore, incorporating findings from fNIRS studies might lead to a more comprehensive understanding of typical and atypical patterns of neural function.

Functional lateralization has been repeatedly documented in the human neural system; a number of studies have generally shown leftward-lateralization of linguistic function (Crow, 2000) and right-lateralization of attentional function and visuo-spatial cognition (Toga and Thompson, 2003; Hervé et al., 2013). There is a long history of studies investigating lateralization in atypical neural function in developmental disorders (McCann, 1982; see, Klimkeit and Bradshaw, 2006, for a brief review). However, despite the abundance of relevant studies, there is still controversy over whether people with developmental disorders exhibit lateralization in atypical neural function.

Since its introduction, the number of fNIRS studies focused on people with developmental disorders has been steadily increasing (for a review, Ehlis et al., 2014). Because the majority of these studies have used bilaterally-placed multichannel emitter-detector probe sets, the resulting datasets offer an invaluable opportunity to examine lateralization in atypical neural function in individuals with developmental disorders.

**AIM**

Here we provide a qualitative overview of the existing fNIRS studies of individuals with developmental disorders, with a specific focus on lateralization in atypical neural function. Although several reviews of fNIRS research have been published (Doi et al., 2013; Koike et al., 2013; Ehlis et al., 2014; Balconi et al., 2015; Adorni et al., 2016), to the best of our knowledge, this is the first to focus on this aspect. The conditions discussed here include attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Previous studies have indicated the possibility that individuals with these conditions (McCann, 1982; Klimkeit and Bradshaw, 2006) show lateralization in atypical neural function, but these findings are not often consolidated into theoretical overviews. Therefore, our primary goal here is to establish a scaffolding for the organization and consolidation of findings obtained using fNIRS regarding the lateralization in atypical neural function in people with ADHD and ASD.

As per convention, we treat task-related increases in oxyHb as the primary indicator of neural function (Minagawa-Kawai et al., 2009a; Doi et al., 2013). The atypicality of neural function observed so far comes mainly in three forms. First, some studies have quantitatively compared oxyHb changes between patient and control groups. As a result, many studies found statistically significant between-group differences in the level of task-related oxyHb change in either one or both hemispheres. In the second type of atypicality, hemispheric asymmetry is observed in either the patient or control group, but not in both. More specifically, in some such cases the patient group does not show the lateralized oxyHb changes observed in the control group (lack of lateralization), while in others patients show lateralization not normally observed in matched-controls. Third, several studies have revealed a lack of significant task-related changes in oxyHb from the preceding baseline period in the patient group in either one of the hemispheres when matched-controls showed significant task-related changes.

Of the three types of atypicality described above, we focus mainly on the first, as only this type is ascertained by the direct comparison of patient and matched-control groups. For descriptive brevity, we refer to such reduced/enhanced levels of task-related oxyHb increase in patients compared with matched controls as "hypo-/hyper-activation." In the following, the term "lateralization in atypical neural function/activation" refers mainly to hypo-/hyper-activation being observed only in one hemisphere.

**LATERALIZATION IN ATYPICAL NEURAL FUNCTION IN ADHD**

ADHD is a developmental disorder with inattention, impulsivity, and hyperactivity as core symptoms. Children with ADHD often have poor social skills and learning disabilities. Approximately 10% of school-aged children and 5% of adults are estimated to suffer from ADHD (Pietrzak et al., 2006; Safren et al., 2010; Thomas et al., 2015).

It has long been postulated that the symptoms of ADHD are associated with right-hemisphere abnormalities (Stefanatos and Wasserstein, 2001). This is largely because functions such as attentional control, visuo-spatial processing, and socio-emotional processing, for which ADHD children show relatively poor performance, are generally right-lateralized in typically developing people (Toga and Thompson, 2003; Hervé et al., 2013). This notion has gained support from studies utilizing behavioral experiments and neuroimaging techniques for review, Stefanatos and Wasserstein, 2001; Valera et al., 2007. However, several recent studies have shown a more nuanced pattern of atypical lateralization (Silk et al., 2016) or have shown atypical interhemispheric integration (Hale et al., 2009).

The number of fNIRS studies of individuals with ADHD is relatively small, but these generally support right-lateralized atypicality in wide cortical regions in ADHD. To further verify this observation, we surveyed relevant peer-reviewed studies using the Scopus database. We mainly included studies that compared task-related oxyHb changes in bilaterally-placed channels, between people with ADHD and matched controls. Conference proceedings and review papers were excluded. This resulted in a total of 24 eligible studies. The details of these studies are summarized in Table 1. The distribution of observed group-differences are described in Figure 1.

Most of the studies of children with ADHD show atypical patterns of oxyHb more prominently in the right hemisphere during a variety of tasks such as the reverse-Stroop task (Yasumura et al., 2014), executive attention control task (Tsujimoto et al., 2013), verbal fluency task (VFT; Scheidt et al., 2009), Go/NoGo task (Monden et al., 2012, 2015; Xiao et al., 2012; Nagashima et al., 2014a), oddball task (Nagashima et al., 2014b,c), passive viewing of facial expression (Ichikawa et al., 2014), and emotional prosody recognition (Köchel et al., 2015).
### TABLE 1 | The details of the main fNIRS studies on people with ADHD explained in the present mini-review: only the results of group comparison with matched-controls are shown.

| Age                  | Model of NIRS machine | Number of channels | Task requirements                                    | Measured regions         | Dependent variables                                                                 | Main analysis of fNIRS data                                                                 |
|----------------------|------------------------|--------------------|------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| **Children**         |                        |                    |                                                      |                          |                                                                                     |                                                                                          |
| Weber et al., 2005   | NIRO-300               | 2                  | Trail-making task                                    | Frontal lobe             | Oxy-Hb, Deoxy-Hb, Cytochrome oxidase aa3, Tissue oxygenation index, Cerebral blood volume | Test of task-related change of dependent variables from baseline                           |
| Jourdan Moser et al., 2009 | NIRO-300               | 4                  | Stroop task                                          | Frontal lobe             | Oxy-Hb, Deoxy-Hb, Behavioral performance                                            | Group difference of dependent variables                                                  |
| Schecklmann et al., 2010 | ETG-4000               | 52                 | Spatial working memory task                          | Frontal lobe             | Oxy-Hb, Behavioral performance                                                      | Channel-wise analysis of group difference and task-related change from baseline         |
| Negoro et al., 2010  | ETG-100                | 24                 | Stroop color word task                               | Frontal lobe             | Oxy-Hb                                                                             | Channel-wise analysis of group difference                                                 |
| Schecklmann et al., 2011a | ETG-4000               | 24                 | Olfactory stimulation                                | Frontal lobe, Temporal lobe | Oxy-Hb, Deoxy-Hb, Olfactory test score                                            | Test of task-related change from baseline and group comparisons in each of the four ROIs (inferior frontal, temporal) |
| Xiao et al., 2012    | JH-NIRS-BR-05          | 16                 | Go/NoGo task                                         | Frontal lobe             | Oxy-Hb, Behavioral performance                                                     | Group comparison of mean oxy-Hb by t-tests                                                |
| Inoue et al., 2012   | Cognoscope             | 16                 | Go/NoGo task                                         | Frontal lobe             | Oxy-Hb, Behavioral performance                                                     | ANOVA on mean oxy-Hb values in four ROIs (left/right VLPFC, DLPFC, SFS) with the factors of Group × Hemisphere × Condition |
| Tsujimoto et al., 2013 | OEG-16                 | 16                 | Spatial working memory task                          | Frontal lobe             | Oxy-Hb, Behavioral performance                                                     | ANOVA on mean oxy-Hb values in three ROIs (left/middle/right PFC) with the factors of ROI × Group |
| Yasumura et al., 2014 | OEG-16                 | 16                 | Stroop task, Reverse stroop task, With/without attentional distractor | Frontal lobe             | Oxy-Hb, SNAP questionnaire, Behavioral performance                                  | ANOVA on mean oxy-Hb in each hemisphere with the factors of Hemisphere × Group           |
| Ichikawa et al., 2014 | ETG-4000               | 24                 | Passive viewing of emotional faces                   | Temporal lobe            | Oxy-Hb, Deoxy-Hb, Total Hb, Timing of peak activation                               | ANOVA with the factors of Group × Hemisphere × Condition                                |
| (Continued)                                                     |                        |                    |                                                      |                          |                                                                                     |                                                                                          |
| Study                          | Age                                      | Model of NIRS machine | Number of channels | Task requirements     | Measured regions          | Dependent variables | Main analysis of fNIRS data                                                                 |
|-------------------------------|------------------------------------------|-----------------------|--------------------|-----------------------|---------------------------|----------------------|--------------------------------------------------------------------------------------------|
| Nagashima et al., 2014a       | 19 boys and 3 girls with ADHD (M = 9.5 ± 2.0) | ETG-4000              | 22                 | Oddball task          | Frontal lobe, Parietal lobe, Temporal lobe | Oxy-Hb, Deoxy-Hb, Behavioral performance | Channel-wise analysis of group difference between control, post-/pre-medicated ADHD          |
| Nagashima et al., 2014b       | 3 girls and 12 boys with ADHD (M = 9.9 ± 2.1) | ETG-4000              | 22                 | Oddball task          | Frontal lobe, Parietal lobe, Temporal lobe | Oxy-Hb, Deoxy-Hb, Behavioral performance | Channel-wise analysis of group difference between control, post-/pre-medicated ADHD          |
| Nagashima et al., 2014c       | 2 girls and 14 boys (M = 8.8 ± 2.2)       | ETG-4000              | 22                 | Go/NoGo task          | Frontal lobe, Parietal lobe, Temporal lobe | Oxy-Hb, Deoxy-Hb, Behavioral performance | Channel-wise analysis of group difference between control, post-/pre-medicated ADHD          |
| Monden et al., 2015           | 5 girls and 25 boys with ADHD (M = 9.1 ± 2.6) | ETG-4000              | 22                 | Go/NoGo task          | Frontal lobe, Parietal lobe, Temporal lobe | Oxy-Hb, Deoxy-Hb, Behavioral performance | Channel-wise analysis of group difference between control, post-/pre-medicated ADHD          |
| Köchel et al., 2015           | 14 boys with ADHD (M = 10.4 ± 1.5)       | ETG-4000              | 24                 | Emotional prosody recognition task | Parietal lobe, Temporal lobe | Oxy-Hb, Deoxy-Hb, Behavioral performance | ROC analysis Group comparison of mean Oxy-Hb values of four ROIs (left/right Parietal/Temporal region) |
| Yasumura et al., 2015         | 7 girls and 15 boys with ADHD (M = 10.3 ± 2.0) | OEG-16                | 16                 | Dimensional card sorting task | Frontal lobe | Oxy-Hb, PARS, SNAP, Behavioral performance | Channel-wise analysis of group difference                                              |
| Ishi-Takahashi et al., 2015* | Drug naïve children with ADHD (4 girls and 18 boys; M = 8.6 ± 1.4) | ETG-4000              | 52                 | SST                   | Frontal lobe | Oxy-Hb, CGI-S, ADHD-RS-IV, CBCL, Behavioral performance | ANOVA with the factors of Group × Hemisphere × Session (baseline, 4-to-8 week open trial) |

(Continued)
| Age          | Model of NIRS machine | Number of channels | Task requirements                  | Measured regions                  | Dependent variables                  | Main analysis of fNIRS data                                      |
|--------------|------------------------|--------------------|------------------------------------|-----------------------------------|--------------------------------------|---------------------------------------------------------------|
| Araki et al., 2015 | ETG-100                | 24                 | Continuous performance test         | Frontal lobe                      | Oxy-Hb                              | In the analysis of pre-/post-medication, ANOVA with the factors of channel and time-segment within each group |
| Adult        | ETG-100                | 24                 | Letter n-Back task                 | Frontal Lobe                      | Oxy-Hb                              | Channel-wise comparison of group difference                   |
| Ehlis et al., 2008 | ETG-100                | 22                 | Phonological and Semantic VFT      | Frontal Lobe, Parietal Lobe, Temporal Lobe | Oxy-Hb                              | Group-difference for the average of active channels which showed the expected pattern of activation in both control and ADHD groups |
| Schecklmann et al., 2009 | ETG-4000              | 22                 | Olfactory stimulation by odors with three levels of concentration | Frontal Lobe, Temporal Lobe       | Oxy-Hb                              | Test of oxy-Hb change from zero and group difference in each of the 5 ROIs (Temporal region, Inferior Frontal region, Somatosensory region, Biocca's area) |
| Schecklmann et al., 2011b | ETG-4000              | 52                 | Working memory task                | Frontal Lobe                      | Oxy-Hb                              | ANOVA on mean oxy-Hb values in ROIs defined in a data-driven manner with the factors of group × Task                  |
| Ishii-Takahashi et al., 2014 | ETG-4000              | 52                 | SST                                | Frontal Lobe, Temporal Lobe       | Oxy-Hb                              | Channel-wise group comparison of oxy-Hb                       |

Typical activation pattern

| Patients compared to controls | Hemisphere | Regions with group difference | Other findings |
|-------------------------------|------------|--------------------------------|----------------|
| Significant bilateral increase of oxy-Hb during extended-attention | n.s        | n.s                            | Deoxy-Hb increase in the left hemisphere was larger in the control group than in the ADHD group |

(Continued)
| JourdanMosser et al., 2009 | Significant oxy-Hb increase during stimulation | n.s. | n.s. | n.s. | The onset of hemodynamic response was generally delayed in children with ADHD. Children with ADHD showed larger conditional effect in deoxy-Hb in the right DLPFC. |
|-------------------------|------------------------------------------------|------|------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Schecklmann et al., 2010 | Smaller deactivation (oxy-Hb decrease) in working memory than in the control condition | n.s. | n.s. | n.s. | Activation level differed between ADHD children with and without medication in the left SFS and right DLPFC. |
| Negoro et al., 2010     | Task-related oxy-Hb increase in bilateral inferior frontal region | ↓    | Bilateral | inferior PFC | Task-related sustained increase in oxy-Hb from baseline |
| Schecklmann et al., 2011a | Significant oxy-Hb increase during olfactory stimulation in bilateral IFC and temporal region | ↓    | Bilateral | Bilateral PFC and temporal region | Significant correlation between activations in left IFC/temporal region and olfactory discrimination performance in pre-medicated children with ADHD. |
| Xiao et al., 2012       | NA                                             | ↓ in NoGo task | ↑ in Stroop task | Right | Frontopolar PFC, VLPFC | Positive correlation between oxy-Hb in the right PFC and error rate. |
| Inoue et al., 2012      | Significantly larger oxy-Hb increase in the NoGo than in go condition | ↓    | Bilateral | Frontopolar PFC, VLPFC | There was significant group difference also in the middle, but not the left, channel cluster. |
| Tsujimoto et al., 2013  | Task-related sustained increase in oxy-Hb from baseline | ↑    | Right  | Frontopolar PFC, VLPFC | Negative correlation between SNAP inattention score and oxy-Hb in Ch4 (Right PFC). |
| Yasumura et al., 2014   | Bilateral oxy-Hb increase in Reverse stroop task | ↓    | Right  | Frontopolar PFC, VLPFC |                                                                                                                                                                                                 |

(Continued)
TABLE 1 | Continued

| Typical activation pattern | Patients compared to controls | Hemisphere | Regions with group difference | Other findings |
|---------------------------|------------------------------|------------|-------------------------------|---------------|
| Ichikawa et al., 2014     | Significantly larger increase of oxyHb in the right than in the left temporal region in response to both angry and happy expressions | ↓ to angry expression | Right | Right superior temporal region | Larger variance in the timing of peak activation in the right hemisphere in boys with ADHD |
| Nagashima et al., 2014a   | Significant oxyHb increase in the right MFG/IFG and right angular/supramarginal gyrus | ↓ | Right | IFG/MFG | The group difference between control and pre-medicated group was eliminated by the administration of MPH |
| Nagashima et al., 2014b   | Significant oxyHb increase in the right MFG/IFG and right angular/supramarginal gyrus | ↓ in MFG/IFG | Right | IFG/MFG | The group difference between control and pre-medicated ADHD was eliminated by the administration of ATX |
| Nagashima et al., 2014c   | Significant oxyHb increase in the right MFG/IFG | ↓ in MFG/IFG | Right | IFG/MFG | The group difference between control and pre-medicated ADHD was eliminated by the administration of ATX |
| Monden et al., 2015       | Significant oxyHb increase during NoGo block in the right MFG/IFG | ↓ in MFG/IFG | Right | IFG/MFG | The activation level in these regions classified ADHD children and healthy controls with high accuracy |
| Köchel et al., 2015       | OxyHb increase in right temporal gyrus, but not in supramarginal gyrus in response to angry prosody | ↓ ↑ | Right | STG | Hyper activation in bilateral supramarginal gyrus to anger, which the authors attribute to compensatory enhancement of attention allocation |
| Yasumura et al., 2015     | Task-related OxyHb increase from baseline in the bilateral PFC | ↓ | Bilateral | IFG | Negative correlation between SNAP scores and oxyHb in Ch1 (right IFG) when both control and ADHD groups were considered |
| Ishii-Takahashi et al., 2015* | OxyHb increase during trial in the bilateral IFC | ↓ | Right | IFC | The hypoactivation in the left IFC approached significance |
| Study | Patients compared to controls | Hemisphere | Regions with group difference | Other findings |
| --- | --- | --- | --- | --- |
| Araki et al., 2015 | Significant task-related oxyHb increase from baseline during CPT in bilateral DLPFC | Bilateral | DLPFC | The activation level in bilateral DLPFC was normalized by the administration of ATX |
| Adult | Task-related increase from baseline in oxyHb in bilateral DLPFC | Bilateral | DLPFC | |
| Schecklmann et al., 2009 | Task-related increase in oxyHb during fluency compared to control task | Bilateral | DLPFC, VLPFC | |
| Schecklmann et al., 2011b | Significant oxyHb increase from baseline in bilateral temporal inferior frontal and somatosensory regions | Bilateral | Superior/middle temporal region | | Positive correlation between oxyHb increase in the right inferior frontal ROI and sensitivity to odor sample |
| | | | | Positive correlation between I7/WURS-k and oxyHb in bilateral temporal and somatosensory ROIs |
| Schecklmann et al., 2012 | Task-related increase of oxyHb in DLPFC in working memory task. The degree of increase was significantly larger when the working memory load was larger. Successful stop trials was accompanied by larger oxyHb increase in IFC than go-trials | Bilateral | DLPFC | During SST, controls showed significant oxyHb increase in bilateral IFC in successful stop compared to go-trials, which was not the case in ADHD children |
| Ishii-Takahashi et al., 2014 | NA | Bilateral | Frontopolar PFC, DLPFC | |
| | | Right | PMA, pre-SMA | |
| | | Left | VLPFC, DLPFC | |

TDC, Typically Developed Children; TDA, Typically Developed Adults; DLPFC, Dorsolateral Prefrontal Cortex; SFS, Superior Frontal Sulcus; MPH, Methylphenidate; LPFC, Lateral Prefrontal Cortex; IFG, Inferior Frontal Gyrus; MFG, Middle Frontal Gyrus; ATX, Atomoxetine; STG, Superior Temporal Gyrus; IFC, Inferior Frontal Cortex; VLPFC, Ventral Prefrontal Cortex; SST, Stop-Signal Task; SMA, Supplementary Motor Area; PMA, Primary Motor Area; CPT, Continuous Performance Test. The results of only baseline assessment in this study are shown here.
These studies have revealed hypoactivation in the right frontal lobe including the prefrontal cortex (PFC; Xiao et al., 2012; Yasumura et al., 2014), middle frontal gyrus (MFG), and inferior frontal gyrus (IFG) (Monden et al., 2012, 2015; Nagashima et al., 2014a,b,c), presumably because NIRS probes can easily be applied to the frontal region (see Table 1). These studies also found hypoactivation in the temporal (Ichikawa et al., 2014; Köchel et al., 2015) and parietal cortices (Nagashima et al., 2014b) as well.

Interestingly, a few studies found atypicality in the pattern of deoxyHb alteration in children with ADHD (Weber et al., 2005; Jourdan Moser et al., 2009). For example, Weber et al. (2005) reported larger deoxyHb increase in the left superior/middle frontal cortex in controls than children with ADHD, without group difference in oxyHb alteration. Low level of deoxyHb increase may reflect inefficient oxygen consumption due to reduced cortical activation. Thus, incorporating the findings on deoxyHb may give us more comprehensive picture about the hemispheric asymmetry in atypical neural function in people with ADHD, although these findings are sporadic at this point.

While the majority of studies that recruited children with ADHD report right-lateralized frontal hypoactivation (Monden et al., 2012, 2015; Xiao et al., 2012; Nagashima et al., 2014a,b,c; Yasumura et al., 2014), bilateral frontal hypoactivation seems more prevalent among adults with ADHD (Ehlis et al., 2008; Schecklmann et al., 2011b). The ADHD symptoms in children are reported to become less severe as they get older, which partly explains the lower prevalence rate of ADHD in adults than pediatric population (Pietrzak et al., 2006; Safren et al., 2010; Thomas et al., 2015). Considering this, the more wide-spread PFC hypoactivation in adults with ADHD raises the possibility that these patients constitute sub-group with severe form of ADHD, whose symptoms persist despite development. However, as the number of fNIRS studies of adult ADHD patients is disproportionately small, this observation requires further empirical validation.

LATERALIZATION IN ATYPICAL NEURAL FUNCTION IN ASD

ASD is an umbrella term collectively referring to heterogenous groups of individuals who share the following core symptoms: Deficits in socio-communicative ability, fixed or restricted behaviors, and repetitive patterns of behavior (APA, 2013). ASD has several sub-groups that differ in symptomatic profiles and cognitive-emotional ability such as intellectual and linguistic prowess (Lenroot and Yeung, 2013).

Since the early days of autism research, investigators have posited that the symptoms of ASD are associated with atypical left-hemisphere function, largely based on the observation that children with Kanner’s autism have impaired linguistic ability (McCann, 1982). Later studies reported reduced leftward lateralization in people with ASD with (De Fossé et al., 2004) or without language delay (Floris et al., 2016). That is, people with ASD show weaker level of leftward lateralization in linguistic function than typically developed people. Furthermore, recent resting-state fMRI studies have shown weaker interhemispheric communication (Anderson et al., 2011) and an increased degree of rightward lateralization in the resting-state activity of non-language brain regions recruited during visual/tactile perception, motor-planning, and executive functioning (Cardinale et al., 2013).

To review fNIRS studies of people with ASD, we searched for relevant papers using the Scopus database. Similar criteria to that described in lateralization in atypical neural function in ADHD were adopted in selecting eligible studies. The details of these are summarized in Table 2. Most of these studies have refuted the notion of a leftward-lateralization in atypical function in ASD by showing bilateral hypoactivation in the frontal cortex including IFG/motor-related cortices (Kajiume et al., 2013), and dorsolateral PFC (DLPFC)/frontopolar PFC (Kawakubo et al., 2009; Iwanami et al., 2011; Iwanaga et al., 2013; Ishii-Takahashi et al., 2014) using tasks such as the VFT (Kuwabara et al., 2006; Kawakubo et al., 2009; Iwanami et al., 2011), mental-state reading task (Iwanaga et al., 2013), stop-signal task (SST; Ishii-Takahashi et al., 2014).
**TABLE 2** The details of the main fNIRS studies on people with ASD explained in the present mini-review; only the results of group comparison with matched-controls are shown.

| Age | Model of NIRS machine | Number of channels | Task requirements | Measured regions | Dependent variables | Main analysis of fNIRS data |
|-----|------------------------|--------------------|------------------|------------------|--------------------|-----------------------------|
| Kuwabara et al., 2006 | • 6 males and 4 females with PDD ($M = 26.5 \pm 7.1$) <br> • 10 TDA (9 males and 1 female; $M = 27.9 \pm 4.1$) | ETG-100 | 24 | Letter fluency task | Frontal lobe | • OxyHb <br> • DeoxyHb <br> • CARS <br> • Behavioral Performance | ANOVA with the factors of Group x Hemisphere x Channel |
| Minagawa-Kawai et al., 2009b | • 7 boys and 2 girls with low- or high-function ASD ($M = 9.2 \pm 1.8$) <br> • 9 TDC (2 girls and 7 boys; $M = 7.3 \pm 1.7$) | ETG-7000 | 8 | Phonemic discrimination task <br> Prosodic discrimination task | Temporal lobe | • Laterality Quotient (LQ) of oxyHb <br> • Functional Lateralization (FL) score of oxyHb <br> • Behavioral Performance | ANOVA on FL score with the factors of Group x Task |
| Kawakubo et al., 2009 | • 12 boys and 2 girls with high-functioning autism ($M = 12.7 \pm 3.4$) <br> • 9 males and 4 females with high-functioning autism ($M = 26.7 \pm 6.1$) | NIRO-200 | 2 | Letter fluency task | Frontal lobe | • OxyHb <br> • DeoxyHb <br> • CARS <br> • Behavioral Performance | ANOVA with the factors of Group x Hemisphere for children and adults separately |
| Kita et al., 2011 | • 10 boys with Asperger Syndrome or high-functioning autism ($M = 10.2 \pm 1.1$) <br> • 13 TDC (13 boys; $M = 10.9 \pm 1.0$) | Spectratech OEG-16 | 16 | Self-face recognition | Frontal lobe | • OxyHb <br> • Eye-movement <br> • Self-consciousness scale <br> • CARS <br> • Behavioral Performance | ANOVA on mean oxyHb values in two ROIs (L-IFG, R-IFG) with the factors of Hemisphere x Group |
| Iwanami et al., 2011 | • 14 males and 6 females with Asperger syndrome ($M = 27.2 \pm 8.5$) <br> • 18 TDA (12 males and 6 females; $M = 31.1 \pm 4.7$) | ETG-4000 | 52 | Letter and category fluency task | Frontal lobe, Temporal lobe | • OxyHb <br> • AQ <br> • Behavioral Performance | ANOVA on mean oxyHb values in each task with the factors of Group x ROI (left/right temporal, frontal) |
| Tamura et al., 2012 | • 16 boys and 4 girls with Asperger Syndrome or PDD ($M = 10.2 \pm 3.4$; 6 autistic disorder, 9 Asperger, 5 PDD) <br> • 20 TDC (16 boys and 4 girls; $M = 9.5 \pm 2.5$) | NIRO-200 | 2 | • Anatomical Imitation (AI) task <br> • Mirror-Image Imitation (MI) task | Frontal lobe | Differential value of oxyHb and deoxyHb between AI and MI (AI-MI) | ANOVA on differential oxyHb with the factors of Group x Hemisphere |
| Xiao et al., 2012 | • 19 boys with high-functioning autism ($M = 10.11 \pm 2.08$) <br> • 16 TDC (16 boys; $M = 9.69 \pm 1.74$) | JH-NIRS-BR-05 | 16 | • Go/NoGo task <br> • Stroop task | Frontal lobe | • OxyHb <br> • Behavioral Performance | Group comparison of mean oxyHb in each hemisphere by t-tests |
| Funahashi et al., 2012 | • 10 males and 1 female with Asperger Syndrome or PDD without language delay ($M = 16.8 \pm 6.1$) <br> • 12 TDC (10 boys and 2 girls; $M = 14.2 \pm 3.8$) | OMM-3000 | 32 | Intentional listening or ignoring tones or stories | Frontal lobe, Temporal lobe | • OxyHb <br> • DeoxyHb <br> • Behavioral Performance | ANOVA on mean oxyHb values in PFC and temporal region with the factors of Group x Hemisphere x Attentional State |

(Continued)
| Age | Model of NIRS machine | Number of channels | Task requirements | Measured regions | Dependent variables | Main analysis of fNIRS data |
|-----|----------------------|-------------------|------------------|-----------------|---------------------|---------------------------|
| Narita et al., 2012 | • 3 males and 8 females with ASD ($M = 29.5$, range = 14–46) | NIRO-200 | 2 | • Visuo-spatial working memory task | Frontal lobe, Temporal lobe | • OxyHb | • Behavioral performance | Comparison of conditional differences in each group |
| | • Typically developed people (6 males and 16 females; $M = 25.2$, range = 19–51) | | | | | | |
| Iwanaga et al., 2013 | • 14 boys and 2 girls with ASD ($M = 11.5 \pm 1.8$) | ETG-4000 | 22 | • Mental State (MS) task | Frontal lobe | • OxyHb | • Behavioral performance | ANOVA on mean oxyHb values in two ROIs (left/right MPFC) with the factors of Group × Hemisphere × Task |
| | • 16 TDC (12 boys and 4 girls; $M = 11.4 \pm 1.8$) | | | | | | |
| Kajiume et al., 2013 | • 6 boys with PDD ($M = 10.9 \pm 1.6$; 3 PDD-NOS, 3 Asperger Syndrome) | ETG-100 | 24 | • Imitation task | Frontal lobe, Temporal lobe | • OxyHb | Behavioral performance | Channel-wise Analysis using ANOVA with the factors of Group × Task |
| | • 6 TDC (6 boys; $M = 10.9 \pm 1.6$) | | | | | | |
| Yasumura et al., 2014 | • 7 boys and 4 girls with ASD ($M = 10.51 \pm 2.3$) | ETG-100 | 24 | • Stroop task | Frontal lobe | • OxyHb | SNAP questionnaire Behavioral performance | ANOVA on mean oxyHb in each hemisphere with the factors of Hemisphere × Group |
| | • 15 TDC (6 boys and 9 girls; $M = 28.8 \pm 5.5$) | | | | | | |
| Ishii-Takahashi et al., 2014 | • 8 males and 13 females with ASD ($M = 30.8 \pm 7.2$; 5 Asperger Syndrome and 16 PDD-NOS) | ETG-4000 | 52 | • VFT | Frontal lobe, Temporal lobe | • OxyHb | Behavioral performance | • Channel-wise group comparison of oxyHb • Classification of groups by linear discriminant analysis using oxyHb |
| | • 21 TDA (13 males and 8 females; $M = 28.8 \pm 5.5$) | | | | | | |
| Jung et al., 2016 | • 8 people with ASD ($M = 15.6 \pm 9.5$) | TechEn CW6 fNIRS system | 14 | 1-back task using pictures of Human and robot face | Frontal lobe, Temporal lobe | • OxyHb | GARS-2 score | ANOVA with the factors of Group × Hemisphere for human and robot face |
| | • 12 typically developed males ($M = 14.5 \pm 10.8$) | | | | | | |

### Typical activation pattern

| Patients compared to controls | Hemisphere | Regions with group difference | Other Findings |
|------------------------------|------------|--------------------------------|---------------|
| Kuwabara et al., 2006 | • Significant task-related increase of OxyHb in bilateral PFC | Bilateral | PFC | oxyHb in the right PFC correlated negatively with CARS verbal communication score |
| Minagawa-Kawai et al., 2009b | • Larger FL score in phonemic than in prosody discrimination task | n.s. | n.s. | Significantly smaller FL score in children with ASD than in controls in phonemic discrimination task |
| Typical activation pattern | Patients compared to controls | Hemisphere | Regions with group difference | Other findings |
|---------------------------|-------------------------------|------------|-------------------------------|---------------|
| Kawakubo et al., 2009     | OxyHb increase during letter fluency task | ↓ in adults | Bilateral | Ventral PFC | OxyHb in R-IFG correlated positively with the level of public self-consciousness and negatively with ASD severity |
| Kita et al., 2011         | Slight oxyHb increase in typically-developed children, which was significantly smaller than in typically developed adults | n.s. | n.s. | n.s. | |
| Iwanami et al., 2011      | OxyHb increase during both tasks. The amplitude is larger in letter than category fluency task | ↓ in letter fluency task | Bilateral | Frontopolar PFC, DLPFC, VLPFC, and Superior Temporal region | n.s. n.s. n.s. OxyHb in R-IFG correlated positively with the level of public self-consciousness and negatively with ASD severity |
| Tamura et al., 2012       | Larger differential value of oxyHb in the left than in the right hemisphere | n.s. | n.s. | n.s. | No hemispheric asymmetry was observed in ASD |
| Xiao et al., 2012         | Larger oxyHb increase in the temporal region when the participants listened to auditory stimuli intentionally | ↓ in GoNoGo task | Right | Frontopolar PFC | Significant interaction between Hemisphere and Attentional state in story listening PFC only in ASD group |
| Funabiki et al., 2012      | Larger oxyHb level during Working Memory (WM) compared to Non-Working Memory (NWM) condition. The overall level of oxyHb level increased as the task load increased | n.s. | n.s. | n.s. | ASD children failed to show clear WM- NWM pattern in oxyHb |
| Narita et al., 2012       | Larger oxyHb level during Working Memory (WM) compared to Non-Working Memory (NWM) condition. The overall level of oxyHb level increased as the task load increased | n.s. | n.s. | n.s. | |
| Iwanaga et al., 2013      | OxyHb increase in bilateral MPFC | ↓ in MS task | Bilateral | MPFC | |
| Kajume et al., 2013       | Task-related oxyHb increase | ↓ in action observation | Bilateral (mostly in the right) | IFG/PMC | |
| Yasumura et al., 2014     | Bilateral oxyHb increase in Reverse Stroop task | n.s. | n.s. | n.s. | |
| Ishii-Takahashi et al., 2014 | ↓ in SST | Bilateral | DLPFC | |
| Jung et al., 2016         | Significantly larger increase of oxyHb in the right than left temporal region to human faces. No hemispheric asymmetry was observed to robot faces | n.s. | n.s. | n.s. | ASD children did not show hemispheric asymmetry in oxyHb level to human faces |

TDC, Typically Developed Children; TDA, Typically Developed Adults; DLPFC, Dorsolateral Prefrontal Cortex; IFG, Inferior Frontal Gyrus; VLPFC, Ventral Prefrontal Cortex; MTG, Middle Temporal Gyrus; PMA, Primary Motor Area; SMA, Supplementary Motor Area; MPFC, Medial Prefrontal Cortex.
et al., 2014), and imitation task (Kajiume et al., 2013). In contrast to ADHD, no clear difference was observed between adult and pediatric population with ASD in the lateralization pattern in atypical neural function. A few of the studies showing bilateral hypoa ctivation report hypoa ctivation in wider cortical regions in the left than in the right hemisphere (Ishii-Takahashi et al., 2014). For example, Ishii-Takahashi et al. (2014) found hypoa ctivation during SST in the left ventrolateral PFC (VLPFC) and motor-related areas, in addition to the bilateral DLPFC/ frontopolar PFC.

Several studies report reduced lateralization in neural function in people with ASD. For example, Minagawa-Kawai et al. (2009b) reported weaker leftward-lateralization of oxyHb increases in Wernicke areas when children with ASD engaged in a phonemic discrimination task, although they did not report the results of direct group-comparisons of task-related oxyHb changes. Likewise, Jung et al. (2016) reported that people with ASD failed to show rightward-lateralization of oxyHb increases in the posterior temporal region in response to human faces as was observed in the matched control group.

One potential reason for such inconsistency among previous studies is the symptomatic heterogeneity of ASD. ASD has several sub-groups that differ in symptomatic profiles and cognitive-emotional ability (Lenroot and Yeung, 2013). The left-hemisphere theory of ASD was originally proposed for individuals with Kanner’s autism with language delay (McCann, 1982). However, most fNIRS studies have recruited people with high-functioning autism or Asperger Syndrome (Kawakubo et al., 2009; Iwanami et al., 2011; Kita et al., 2011; Xiao et al., 2012; Iwanaga et al., 2013; Yasumura et al., 2014), possibly due to the task requirements, with rare exceptions (Minagawa-Kawai et al., 2009b). Considering this, it is possible that evidence supporting a clearer pattern of lateralization can be obtained for specific sub-groups.

**GENERAL DISCUSSION**

Existing fNIRS studies generally support the notion of the right-lateralization in atypical function in children with ADHD. The use of fNIRS for the clinical examination of children is promising, especially because the exclusion rate for fNIRS measurement is reported to be much lower than that for fMRI (Nagashima et al., 2014b). This potential has been gainfully exploited by Monden et al. (2012, 2015), who assessed the efficacy of a pharmacological intervention in children with ADHD using oxyHb increases in the right PFC as an indicator (see also, Nagashima et al., 2014a,b,c). Future research should estimate the sensitivity/specificity of right PFC activation as a biomarker of ADHD (Monden et al., 2015) and investigate whether the rightward-lateralization in atypical activation is uniquely linked to ADHD. We did not find a clear pattern of leftward-lateralization in atypical function for people with ASD. As noted above, this is partly because of the heterogeneity of people with ASD.

There remain several unresolved issues important for the further development of research on the lateralization in atypical neural function. The first is the establishment of a standard analytic method. As summarized in the tables, the analytic approach for multi-channel fNIRS data can be classified into two groups. One is the region-of-interest (ROI) approach, in which neighboring channels are grouped into single ROI and the averaged levels of oxyHb in channels within ROI are analyzed as the main indicators of neural activation. In this approach, corresponding channels in the left and right hemisphere are usually integrated into left/right ROI. The other approach is channel-wise analysis, in which a primary statistical test is conducted for each channel. It is unclear at this point which of these two approaches is more advantageous for detecting lateralized patterns in atypical activation. Channel-wise analysis is more sensitive to highly localized group-differences than the ROI approach, and thus might be more suitable for detecting signs of lateralization in atypical function. The main problem of the channel-wise approach is how to set the significance threshold. Apparently, a large number of statistical tests leads to inflation of the false-positive rate, while a conventional method for adjusting the threshold, e.g., Bonferroni’s procedure, is sometimes too stringent.

The second issue also relates to the analytic procedure. There are several problems in the group comparisons of fNIRS results. First, due to morphological variations in cortical structure, the location and depth of the cortical region through which the infrared light passes might differ between people with and without developmental disorders. Second, it is often noted that children with ADHD/ASD show larger bodily and facial movements than matched controls during experimental tasks, which might introduce group-differences in the level of artifacts and consequently influence the results. Especially problematic is the artifact of skin blood perfusion accompanying facial muscle contractions (Takahashi et al., 2011; Seiyama et al., 2016). To overcome these problems inherent in group-comparisons of fNIRS signals is surely an important agenda for future research.

The third point is the scarcity of fNIRS studies on resting state activation (Medvedev, 2014). Of particular relevance, one of the strongest pieces of evidence for the left-hemisphere theory of ASD comes from a resting state activation study (Cardinale et al., 2013). Thus, more research should focus on the patterns of lateralization of oxy-/deoxy-Hb alteration in the resting state. One of the most popular approaches to characterize resting state activity is the analysis of inter-region functional connectivity. Several fNIRS studies have tried to characterize neural function in developmental disorders (Kikuchi et al., 2013; Zhu et al., 2015; Li and Yu, 2016; Li et al., 2016), and interestingly, several of them found lateralized patterns of atypical connectivity in the patient group (Zhu et al., 2015). We did not review fNIRS studies of functional connectivity in people with ADHD or ASD, as the analysis procedures vary greatly between studies and the number of eligible studies is too small to draw any coherent conclusions. However, considering the rapid development of this field of research, our knowledge of the lateralization in atypical function is further enriched by this novel approach.

The fourth is the potential confound of medication. The number of studies recruiting only drug-naïve patients is relatively few and participants in the patient group are taking various...
kinds of medications in majority of the studies. Furthermore, several fNIRS studies reviewed above have shown that short-term administration of drugs such as methylphenidate changed the pattern of cortical activation in children with ADHD (Nagashima et al., 2014a,b,c; Monden et al., 2015). On the basis of these, more studies recruiting only non-medicated patients are needed to clarify the precise nature of atypicality in neural function.

**CONCLUSION**

In this mini-review, we gave a brief overview of the findings of fNIRS studies about lateralization in atypical neural function in people with ADHD and ASD. The existing studies generally support rightward-lateralization in atypical function in children with ADHD. At the same time, we did not find clear pattern of the leftward-lateralization in atypical function for people with ASD.

Nevertheless, lateralization in atypical neural function might have been obscured by factors such as sample heterogeneity and particular method of analysis.

**AUTHOR CONTRIBUTIONS**

HD conceived this study. HD and KS wrote the manuscript.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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