Received February 5, 2021, accepted February 17, 2021, date of publication March 2, 2021, date of current version March 23, 2021.

Digital Object Identifier 10.1109/ACCESS.2021.3063054

Whole-Head Magnetoencephalogram and Its Application in Developmental Communication Disorders Research: A Review

AIMIN LIANG[1], HUANQI WU[2], YUYU MA[2], XIAOYU LIANG[2], YIFAN JIA[2], YANG GAO[3], XIAOLIN NING[4,5], AND JIANCHENG FANG[5]

[1]Department of Child Health Care Center, Capital Medical University, Beijing Children's Hospital, Beijing 100045, China
[2]School of Instrumentation Science and Opto-electronics Engineering, Beihang University (BUAA), Beijing 100191, China
[3]Division of Quantum Precision Measurement, Beijing Academy of Quantum Information Sciences (BAQIS), Beijing 100193, China
[4]Hangzhou Innovation Institute, Beihang University, Beijing 100191, China
[5]Research Institute of Frontier Science, Beihang University (BUAA), Beijing 100191, China

Corresponding author: Yang Gao (gaoyang@baqis.ac.cn)

This work was supported by the Beijing Municipal Natural Science Foundation under Grant 4212012.

ABSTRACT The human brain undergoes tremendous changes during the first decade of life. The susceptibility of the immature central nervous system to factors such as adverse environments and genetic factors is attributed to its plasticity. Neurodevelopmental disorders (NDDs) occur once the immature brain veers off the typical developmental trajectory. However, little is known about the neurophysiological traits of atypically developing children because it is challenging for them to remain still during recording. Magnetoencephalography (MEG) is a noninvasive neuroimaging technique with high-spatiotemporal resolution. An ultralow magnetic field produced by neural electrical activity can be detected using a highly sensitive whole-head magnetometer array. Current cryogenic SQUID-MEG combined with individual MRI has shown great potential in reflecting neural activity under resting states and during tasks. MEG instrumentation for children is expected to be an effective tool for investigating brain dynamics, which provides neuropsychological evidence for atypical development in communication ability. In this paper, the advantages of pediatric MEG in neurodevelopmental disorder studies are discussed first and compared with those of several noninvasive functional imaging modalities. Existing commercial pediatric MEG systems are summarized based on their respective characteristics and parameters. State-of-the-art newly emerging sensing techniques based on spin-exchange relaxation-free (SERF) along with their application in detecting infants' brain responses are introduced. Recent discoveries on MEG biomarkers in children with NDDs are then summarized concerning disorders that have comorbidities in communication, such as specific language impairment (SLI), autism spectrum disorders (ASD), dyslexia and stuttering. Progress on multimodality research and total-field wearable SERF magnetometers offers insight into the neuropsychological substrates of communication disorders.

INDEX TERMS Pediatric MEG, neurodevelopmental disorders, communication disorders, SERF magnetometer.

I. INTRODUCTION

Magnetoencephalography (MEG) is a powerful electrophysiological tool that enables noninvasive recording of neural activity with high-temporal resolution (to milliseconds) [1]–[3]. It is eligible for investigating brain functional activation patterns at the time scales of cognitive tasks such as auditory and language processing [4]–[6]. Combined with magnetic resonance imaging (MRI) and source-imaging technology, it can provide functional images with high-spatial resolution comparable with functional MRI (fMRI) on the order of millimeters [7]. MEG has shown its high value in a wide range of clinical and explorative uses, such as presurgical evaluation of epilepsy [8], [9], psychiatric research [10]–[12], aging problems [13], [14], cognitive research [15]–[17] and developmental studies [18]–[20], covering a lifespan from the

The associate editor coordinating the review of this manuscript and approving it for publication was Filbert Juwono.

fetus to old age [21], [24]. Among these uses, localization of interictal epileptiform discharges [22], [23] and functional brain-mapping work-ups [24, [25] are the most common clinical applications of MEG. Moreover, spatial-temporal-spectral analysis has been applied to determine biomarkers of psychiatric and neurodegenerative disorders [26], [27].

Although it has been widely recognized in cognitive and clinical neuroscience, the application of MEG in studies of the typical and atypical development of the brain in the early stage of life is still rare despite its ''acoustic silence'', which is a valuable feature that is unavailable in other brain imaging modalities [28], possibly due to the costly SQUID-MEG maintenance and the limitations of individual MRI and MEG acquisition in this age group [29]. However, source-level analysis has been approved to be conducted using age-matched MRI templates in place of individual MRI, thereby facilitating research on developmental disorders and the developing brain [30]. Advances in noncryogenic MEG instrumentation will bring the sensors closer to the head [31], and more extensive coverage of the cortex can be guaranteed using a wearable multichannel system. Thus, MEG recordings are technically feasible for infants and children over seven years old who are experiencing remarkable changes in brain maturation, as long as they can stay reasonably well during the tasks. Specifically, MEG is ideally suited to tracking the dynamic activation pattern that occurs during language processing in the brain from evoked responses, oscillatory activity and connectivity measures; and MEG is equally apt for neurodevelopmental studies of communication disorders [32].

This review aims to help researchers and clinicians in this field follow the development of biomagnetism instrumentation and updates of MEG in communication disorder studies. This article is arranged in the following order. First, different functional imaging methods in neurodevelopmental disorder studies are compared, and the merits of MEG in delineating cortical processing of language tasks are highlighted. Then, we present the mechanism and the development of current sensing methods, i.e., the superconducting quantum interference device (SQUID)-based MEG and optically pumped magnetometer (OPM)-based MEG. The literature on the use of MEG for the development of communication disorder research, such as specific language impairment/language impairment (SLI/LI), autism spectrum disorders (ASD), dyslexia, and stuttering, is reviewed afterwards. Finally, future directions are discussed, with a focus on MEG instrumentation and its applications to better understand brain-development anomalies.

II. WHY MEG FOR NDDs RESEARCH?

The study of neurodevelopmental disorders not only concerns the behavioral differences between atypically and typically developed children but, more importantly, explores the underlying neurophysiological mechanism that correlates with phenotypes in children with disorders at multiple spatial and temporal scales. In the past few years, novel neuroimaging techniques and analytical methods have made it possible to study the functional connectivity patterns of the cerebral cortex of children. FMRI was the earliest neuroimaging tool used in the study of spontaneous-brain activity in the brain, which requires the participants to stay still during scanning sessions [33]. It is widely used in brain connectivity studies, owing to its high-spatial resolution. However, because it relies on the coupling between cerebral blood flow (hemodynamic response) and potential neuron activation, this technique only provides an indirect measure of brain activity. Moreover, even if neuronal events occur within a few milliseconds, the induced changes in blood oxygen spread within a few seconds, thereby significantly limiting the time resolution of fMRI (approximately 2-3 seconds) [34]–[36]. In addition, it is considerably challenging for researchers to examine young children due to the difficulty in commanding their continuous attention during the time period required for behavioral experiments. Recording neural activity with fMRI creates another issue. Since neuroimage recording requires children to stay still for a long period of time in a noisy or closed environment, the requirements for children are exacting and difficult to meet [37]. FMRI studies on young children are usually conducted during natural sleep to conduct resting-state network-related studies; therefore, the ability to directly investigate brain function during tasks is limited (such as facial recognition or language processing) [38]. Near-infrared (NIR) imaging technology, similar to functional magnetic resonance imaging technology, is a noninvasive method for measuring the absorption of near-infrared light through the skull, allowing researchers to speculate on the proxy of nerve activation, which is attributed to the relative changes in oxygenated and deoxygenated hemoglobin concentrations in blood vessels in the cortical structure [39], [40]. Although functional near-infrared spectroscopy (fNIRS) is silent and does not demand strict motionless, it has a relatively lower spatial resolution than fMRI [41]. NIR light only reaches the cortical surface, not the subcortical structure, and full-head fNIRS exerts the weight of all photodiodes on the child's head, which reduces the child's endurance to a certain extent. Since NIR light passes through multiple layers before reaching the cortex, the signal-to-noise ratio is not ideal.

Researchers have explored many electrophysiological traits and have found that these measures have different relationships with the severity and specificity of symptoms of the neurodevelopmental disorders [42]–[44]. Although the association of these observations with symptoms and the noninvasive recording of brain physiological activity are not unique to electrophysiological methods, other imaging methods such as fMRI/fNIRS/positive electron tomography (PET) also exhibit these characteristics [45], [46]. However, electrophysiological tools such as electroencephalography (EEG) and MEG have complementary characteristics with high-temporal precision, which can provide direct information about the electrical activity of neurons at a higher temporal resolution ($<$1 ms, depending on sampling rates). Different from imaging methods based on changes in

functional metabolism and brain structure, electrophysiological methods characterize brain functional connectivity (FC) by recording rhythmic oscillations of clusters of neurons during excitation and inhibition, thereby calculating neural activity synchronization/desynchronization in different cortical regions in a wide frequency band (0-1000 Hz), which hemodynamic response methods such as fMRI and fNIRS are unable to cover [37], [47]. This is particularly important for the study of neurodevelopmental disorders related to language function and learning disabilities such as ASD, SLI/LI, stuttering and dyslexia, since auditory and language processing occur within a transient period of time of milliseconds. Due to the excellent temporal resolution of the EEG and the fine-grained spatial-temporal resolution of MEG, the electrophysiological traits during the resting state and cognitive tasks can be used as biomarkers for neurodevelopmental disorders [44]. As shown in Fig. 1, electrophysiological methods, especially MEG, outperform other imaging modalities in pediatric neuropsychological studies.

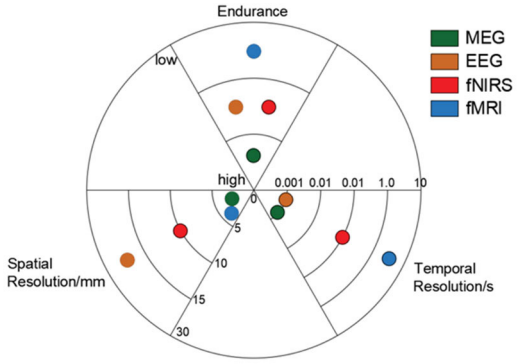


FIGURE 1. Comparison of noninvasive functional-imaging methods based on the aspects of temporal and spatial resolution and child endurance.

Although EEG and MEG measure the signals generated by the same clusters of neurons in the brain (especially the postsynaptic potentials in the dendrites of cortical pyramidal neurons) and both have common merits for neural recording in children, such as quietness, noninvasiveness and ideal temporal resolution, their sensitivity to sources in different orientations varies [48]–[52]. MEG is preferentially sensitive to tangential sources located at sulci and fissures, whereas EEG is more sensitive to radial sources located at gyri. However, absolute tangential or radial sources are nonexistent; therefore, the cortical area to which MEG is sensitive largely overlaps with that to which EEG is sensitive [53], [54]. This explains why MEG and EEG are complementary tools in reflecting neuronal activity. MEG has the advantage of recording the absolute biomagnetic field without reference channels [55]. Combined with structural MRI, the spatial resolution of MEG is similar to fMRI by constraining the locations of the MEG sources [56], [57]. Considering comfort issues for children while recording, MEG can reduce body contact compared to EEG, which is less constrained for child participants [54]. In addition, MEG is relatively immune to (using spatial filtering for source localization) high-frequency, electrical-muscle artifacts arising from scalp and facial muscles, as well as from microsaccadic eye movements [55]. For the source localization in infants, MEG has another advantage over EEG. It is not sensitive to volumetric current distortion caused by incompletely developed (i.e., open) fontanels and sutures. As for EEG recordings, the challenges from inaccurate forward modeling of the conductivity path, which in turn leads to inaccurate estimation of the neural current source, have little adverse effect on the estimation results from MEG [58]. Electrophysiological methods, especially the characteristics of MEG, provide a potential opportunity to improve the specificity and sensitivity of neurophysiological abnormality diagnosis, making it the most favorable technology for exploring the spatiotemporal brain activity in children [58], [59]–[61].

III. WHOLE-HEAD PEDIATRIC MEG INSTRUMENTATION

A. PEDIATRIC SQUID-MEG INSTRUMENTS

A nerve magnetic field generally covers the range of 50-500 fT. As shown in Fig. 2, the neural magnetic field is very weak compared to fluctuations in the geomagnetic field, other biomagnetic interferences and urban noise [62]. The superconducting quantum interference device (SQUID) meets the sensitivity requirements for brain magnetic measurements [63], [64].

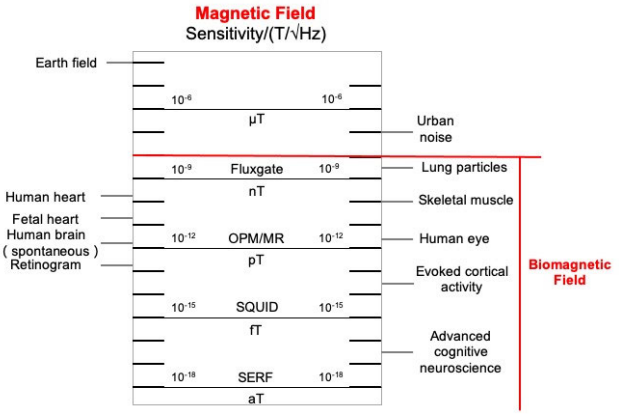


FIGURE 2. Typical signal strengths and frequency ranges for various biomagnetic signals. MR: magnetic resonance, 1 fT = 10-15 Tesla.

SQUID is a novel magnetoelectric sensor, which is actually a superconducting ring inserted by one (rf SQUID) or two Josephson junctions (dc SQUID), formed by insulation that is only the width of an atom. As shown in Fig. 3(a) [53], the brain magnetic flux, $\vec{B}_{ext}$, generates an induced current through the pickup coil, and then the current flows through the input coil to generate a coupled magnetic field, $\vec{B}_{coulpled}$, which is sensed by the surrounding SQUID ring (gray ring in Fig. 3(a)). The voltage over the SQUID becomes a periodic function of the magnetic flux threading the SQUID loop [65], as shown in Fig. 3(b). Increasing the number of input coil turns or increasing the area of the pickup coil can

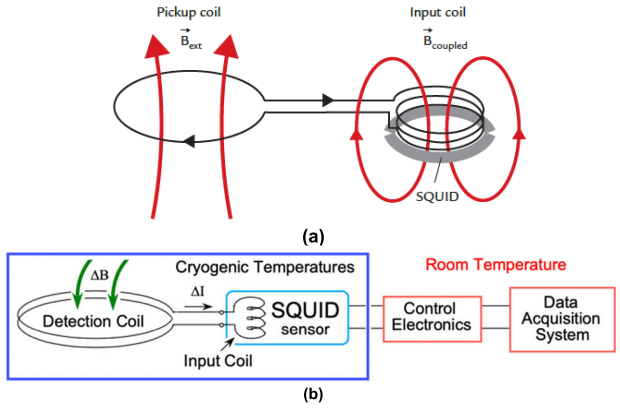


FIGURE 3. (a) The principle of SQUID sensors (images from Hari, R. and A. Puce, 2017). (b) Block diagram of the SQUID magnetometer (images from Fagaly RL, 1990).

improve the sensitivity of SQUID to the magnetic field of the brain. Currently, cryogenic SQUID-MEG systems have excellent sensitivity in the low-frequency range, especially in the low-frequency range below a few Hz. Moreover, recent years have witnessed a surge in clinical SQUID-MEG scanner installations worldwide, and the manufacturing process for commercial SQUID-MEG instrumentation is very complete with reasonable consistency [55], [7].

Many existing neurodevelopmental studies have utilized the adult SQUID-MEG system [66]–[70]. However, the limitation of this method is that the shape of the traditional MEG helmet is fixed, enlarging the distance between the cortical activity of the child participants and the MEG sensors. The magnetic field strength related to nerve activity decays rapidly with increasing distance ($1/\text{distance}^2$) [63]. The application of traditional MEG systems to record nerve magnetic fields in children provides poor results, and is incapable of guaranteeing the required signal-to-noise ratio and the solution accuracy of inverse problems and thus the imaging resolution [71]. To solve this problem, developmental research using adult MEG systems usually places the participant's head in the MEG helmet to shorten the distance between the brain and the sensors. This can be achieved by placing a foam pad inside the MEG helmet to push the child's head to the side of the helmet or placing the participant supine in the scanning helmet in a head-up position so that one side of the child's head is placed directly against the helmet. The shortcoming of this method is that it cannot achieve the synchronous acquisition of the brain magnetic signals of the child's entire brain. Inevitable inconsistency problems and positioning errors are introduced if functional MEG signals are recorded separately in the two hemispheres, since the repositioning process should be implemented between recording sessions [72]. Furthermore, the same experiment produces the effect of habituation and vigilance; thus, the observation outcomes of the two hemispheres under the same experimental paradigms are different. Moreover, this method also doubles the record time and adversely affects the location accuracy of localizing distributed sources and the functional connectivity analysis [73].

The existing pediatric SQUID-MEG systems that satisfy the MEG recording demand from perinatal fetuses to school-age children are shown in TABLE 1 and Fig. 4. Among them, SARA I and II are designed for recording MEG signals from the perinatal period to the newborn. To ensure high-quality detection of the fetal heart and brain signals, and to enable the mother to maintain a comfortable position on the device, the shape of the sensor array is suitable for the pregnant woman's abdomen. For neonatal magnetic measurement, the system is equipped with a customized cradle to ensure that the newborn is lying safely and comfortably. All three pediatric MEG instruments from Tristan Technologies Inc. use a ''coil-in-vacuum'' layout, which reduces the distance from the SQUID-sensitive units to the scalp and satisfies the brain magnetic acquisition of children from newborns to school age. The BabySQUID acquisition system has a fast slew rate (up to 10 μ T/ms) that enables SQUID to operate in the midst of low-frequency, magnetic-field changes and line-frequency noise environments without losing the lock on the flux-locked feedback loop, which facilitates the MEG acquisition of babies in lightly shielded environments. The Artemis 123 acquisition system improves the coil layout of the traditional SQUID-MEG system in which the SQUID coils are immersed in liquid nitrogen, and the distance of the SQUID-sensitive element from the scalp is shortened from 15-20 mm to 6 mm. The latest generation of MEG devices, BabyMEG, has more sensor channels and provides higher functional imaging resolution in children. The original two-layer sensor (one-layer reference sensor, one-layer gradiometer) layout allows the system to collect in a lightly shielded environment. In addition, the MEG system is equipped with a liquid helium recycling device, which reduces the annual cost of refilling the cryogenic medium.

FIGURE 4. The pediatric MEG recording systems for children from (a) perinatal fetuses (©University Hospital Tübingen) to (b) preschoolers (images from TPL Roberts, 2014).

It is noteworthy that compared with the adult whole-brain SQUID-MEG acquisition device, SQUID-MEG systems for children are generally equipped with more customized helmets that consider the child's head circumference while shortening the gap between the sensitive units and the scalp to a considerable extent. Equipped with reference channels, MEG systems enhance the acquisition performance in lightly shielded or total earth fields. It is unrealistic for children to

TABLE 1. Existing pediatric MEG performance and application in clinical research.

System	Channel parameters	Pick-up coil parameters and baseline	Age(s) Studied	Organization	Pros & Cons	Applications
SARA I	151 channels Noise level: 5 fT/Hz$^{1/2}$	Diameter: 20 mm Baseline: 80 mm	Perinatal fetuses, Neonates 0-3 month	University of Arkansas at Little Rock VSM Med Tech Ltd	Suitable for fetus and neonatal research, not for older children	Maturation of auditory processing [75],[76]
SARA II	156 channels, 29 reference channels 4 positioning coils Noise level: 5 fT/Hz$^{1/2}$	Diameter: 20 mm Baseline: 80 mm	Perinatal fetuses, Neonates 0-4 month	University of Tübingen VSM Med Tech Ltd		
Artemis 123®	135 channels: 123 first-order coaxial gradiometers, 12 reference channels (2 sets of 3-axis magnetometers, 2 pairs of 3 reference magnetometers) Noise level: <10 fT/Hz$^{1/2}$	Diameter: 15 mm Baseline: 60 mm	Infant 14-48 month	Tristan Technologies Inc.	Coil-in-vacuum configuration with reduced cool-to-warm distance	Preterm research [77]
BabySQUID®	76 channels of first-order coaxial gradiometer Noise level: <10 fT/Hz$^{1/2}$	Diameter: 6 mm Baseline: 30 mm Coil spacing: 12-14 mm	Infant <3 years old	Tristan Technologies Inc.	Fit for infants; half-shell-shaped coverage, not for whole-head imaging	Developmental research [78],[79], ASD [80]，Epilepsy [81]
BabyMEG®	375 channels Double layers: inner layer: 270 magnetometers, ~9.4 fT/Hz$^{1/2}$; outer layer: 35 3-axis magnetometers 9 reference magnetometers ~5 fT/Hz$^{1/2}$	Diameter: 10 mm (inner layer); 20 mm (outer layer) Coil spacing: 12-14 mm	3-year-old boys (95% fit)	Tristan Technologies Inc.	More sensors; helium-recycling system, with minimum cool-to-warm distance	Epilepsy and auditory processing [82]
KIT	PQ1064R- N2 m: 112 channels first-order coaxial gradiometers PQ1151R: 151 first-order axial gradiometers Noise level: <5 fT/Hz$^{1/2}$ @white noise band	Diameter: 15.5 mm Baseline: 50 mm	Preschool-aged children	Yokogawa/KIT Corp	Fits well with US Caucasian children	Stuttering [83], cognitive research [84], auditory processing [85]

constrain head movement during recording sessions. To this end, MEG devices, such as BabyMEG and BabySQUID, are integrated with head-position indexing (HPI) coils, which enable the continuous tracking of head movement. Given the acquisition of continuous HPI data, procedures can be developed to compensate for head motion [85]. Additionally, a BabySQUID equipped with an infrared camera functions as a head-positioning system monitoring head position during the entire process.

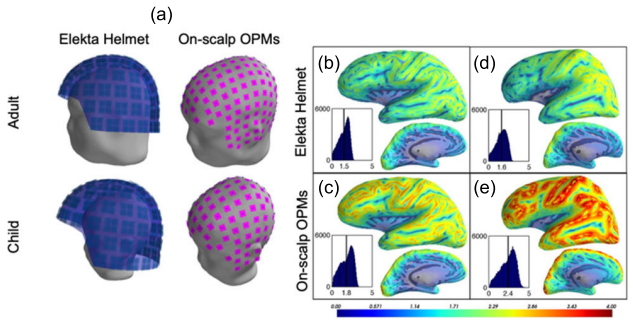


FIGURE 5. (a) Comparison of registration to adult and child with the Elekta helmet and on-scalp OPMs. (b)-(e) SID results for cryogenic and noncryogenic configurations sampling adult (left) and child (right) brains. Histograms for the spatial information density (SID) value distribution are shown in the bottom-left corner, indicating roughly more uniform coverage for both groups with wearable OPMs. The peak value and average SID were significantly higher in children with OPMs than in those with the Elekta Helmet (images adapted from B. Riaz *et al.*, 2017).

B. WEARABLE PEDIATRIC SERF-MEG INSTRUMENT

However, it is the fixed and 'one-size-fits-all' configuration of SQUID-MEG that limits its application in developmental studies and diagnosis, since it is unrealistic to expect children with disorders to stay peacefully motionless with their heads in a half-enclosed hollow space for a period of time, and the increased sensor-to-scalp stand-off causes significant signal loss during task-based data acquisition [86]. As shown in Fig. 5(a) on the left, the front part of the head is far from the inner surface of the SQUID-MEG, with the back part in contact with the helmet and the top part as high as possible. Although a customized MEG, as listed above, ameliorates the situation to some extent, few hospitals and research organizations can afford a range of them to fit head sizes of different ages [87].

It is of note that the utilization of advanced OPMs can further reduce the distance between the sensing units and the scalp, as shown in the right side of Fig. 5. (a), and the customized whole-brain 3-D printed helmet can be suitable for

the study of neurodevelopmental disorders [88], [89]. Unlike other atomic magnetometers, ultrahigh-sensitivity magnetometers based on the spin-exchange relaxation-free (SERF) effect work in the SERF regime, which is also a kind of OPM. The alkali-metal atoms undergo a spin-exchange relaxation (SER) state due to mutual collision followed by broadening of the atomic resonance line width. Under most circumstances, the SER regime is in the dominant state. However, the situation varies when the atom density and the alkali-metal atom temperature are high enough. When the SE rate is greater than the Lamor precession frequency, it is proportional to the square of the external magnetic field. Therefore, spin-exchange relaxation is considerably attenuated or even completely suppressed [90]. At this time, the atoms are in the state of SERF. As shown in Fig. 6, the alkali-metal atom under the SERF state (the blue ball) transits from the ground state to the excited state pumped by a beam from a circularly polarized laser (the arrow in yellow), thereby realizing the spin polarization process of the atom. Lamor precession of the atom is achieved when exposed to an external magnetic field (arrow in blue), and the frequency of Lamor precession (ω) is proportional to the magnetic intensity (B). Thus, the external magnetic field intensity can be obtained as long as ω is properly reflected using a linearly polarized laser (arrows in red) [91]–[93].

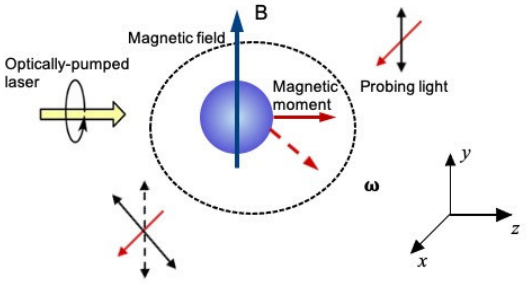


FIGURE 6. The basic principle of extrahighly sensitive magnetic field detection.

The main advantage of SERF magnetometers for neural activity measurements is their excellent temporal and spatial resolution. Compared with the traditional commercial SQUID-MEG instrument with a helmet-shaped Dewar, SERF-MEG increases the spatial bandwidth of the magnetoencephalogram utilizing on-scalp measurements. The current development of SERF technology has made it possible to mount MEG sensors on the scalp, which is only twelve millimeters away [94].

At present, simulation studies have been carried out to compare the imaging performance between cryogenic SQUID-MEG and noncryogenic on-scalp SERF-MEG [95]-[96]. It can be seen from Fig. 7 that the OPMs measuring the normal components of the neuromagnetic field yield roughly higher power than those measuring the tangential components, but both were 7.5 and 5.3 times higher than

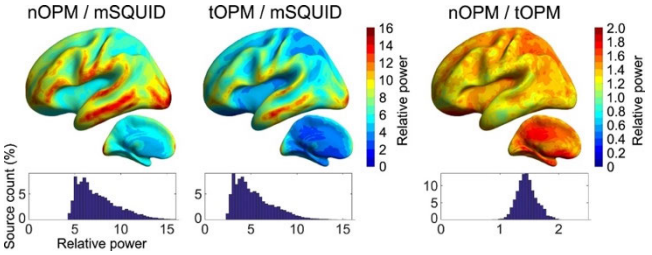


FIGURE 7. Simulation of the signal power in two detection orientations (normal and tangential) of OPM magnetometers relative to SQUID magnetometers (nOPM: 102 OPMs measuring normal field component; tOPM: 204 OPMs measuring tangential components; mSQUID: 102 SQUID magnetometers; images from Iivanainen, Joonas, 2020).

cryogenic MEG systems on average, respectively. The bar chart at the bottom of Fig. 7 indicates that OPM sensors are more sensitive to overall sources in cortices than SQUID sensors at the same location regardless of the sensing direction, but nOPMs are more sensitive than tOPMs at overall sources, especially in the medial sides of the brain hemisphere. As shown in Fig. 5(b)-(e), gradients of SID from the frontal to occipital area were more salient for the child than for the adult. Furthermore, information sampled using the on-scalp configuration is richer than that sampled using the cryogenic configuration. As shown in Fig. 8, the simulation results demonstrated that a wearable OPM-MEG array increases the channel information capacity compared with SQUID magnetometers with the same number of channels.

Analysis of the neuromagnetic field can be applied to estimate the optimal number and spacing of sensors. It has

Label	Array	Number of sensors	Average (bits/Sa)	Normalized (bits/Sa/ch)
	aOPM	306	1307	4.3
	tOPM	204	939	4.6
	nOPM	102	656	6.4
	aSQUID	306	506	1.7
	mSQUID	102	413	4.0
	gSQUID	204	383	1.9

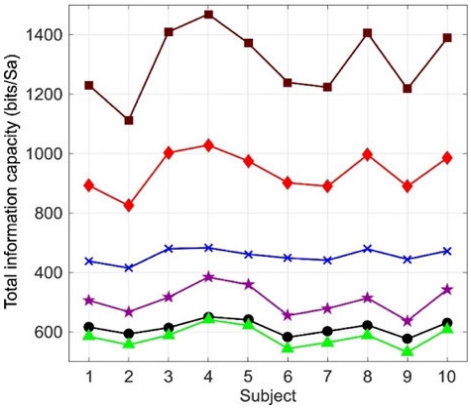


FIGURE 8. Comparison of OPM-MEG and SQUID-MEG on information capacity (aOPM: all components, 306 OPM channels; mSQUID, 102 SQUID magnetometers; gSQUID, 204 SQUID gradiometers; aSQUID; all SQUID components, 306 channels; images from Iivanainen, Joonas, 2020).

been reported that compared with a traditional MEG system, the normal component of the neural magnetic field sensed by the SERF system is three times greater than that of SQUID [96]. For a typical adult head, the optimal number of sensors for on-scalp measurement is approximately 300. A study at the University of Nottingham designed a 49-channel SERF-MEG array to record visual and sensorimotor neural activity and to validate the localization result of a wearable system [97]. It was found that the 49-channel SQUID reached the resolution level of the 275-channel SQUID, further indicating proximity to the scalp. The enhancement of the amount of recorded information has an important effect on the analysis of MEG-source activity [98].

The rapid development of whole-head wearable neuroimaging technology has broadened its application in the field of neuroimaging. Future research on neurodevelopmental disorders will definitely focus on on-scalp wearable measurement methods with higher information capacity. Ryan M. Hill *et al.* [99] modified the children's bicycle helmet and collected MEG from two children aged 2 and 5 years old, as shown in Fig. 9. In the experiment, the mother of the child brushed the child's thenar eminence to elicit a somatosensory-evoked response. Time-frequency analysis of the averaged epoch showed an obvious reduction in the amplitude of the μ/β band at the onset of stimulation, which is consistent with previous studies. The activation of β-band activity in the contralateral primary somatosensory cortex is obtained after mathematical-mapping analysis combined with individual structural MRI.

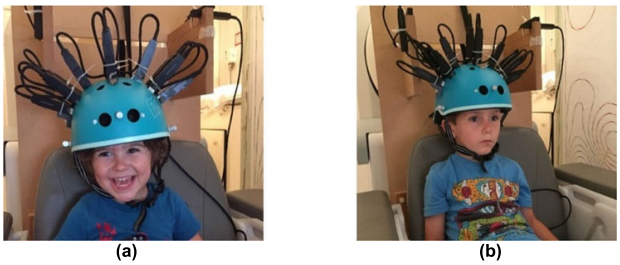


FIGURE 9. Somatosensory evoked SERF-MEG recordings on a (a) two-year-old boy and a (b) five-year-old boy (images from Ryan M. Hill, 2019).

C. PROSPECTS IN WEARABLE NON-CRYOGENIC OPM-MEG

Before using the OPM system in children, it is necessary to overcome some technical difficulties. For example, traditional wearable OPM devices are physically too clumsy for pediatric research. Moreover, the rigid wearable helmet imposes an uncomfortable experience on young participants, which introduces undesirable biomagnetic interferences into the outcome. A flexible EEG-like cap for the OPM-MEG system is a desirable design for pediatric MEG detection. The University of Nottingham [97] designed a flexible cap shown in Fig. 12 (a), on which a maximum of 64 SERF-OPM sensors manufactured by QuSpin, Inc. (Colorado, USA) were mounted. The cap is composed of elastic fabric, and the structure of this fabric is combined with a bone-frame structure, which is designed to help maintain its shape and to limit the movement of the SERF magnetometers relative to the scalp. Although there are some shaped structures, the cap is still easy to deform to a reasonable extent. Thus, it is easy to fit most of the participants' head shapes across age groups. However, there are currently some problems with wearable noncryogenic, whole-head MEG systems:

1) The modulation field crosstalk between sensors will render the deflection of the effective orientation (i.e., the real sensitive axis) of the sensors different from its physical orientation (i.e., the orientation along which we expect to measure the field), thus leading to erroneous forward modeling results followed by inaccurate source-level analysis.

2) The dynamic shift of the background magnetic field changes the gain of sensors, which is determined at the beginning of the experiment, resulting in deviations of the lead field matrix. Dynamic field stabilization techniques are essential to prevent the gain from deflection with a background magnetic field shift.

3) The capacitive coupling introduced by the electrical heating of the gas chamber can introduce crosstalk in the measurement task.

4) The sensitivity of the optically pumped magnetometer in detecting low-frequency magnetic field signals is currently not as good as that of the SQUID magnetometer, which means that low-frequency measurement is still challenging for OPM-sensing systems.

The current OPM system needs to be operated in an environment close to a zero-background magnetic field (the background magnetic field is approximately nT level) and has higher requirements for the ambient gradient field and the dynamic change of the magnetic field. The MEG magnetically shielded system designed by the University of Nottingham [97] for an optically pumped magnetometer is composed of an MSR consisting of two layers of permalloy and a copper layer equipped with a demagnetizing coil, and the design of the planar compensation coil is shown in Fig. 12 (b). The background static magnetic field can be reduced to $\sim$1.5 nT, and the magnetic field gradient is less than 2 nT$\cdot$m^{-1}. The participants are currently available in a limited space ($\sim$40 cm). In the latest research results, Limes ME *et al.* [156] proposed an optically pumped magnetometer with a resolution of parts per billion, which can detect the human brain and biomagnetic signals generated by the heart in a geomagnetic environment. The outdoor sensitivity of the gradiometers is 16 fT/cm/Hz$^{1/2}$, which can be used to detect neuron current and magnetocardiographic (MCG) signals. This work demonstrates the possibility of dense and wearable biomagnetic sensor arrays that can be deployed in various natural environments, which provides a reference for the acquisition of children's neuromagnetic fields without shielded conditions or with poorly shielded conditions. Progress in this area will increase opportunities for applied research in wearable MEG recordings.

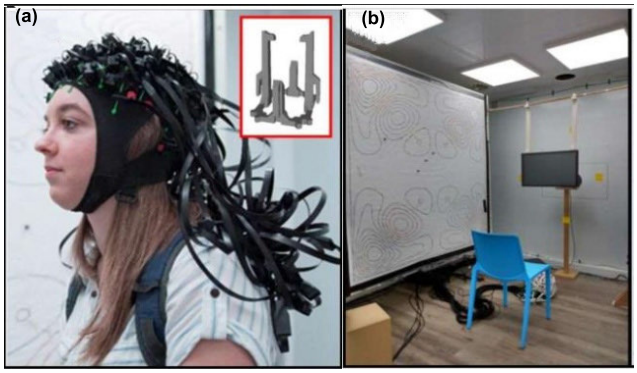
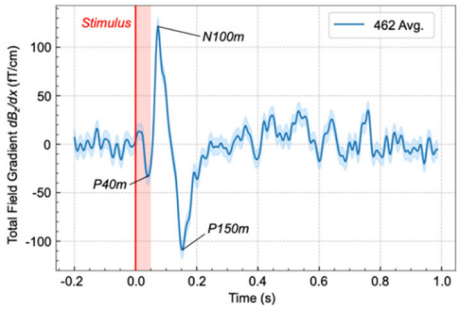


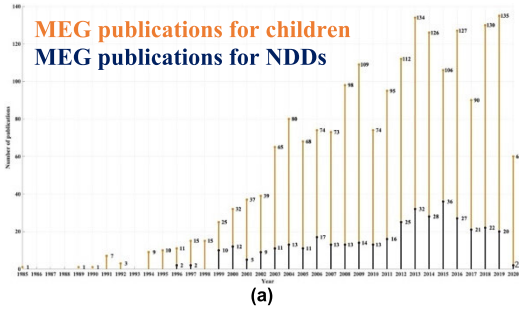
FIGURE 10. (a) A flexible EEG-style cap and (b) magnetic-shielded room (MSR) for a wearable OPM-MEG system designed by the University of Nottingham group (images from Ryan M. Hill *et al.*, 2020).

(a)

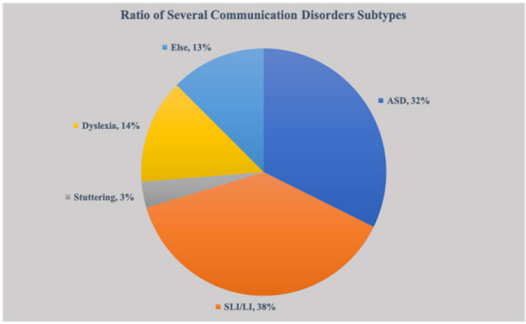


(b)

FIGURE 11. (a) A picture of the recording setup with a subject in a total nonshielded magnetic field. (b) Auditory evoked fields detected unshielded in Earth's field, in which prominent N100 m peaks along with indications of P40 m and P150 m responses are shown.



(a)



(b)

FIGURE 12. (a) Number of magnetoencephalography (MEG) publications in the period of 1985–2020. (b) The publication ratio of subtypes of communication disorders in NDDs.

IV. REVIEW OF MEG IN COMMUNICATION DISORDER RESEARCH

Neurodevelopmental disorders (NDDs) are heterogeneous disorders that cause atypical brain development due to abnormal development of the central nervous system. People with these disorders typically behave in several aspects, such as motor function, learning, cognitive and/or communication disorders, or neuropsychiatric problems. The disorders occur early in life, cover the whole lifespan, and cause significant damage in social, communicative, cognitive, and behavioral functions. The damage caused by NDDs covers a wide range and involves all aspects of intelligence and social abilities [3-4]. In the United States, approximately one out of six children is diagnosed with NDDs. These disorders include intellectual disabilities (formerly known as intellectual disabilities), communication disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), special learning disabilities (such as dyslexia) and motor disorders. Many neurodevelopmental disorders (such as ASD and SLI) may include or create challenges in language and communication and/or may cooccur with typical communication disorders such as stuttering and phonological disorders.

The last three decades have witnessed a steady surge of MEG studies, with a plateau of approximately 100 studies per year in the last six years (shown in Fig. 11(a)). Furthermore, MEG studies on communication disorders account for a considerable proportion of NDD MEG studies (shown in Fig. 11(b)).

There are some common phenotypes in several neurodevelopmental disorders, and it is necessary to identify biomarkers for aided diagnosis, developmental-outcome prediction, and treatment-performance monitoring and to verify their clinical utility since they provide an opportunity to understand and diagnose these disorders at the neurobiological level and to improve our understanding of their underlying mechanisms. Thus, studies on neurodevelopmental disorders transfer from behavioral phenotypes to biological endophenotypes. The focus of searching for biomarkers is to measure the structure and function of the brain and, more specifically, to measure the connectivity of the cerebral cortex [43], [100].

In this section, we study MEG research publications on neurodevelopmental disorders related to several typical

communication disorders in children. PubMed and Web-of-Science searches were conducted using keywords or their combination, and a total of 1907 related research papers were included in the period of 1985-2020. The latest search was conducted on June 2, 2020. Data were exported and replotted from the online PUBMED database (pubmed.gov; as of June 2, 2020) and online Web of Science (webofknowledge.com; as of June 2, 2020) with a search of the target words ''Magnetoencephalography'' and ''Children'' OR ''Infant'' in the title or abstract for ''MEG publications for children''; and a search of target words (Magnetoencephalography or MEG) and (neurodevelopmental disorder) in the title or abstract. The following sections highlight how MEG plays a role in the study of several typical neurodevelopmental disorders to reveal the neurophysiological and electrophysiological internal phenotype mechanisms under abnormal external phenotypes.

A communication disorder is defined as all disorders that weaken the capability of an individual to process, perceive or apply language and to produce speech to communicate effectively with others [98]. Delays and disorders can occur from simple voice replacement causing incomprehension or inability to acquire native language [101]. Exploring the way that the human brain engages in language-processing pathways and its impact on society and emotion are essential for brain-science research. Since Wernicke and Geschwind developed the first language model [102], neurologists and neuropsychologists have been trying to determine how the brain processes language tasks and which cortical regions are in charge of specific language functions. MEG is the only noninvasive technique that satisfies the high-demand temporal and spatial resolution requirements for depicting rapid language processing at the millisecond and millimeter levels, respectively [103]. It provides a noninvasive and high-resolution tool for understanding the language and speech neural-circuit mechanisms in children with communication disorders. It facilitates studies concerning language and communication difficulties and/or comorbidities that may have common features with speech-impairment types, such as autism spectrum disorders (ASDs) [104], stuttering [105], specific language impairments (SLIs) [106], and dyslexia [107].

A. MEG IN SLI STUDIES

SLI is a developmental disorder that occurs first during childhood and persists, fully or partially, into adulthood, characterized by the inability to master spoken and written language expression and comprehension, despite normal nonverbal intelligence, hearing acuity, and speech-motor skills, and no overt physical disability, recognized syndrome, or other mitigating medical factors known to cause language disorders in children [108], [109]. The description of SLI children has a history of more than 100 years. However, despite decades of research, the cause of the disorder is still unknown [106]. Existing explanations are mainly derived from observations of experimental data and behavior. Although SLI children are heterogeneous in severity and symptoms, their most common deficit profiles are delayed response and slower acquisition of lexical, syntax, and grammatical morphological aspects of spoken and written languages, as well as written language coupled with nonlinguistic cognitive processing, learning, and memory impairments [109]. Nonverbal deficiencies usually involve slow-processing speed, poor speech and verbal-working memory, poor auditory processing, and deficiency in procedural learning and memory [111].

In the MEG study of language functional lateralization in children with language disabilities, Helenius P *et al.* [115] observed that SLI children did not show attenuation of the response in the superior temporal gyrus (STG) as the TD group did when the same words were repeated. Activation persists longer in the left hemisphere in typically developing (TD) children. The SLI group showed impaired leftward-lateralized short-term maintenance of linguistic activation, which underlies the poor performance of spoken-word recognition. Van Bijnen, Sam, *et al.* [116] observed a prolonged auditory response (N250 m) that was specifically present in children with SLI and was associated with the level of language skills. Their study found that the N250 m response in the left hemisphere of children with language impairment was stronger than that of the TD group, whereas the same pattern did not occur in the right hemisphere. Therefore, children with impaired language ability were devoid of normal rightward lateralization. Additionally, the N250 m components in the right hemisphere were positively associated with the speech-processing ability of the SLI group, which indicated the mature compensatory mechanism for delayed maturation of language processing. Recent MEG studies on SLI have shown that the language system of the SLI group is qualitatively and quantitatively different from that of TD peers in the way it is organized. The differences involve atypical right-hemisphere specialization for specific subcomponents of language, such as word meaning and semantic representation of concrete entities [115]. In a study of SLI using an auditory-evoked mismatch negative paradigm, Roberts *et al.* [114] observed that delayed mismatch field (MMF) is a general precursor related to language impairment, whereas delayed M100 particularly occurs in autistic children. In an early study of mismatched negative fields in children with SLI [113], two sets of two-syllable, auditory-evoked, oddball paradigms (one changing consonants, and another changing vowels) were utilized. It was found that the P1 m response to the onset of repetitive stimuli was weaker in SLI children and indicated that SLI children were not sensitive to the onset of sounds, thus leading to depressed sensory encoding.

B. MEG IN ASD STUDIES

Children with autism spectrum disorders (ASDs) have deficits in language ability [117], lacking the ability to recognize speech [118] and to respond to names [119], [120], in previous research. Studies have observed that these traits can predict a wide range of expressive language problems.

However, because of limited social motivation, the challenge for ASD children to perceive auditory information reflects the difficulty in conducting experiments on them. Although in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) [121], language impairments are listed within the scope of social communication disorders; they are still a prominent feature of ASD. Several studies have reached consensus on the core deficits of semantic processing [117], [122] and delayed sound perception [123]- [124], [59] in autism. Berman *et al.* [125] used pediatric MEG technology as a passive measurement of early auditory processes to obtain the M100 latency of pure-tone stimulation originating from the STG of TD children and ASD children, in which M100 latency indicates the conduction velocity of the auditory system. In this study, concerning the relationship between children's auditory and language-system structural-functional abnormalities, MEG was applied to reflect the conduction velocity of the auditory system as the latency of M100 component evoked in STG in response to pure-tone stimuli can be indicative and informative; and the vowel-contrast mismatch paradigm preattentively yielded MMF whose latency indicated maturation of early linguistic processes. Compared with children with normal development, ASD children have abnormalities in the coupling between the function and structure of their hearing and language systems. This study suggests that the delayed latency of the M100 component can be used as a sign of the degree of autism, and the mismatch field is more related to language disorders. In a lateralization study, Matsuzaki *et al.* [126] explored the neural correlation between language and communication skills in children with ASD who had extreme language impairment. It was found that compared with ASD children with language impairment and ASD children with mild or no language disorder, delayed bilateral MMF was shown in ASD children with severe language impairment. Although TD children mismatch field amplitude to the left side, severe language impairment ASD and language ASD (mild or no language disorder ASD and language disorder ASD) showed an abnormal field amplitude to the right side. TD children show dominant leftward hemisphere lateralization, whereas ASD children show atypical rightward lateralization.

The results of the study suggest that the slow process of auditory discrimination and the abnormality of rightward lateralization are the electrophysiological traits of language/communication skills in children with ASD and severe language impairment. MEG is utilized to measure the auditory evoked M100 response to pure tone stimulation in the superior temporal region. The M100 component and the latency of the auditory vowel-contrast mismatch field (MMF) are suggested as indicators of the conduction velocity of the auditory system and the early language process, respectively.

C. MEG IN STUTTERING STUDIES

Stuttering is a speech disorder that frequently occurs during early childhood (developmental stuttering) and disrupts the forward flow of speech. Approximately 5% of people stutter at a certain stage of their lives [137]. Approximately 1% of these children continue to stutter into adulthood [132]. MEG has been used to localize brain regions activated during language processing [138], [139] and has been used to evaluate stuttering in several related studies [122], [140]. However, most studies on stuttering have investigated adults, whereas studies on developmental stuttering are relatively limited. It is extremely important to understand how age affects the outcome. For many years, researchers have highlighted that it may be incorrect to draw conclusions on the reason and characteristics of developmental stuttering in children from adult stuttering studies [141] since it ignores the ''development, learning history, and experience effects''. The first study using MEG for stuttering in children showed that the auditory evoked M50 component was delayed compared to children who did not stutter, which indicated that the children in the stuttering group had slower auditory processing, suggesting that these children may not have been able to effectively integrate auditory information to establish the neural representation of speech [142]. It is of note that this is similar to their previous study on stuttering in adults [122], that is, the peak of the M100 component was delayed relative to the group without stuttering [143]. However, it should be highlighted that this study was conducted on children 6-12 years of age who exceeded the age of onset of stuttering. In addition, they used traditional MEG instead of pediatric MEG, which may not have been optimal for the detection of the children's neuromagnetic fields. In the follow-up study by Sowman *et al.* [37], in which pediatric MEG was first introduced in stuttering, hemisphere lateralization of stuttering and nonstuttering children aged 3-6 years was examined in the picture naming task. There was no difference between the two groups, which indicated that atypical lateralization in stuttering only developed later. This conclusion was also confirmed in the study by Choo *et al.* [144]. In a recent study from the same research group, Etchell *et al.* [136] demonstrated that stuttering-children's response to synchronized sounds at intervals of 450 ms showed an out-of-phase pattern of β-band activity. The authors believed that this supported the claim that stuttering children are defective in timing ability rather than sound processing; see Alm [145], which is consistent with fMRI and diffusion tensor imaging (DTI) studies of stuttering children by Soo-Eun and Zhu [146].

D. MEG IN DYSLEXIA STUDIES

Dyslexia, also known as reading disorder, is characterized by difficulty in reading despite normal intelligence [150]. In individuals with dyslexia, this disorder seems to appear in speech processing in the early stage of life, which is evident in tasks such as absolute perception of speech. People with developmental dyslexia usually have disorders in neural-language processing, and research in this field requires a neural-activity recording method with high-temporal resolution to describe the neural-activity profile under language tasks, as well as a high-spatial resolution to reflect the cortical

TABLE 2. MEG for research on SLI children.

Author	Age/year	Paradigm	ERF Components	Recording Parameters and instrumentation used	Source Modeling	Other analysis	Results
E. Pihko et al. (2008) [115]	SLI: 5.5-7.1 TD: 5.9-7.1	Isolated syllables	AEF, MMF	102 locations (Elekta Oy, Helsinki, Finland); EOG	ECD	Two-way ANOVA	SLI: P1 m for onset of repetitive responses ↓ , depressed sensory decoding
T. P. L. Roberts et al. (2012) [116]	SLI: 10±3 TD: 10±3	Sinusoidal tones	M100, MMF	275 channels (VSM MedTech Inc., Coquitlam, British Columbia, Canada); EOG; ECG	N/A	5-fold cross-validation	delayed MMF→ language impairment; delayed M100→ autism
P. Helenius et al. (2014) [117]	SLI: 9.2-9.8 TD: 8.8-10.6	Block; 7-8 letters real words (150); Pseudowords (100)	AEF, N100 m, N250 m, N400 m	102 locations (Elekta Oy, Helsinki, Finland); EOG	MCE, ECD	Not mentioned	SLI: no attenuation in response to repeated words in STG TD: longer activation in left hemisphere
S. van Bijnen et al. (2019) [118]	SLI: 8.8-10.6 TD: 9.2-9.8	Block; Sine wave tone	AEF, N250 m	102 locations (VectorviewTM, Elekta Neuromag Oy, Helsinki, Finland); EOG;	ECD	LMM	SLI: prolonged N250 m associated with language skills

Note. AEF: auditory evoked field, ECD: equivalent current dipole, LMM: mixed linear model, MCE: minimum-current estimation, ANOVA: analysis of variance, EOG: electrooculogram, ECG: electrocardiogram

activation pattern for language tasks. fMRI measures brain activity indirectly through a slow hemodynamic response and can only track fluctuations of <1 Hz, while MEG can directly measure the electrical activity of neuronal populations in milliseconds. MEG signals enrich the information to extract using synchronization methods (such as phase coupling, envelope correlation, and cross-frequency coupling) in cross-frequency bands during resting-state or tasks [151]; through this, the atypical neural circuits of language processing are investigated in terms of functional segregation and integration. In the study of syllable or phoneme sampling and rhythm entrainment effects, Molinaro *et al.* [147] recorded neuromagnetic oscillations from dyslexic and TD children while listening to sentences for up to 10 seconds. Compared with the TD group, dyslexic readers showed the following specific traits:

1) impaired-nerve entrainment to speech flow presented in the δ-band (0.5-1 Hz);
2) simultaneously reduced δ-band activity in the right auditory cortex and left inferior frontal gyrus;
3) impaired feedforward connectivity between the oscillations in the right auditory cortex and left inferior frontal lobe.

This indicates that during speech listening tasks, individuals with developmental dyslexia may have impaired feedback communication in the lower left frontal lobe and auditory cortex. The assessment of speech-brain synchronization may be used as a diagnostic tool for the early detection of children at risk for dyslexia. Lizarazu *et al.* [82] used MEG to measure the auditory nerve synchronization of children and adults with dyslexia at different frequency bands, which correspond to the relevant spectrum components of phonemes. Studies have demonstrated that children with dyslexia show abnormal brain synchronization and lateralization patterns at different phonological levels (e.g., syllable and phoneme). That is, dyslexics with the same structural indexes as the TD group show rightward lateralization for neural entrainment to syllable-level stimuli, whereas the TD group exhibits the opposite laterization outcomes at phoneme-level stimuli. In conclusion, children with developmental dyslexia share acoustic sampling impairment, which probably relates to aberrant specialization of the auditory cortex to nerve entrainment at both low- and high-phonology rates. In MEG and behavioral tests by Lehongre *et al.* [152], children with dyslexia showed weakened entrainment of $\sim$30 Hz sound modulation by the left-auditory cortex, reflecting impaired left-hemisphere lateralization for phoneme processing. This electrophysiological trait correlates with the performance of speech processing and rapid-naming tasks. It was further observed that the frequency of cortical entrainment in patients with dyslexia exceeds 40 Hz, which may be related to disorders in speech memory. Oversampling of phonemes in the left-auditory cortex can reveal the causes of the three main traits of language impairment in dyslexia.

In the study of brain networks of children with dyslexia, Dimitriadis *et al.* [149], [153] observed that cross-frequency coupling (CFC) can be used as a measurement parameter for the information interaction of neural groups in specific brain regions. The time domain variability of CFC in dyslexic children is atypically large. Dyslexic school-aged children have interactions between adjacent channels mainly within a one-frequency band, while normal children mainly interact between multiple frequency bands using the weighted-phase synchronization index (wPSI) to construct resting-state functional connectivity. The statistical dependence of sensor channels between children with dyslexia and children with dyslexia found that dyslexic students showed a significant decrease in overall sensor-level network organization efficiency (global efficiency) in all frequency bands, as well as sensors in the left temporal parietal region. The time-domain correlation between $\beta 3$ (20–29 Hz) decreased with the remaining sensor channels (local efficiency). In studies related to laterality

TABLE 3. MEG for research on communication disorders in ASD children.

Author	Age/year	Paradigm	ERF Components	Recording Parameters and instrumentation used	Source Modeling	Other analysis	Results
Y. Yoshimura et al. (2013) [129]	HF-ASD: 3-7 TD:3-7	Syllable/ne/; steady pitch (standard); falling pitch (deviant)	AEF, Oddball, P50 m	151 channel pediatric SQUID (PQ 1151R; Yokogawa/KIT, Kanazawa, Japan);	ECD	Two-way ANOVA	ASD: P50 m left lateralization ↓, atypicality in auditory cortex
J. C. Edgar et al. (2014) [125]	Younger: 6-10 Older: 11-15	Pure-tone stimuli (1000 Hz/2000 Hz)	AEF, M50, M100, M200	275 channels SQUID (VSM MedTech Inc., Coquitlam, BC, USA); ECG; EOG	MSA	ANOVA	ASD: delayed M50 response, lack of M100→cognitive impairment in autism
J. C. Edgar et al. (2015) [126]	ASD: 6-14 TD: 6-14	Sinusoidal tones	AEF, M50, M100, M200	306-channel Vector View system (Elekta-Neuromag, Helsinki, Finland); ECG; EOG;	N/A	Time-frequency analysis; ANOVA	ASD: abnormal M100 latency, M200 intensity, atypical asymmetries
Mamashli F et al.(2016) [130]	ASD: 13±3 TD: 12±2	Complex tone (standard); ICRA noise (deviant)	AEF, Oddball, MMF	306-channel Vector View system (Elekta-Neuromag, Helsinki, Finland); ECG; EOG;	wMNE	Time-frequency analysis; FC analysis (Coherence):	ASD: coherence ↓, atypical MMF under noise condition
R. G. Port et al. (2016) [131]	Mean age: 12.1	Sinusoidal tones	AEF, M100	275 channels SQUID (VSM MedTech Inc., Coquitlam, BC, USA); ECG; EOG	LCMV	LMM; ITC	ASD: delayed M100, γ -band power and ITC ↓
J. I. Berman et al. (2016) [127]	ASD: 10.2 ± 2.6 TD: 10.4 ± 2.4	Pure-tone stimuli; Vowel	AEF, M100, MMF	275 channels SQUID (VSM MedTech Inc., Coquitlam, BC, USA); ECG; EOG	N/A	LMM; MVR; GC	ASD: MMF→severity of LI, M100→degree of ASD
Yoshimura Y, Kikuchi M, Hayashi N, et al. (2017) [132]	ASD-SOD: 3.3-6 ASD-NoSOD: 3.3-6 TD: 5.3	Syllable/ne/ steady pitch (standard); falling pitch (deviant)	AEF, Oddball, MMF	151 channels pediatric SQUID (PQ 1151R; Yokogawa/KIT, Kanazawa, Japan);	MNE	ANOVA; ANCOVA; MLR	ASD: MMF amplitude in LPO negatively correlated with language performance
J. Matsuzaki et al. (2017) [133]	ASD+AAS: 9.62±1.82 ASD-AAS: 9.07±1.31 TD: 9.45 ± 1.51	Pure-tone stimuli (std:300 Hz; deviant:700 Hz)	AEF, Oddball, MMF, M100	160 channels (PQ 1160C, Yokogawa Electric Corporation, Tokyo, Japan); Video surveillance;	wMNE (L2-norm estimator)	ANOVA; Partial correlation	ASD: delayed bilateral MMF, language ↓, atypical lateralization
T. P. L. Roberts et al. (2019) [135]	ASD-MVNV: 9.85 ± 1.32 ASD-V: 10.64 ± 1.31 TD: 10.18 ± 1.36	Sinusoidal tones	AEF, M50, M100	275 channels (VSM MedTech Inc., Coquitlam, BC); EOG; ECG	MSA	LMM	MVNV-ASD: delayed M50 and M100 latencies
L. Bloy et al. (2019) [136]	ASD: 9.4 ± 1.1 TD:8.8±1.4	Words/nonwords	AEF, ERD	275 channels (VSM MedTech Inc., Coquitlam, BC); EOG; ECG	MNE	TFA; LMMs	ASD: diminished ERD in STG
J. Matsuzaki et al. (2019) [137]	ASD-MVNV: 9.67±1.41 ASD-V: 10:55±1.21 ASD-LI: 10.67±1.20 TD: 10.14±1.38	Vowel stimuli	MMF	275 channels (VSM MedTech Inc., Coquitlam, BC); EOG; ECG	Spatial filter	LMM	ASD: delayed MMF, atypical lateralization in MMF amplitude

Note. HF-ASD: high-functioning ASD, MSA: multiple source analysis, (w)MNE: (weighted) minimum-norm estimation, MMF: mismatch field, ITC: intertrial coherence, GC: Granger causality, TFA: time–frequency analysis, LCMV: linearly constrained minimum variance, ICA: independent component analysis, ERD: event-related desynchronization, PCA: principal component analysis, FC: functional connectivity. LPO: left pars orbitalis, MVR: multivariate regression, ANCOVA: analysis of covariance, SOD: speech onset delay, AAS: abnormal auditory sensitivity, MVNV: minimally verbal/nonverbal

and compensation, the excessive activation of resting low-frequency activity in the right-temporal lobe, left-subfrontal, and right-frontal regions may be some kind of compensation mechanism. It was also found that the asymmetry of the hemispheric language function of children with speech impairment was reduced, as well as increased right-lower, frontal-lobe activity [153], [154].

V. DISCUSSION

MEG combined with structural MRI has the advantage of high spatial and temporal resolution, which has promoted the research of children with neurodevelopmental disorders, especially in neurolinguistic studies and communication disorders. MEG provides a complementary and nonoverlapping method to understand the functional brain activity of neurodevelopmental disorders [87]. Here, we discuss future directions from the perspective of whole-head pediatric MEG devices and language and communication disorders.

In the past three decades, the research and development of MEG equipment have accelerated, and the availability of MEG equipment has further improved.

TABLE 4. MEG for research on communication disorders in stuttering children.

Author	Age (years)	Paradigm	ERF component	Recording Parameters and Instrumentation Used	Source Modeling	Other analysis	Results
D. S. Beal et al. (2011) [124]	CWS: 6~12 TD: 6-12	Vowel listening Tone; listening Vowel speaking	M50	151 channels CTF Omega; Video surveillance;	Beamformer	Two-way ANOVA Three-way ANOVA	Stuttering: delayed M50 →auditory processing speed ↓
P. F. Sowman et al. (2014) [37]	CWS: 3~5 TD: 2.1-5.5	Picture-naming	M450	64 channels Pediatric system (PQ1064R- N2 m)	Bayesian model	Multivariate ANOVA	Stuttering: atypical lateralization
A. C. Etchell et al. (2016) [138]	CWS: 3~9 TD: 3~9	SOA	AEF	64 channels pediatric system (PQ1064R- N2 m) 160 gradiometers (PQ1160R-N2);	N/A	Nonparametric ANOVA; Time-frequency analysis	Stuttering: desynchronized β-band, defective timing ability

Note. CWS: child who stutters, SOA: stimulus onset asynchronization

TABLE 5. MEG instrumentation for research on communication disorders in dyslexic children.

Author	Age/year	Paradigm	ERF Components	Recording Parameters	Source Modeling	Other analysis	Results
N. Molinaro et al. (2016) [151]	Dyslexic: 9.6~12.5 TD: 22.2~37.3	Sentence listening	AEF	102 locations (Elekta Oy, Helsinki, Finland); EOG	DICS	GC; EC (PDC); FC	Dyslexic: impaired entrainment, δ -band ↓, impaired EC
S. I. Dimitriadis et al. (2018) [152]	Dyslexic: 7-14 TD: 7-14	Resting-state	N/A	248 channels (4-D Neuroimaging MagnesWH3600	N/A	SMI	Dyslexic: atypical CFC variability, decreased overall FC efficiency
S. I. Dimitriadis et al. (2016) [153]	Dyslexic: 7-14 TD: 7-14	Resting-state	N/A	248 channels (4-D Neuroimaging MagnesWH3600	N/A	PAC	
M. Lizarazu et al. (2016) [83]	Children: 8-14.3 Adult: 17.3-44.9	White noise listening	AEF	102 locations (Elekta Oy, Helsinki, Finland); EOG	DICS	PLV; ANOVA	Dyslexic: abnormal synchronization and lateralization at phonological levels

Note. SSP: signal-space projection, DICS: dynamic imaging of coherent sources, SMI: symbolic mutual information, PAC: phase-amplitude coupling, PLV: phase-lag value, PDC: partial direct coherence, EC: effective connectivity

A. POTENTIAL SLI STUDIES USING WHOLE-HEAD MEG

In the study of SLI children, for certain language processing (such as phonological processing), both temporal features (e.g., syllabic-rate auditory input and phonemic-rate auditory input) must be taken into consideration. Concerning the hemisphere lateralization issues related to language and auditory processing between the SLI and TD groups, it is of great importance to consider the dynamic properties of brain asymmetry and to discuss the underlying neural substrates using inter-hemisphere connectivity [110], [112]. Further research with neuroanatomical and functional (MEG) data is needed to clarify the lateralization of auditory and language processing in developmental language disorders. Future research should incorporate these multimodal imaging techniques (MEG+EEG, MEG+fMRI, and MEG+fNIRS) that facilitate a complementary study on functional cortices during tasks, which improves the understanding of both typical and atypical language systems in cortical and subcortical regions [116]. Advances in noninvasive, safe, functional-brain imaging technologies coupled with a richer integration among neuroscience, cognitive psychology, and linguistics have led to an explosion of new research in the neuroscience of language and in our understanding of the nature of language and cognition in the brain [157]. With the advent of better imaging technology and the continuous development of SLI research, neurobiological models of SLI language disorder are being reconceptualized and built on a richer theoretical basis. Emerging studies no longer focus on one aspect or one trait that the SLI group shares but they utilize cutting-edge, imaging techniques to further unravel the endophenotypes of SLI [158]–[160]. Therefore, it is necessary to not only focus on a single factor (e.g., the classic left-brain, language lateralization model) to describe neural substrates but also to regard this dynamic neurodevelopmental phenomenon as a complex system that may ultimately be the way to discover the cause of SLI [159].

B. POTENTIAL ASD STUDIES USING WHOLE-HEAD MEG

For auditory encoding impairments shown in autistic children, functional studies coupled with structural findings may yield informative insights concerning atypical brain maturation [125], which also has the potential to develop accurate lifetime biomarkers reflecting impaired-language ability in autistic individuals [105]. Concerning the relatively slower development of language-related fascicular pathways in the ASD group, as previous research has reported,

abnormalities in neurotransmitter levels may provide an in-depth explanation of MEG hints in both the verbal and MVNV ASD groups, which can be directly or indirectly depicted using DTI and/or GABA magnetic resonance spectroscopy (MRS) [135]. In recent years, MEG integrated with functional and structural brain imaging modalities has made it possible to reveal cortical-subcortical long-range connectivity, which paves the way for neuropsychiatric pathology studies. For example, the increased connectivity between the auditory cortex and thalamus provides evidence for the closed relationship between these abnormalities and impaired cognition and behavioral capabilities [161]. However, further studies should investigate the causalities between primary sensory perception and high-level cognitive skills using paradigms such as sentence-listening tasks, words and pseudowords.

C. POTENTIAL STUTTERING STUDIES USING WHOLE-HEAD MEG

Current research is striving to determine biomarkers to distinguish stuttering children who outgrow their symptoms in the future from those who are at risk of not outgrowing their symptoms into adulthood. Innovative studies targeted to specific language-related functional networks are working to determine the abnormal connectivity patterns at the exact onset of disfluencies, which may demonstrate how speech production networks differ from controlled networks. Longitudinal research on developmental trajectories offers evidence on the plan of individualized treatment and making adjustments according to the performance at each developmental stage. Moreover, longitudinal studies of temporal processing in the CWS group combined with analysis of the different traits between the outgrown and persistent groups may further advance our perception of the neural substrates of how disfluencies evolve with age and nail down the exact electrophysiological parameters (e.g., β-band oscillations in the putamen [162] and power in the cortex [163]) that better indicate the treatment effects [37].

D. POTENTIAL DYSLEXIA STUDIES USING WHOLE-HEAD MEG

Future studies may investigate the effect of age on dyslexic participants. Along with the maturation process of the developing brain, elderly individuals with dyslexia develop compensatory mechanisms and strategies for reading regardless of atypicality [164]. Thus, cohort studies would be essential to separate the enrolled participants according to the milestones of the developing process, such as the exact period when reading acquisition is acquired, to determine whether genetic or environmental factors influence the most when atypical synchronization effects in dyslexia occur.

VI. CONCLUSION

The analysis concerning functional connectivity and lateralization on MEG data is of great importance in the latest developmental research when considering the brain as a whole, functionally interconnected hub [47]. To our knowledge, this is the first systematic review to summarize the current state of both MEG instrumentation and its application to communication disorders in the pediatric population. This study provides a detailed description of the existing commercial cryogenic MEG systems and noncryogenic wearable MEG systems based on the SERF effect and their applications in exploring the underlying neurophysiological mechanism of communication disorders. Overall, MEG has been widely recognized as a complementary and nonoverlapping neuroimaging method in investigating language processing neural systems, which is strictly demanding at high temporal and spatial resolution. In the upcoming future, a wearable optically pumped wearable MEG whole-head system equipped with advanced background magnetic-field nulling coils will be envisaged for integration into pediatric electrophysiological research for communication-relevant studies due to its promising physical merits that traditional MEG systems do not share. Considering the intrinsic characteristics of NDDs, the results of the reviewed studies are highly heterogeneous, precluding the possibility of drawing specific and quantitative diagnostic conclusions based on a single cause or single imaging modality and emphasizing the considerable importance of conducting research in this field.

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