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Infant brain imaging using magnetoencephalography: Challenges, solutions, and best practices

Maggie D. Clarke[1] | Alexis N. Bosseler[1] | Julia C. Mizrahi[1] | Erica R. Peterson[1] | Eric Larson[1] | Andrew N. Meltzoff[1,2] | Patricia K. Kuhl[1,3] | Samu Taulu[1,4]

[1]Institute for Learning & Brain Sciences, University of Washington, Seattle, Washington, USA
[2]Department of Psychology, University of Washington, Seattle, Washington, USA
[3]Department of Speech and Hearing Sciences, University of Washington, Seattle, Washington, USA
[4]Department of Physics, University of Washington, Seattle, Washington, USA

Correspondence
Maggie D. Clarke, Institute for Learning & Brain Sciences, University of Washington, Seattle, WA 98195-7988.
Email: mdclarke@uw.edu

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Abstract
The excellent temporal resolution and advanced spatial resolution of magnetoencephalography (MEG) makes it an excellent tool to study the neural dynamics underlying cognitive processes in the developing brain. Nonetheless, a number of challenges exist when using MEG to image infant populations. There is a persistent belief that collecting MEG data with infants presents a number of limitations and challenges that are difficult to overcome. Due to this notion, many researchers either avoid conducting infant MEG research or believe that, in order to collect high-quality data, they must impose limiting restrictions on the infant or the experimental paradigm. In this article, we discuss the various challenges unique to imaging awake infants and young children with MEG, and share general best-practice guidelines and recommendations for data collection, acquisition, preprocessing, and analysis. The current article is focused on methodology that allows investigators to test the sensory, perceptual, and cognitive capacities of awake and moving infants. We believe that such methodology opens the pathway for using MEG to provide mechanistic explanations for the complex behavior observed in awake, sentient, and dynamically interacting infants, thus addressing core topics in developmental cognitive neuroscience.

KEYWORDS
analysis, guidelines, infant, magnetoencephalography, MEG, processing, recommendations

1 | INTRODUCTION

The earliest phases of human development invoke a special fascination because they allow invaluable insights into the origins and functions of the human mind. The last decades have produced rapid advances in noninvasive brain imaging techniques that provide a window into infant brain function.

Magnetoencephalography (MEG) measures the magnetic fields produced by neuronal currents in the brain (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Unlike other noninvasive neural measures such as, electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIRS), MEG has both excellent temporal resolution (<1 ms), and advanced spatial resolution. MEG is noninvasive, silent, and generally does not require participant sedation. Setup is simple and quick, and minimally demanding on the participant. The participants can be easily monitored and optionally accompanied by a caregiver or assistant during the measurement. For these reasons, MEG makes an excellent tool to study infants and young children.

1.1 | Challenges presented by infant MEG measurements

Nonetheless, a widespread belief persists that collecting infant MEG data presents a number of limitations that are difficult to overcome (Azhari et al., 2020; Nevalainen, Lauronen, & Pihko, 2014). Due to this notion, many researchers either avoid conducting infant MEG research or believe that in order to collect high-quality data, they must impose limiting restrictions on the infant. Besides the many general challenges of collecting data from infants and young children, the two most prevalent technical challenges are: (a) compromised signal-to-noise ratio (SNR) due to increased scalp-to-sensor distance, and (b) signal distortion caused by participant movement. In mathematical terms, the leading term of the magnetic field, the dipolar component, decays as the square of the distance between the source and the point where the magnetic field is evaluated. The higher-order components, corresponding to more complex features of the magnetic field, decay even faster. Consequently, the magnitude and the information content of the detected MEG signal decays as the head moves farther away from the (noisy) sensors.

The obvious solution to overcome such challenges is to request the participant to keep the head still and as close to the sensors as possible. In the case of infants, such a request would limit the MEG studies to sedated or sleeping infants. The smaller head size of infants also allows for a considerable range of movement inside adult-sized whole-head helmets. This leads to distortions of the spatial topography in the MEG signal distribution and errors in subsequent source localization if these distortions are not compensated for. Interestingly, from a physics point of view, head movements can be equivalently considered as movements of the sensor array around a static head. Provided that the distance between the head and the sensors remains reasonably short, this can actually lead to more comprehensive spatial sampling of the field, leading to increased information of the underlying neural currents (Medvedovsky et al., 2016). Thus, head movements do not necessarily deteriorate signal quality as long as their effects are taken into account mathematically. This requires that the head be transformed to a representation that is independent of the measurement device. Existing solutions can be divided into types of methods that either utilize a standard representation of the signal at the level of cortical sources, such as the minimum-norm estimate (MNE) (Uutela, Taulu, & Hämäläinen, 2001), or a series expansion of the magnetic field with minimal assumptions about the neural current configuration. The latter approach can be accomplished by signal space separation (SSS) (Taulu & Kajola, 2005; Taulu, Simola, & Kajola, 2005), which is the method applied in this article. However, our suggested workflow could also utilize the MNE-based movement compensation in which the sensor-level signals are transformed into a source-level MNE estimate for a device-independent representation. The signals are then transformed back to a sensor-level representation corresponding to a specified target head position. In SSS, the sensor-level signals are transformed to device-independent magnetostatic multipole moments, followed by a transformation back to the target sensor-level representation. A benefit of SSS is that the effect of external interference signals can be compensated for in the same processing step that does the head movement compensation.

In this article, we focus on the overall workflow of conducting infant MEG studies for a wide range of neuroscience questions while our recent methodological article (M. D. Clarke et al., 2022) describes the associated mathematical signal processing and source analysis in more detail. Many researchers have avoided some of these challenges (i.e., lack of compliance and movement) by only performing MEG experiments with infants or young children who are sleeping (Hartkopf et al., 2016; Pihko et al., 2004), or in some cases, sedated (Birg, Narayana, Rezaie, & Papanicolaou, 2013). While these measurements are appropriate for studying the brain during sleep, active forms of cognition such as language, visual perception, attention, memory, decision-making, social interaction, and theory-of-mind, can only be measured in awake infants. Furthermore, a common practice is to position a sleeping infant's head in a particular location in the helmet closest to a small number of sensors in a region of interest. Although this method reduces movement and ensures close head-to-sensor distance, it also limits the scope of a study, and suggests the brain process in question is tied to activity exclusive to that brain region, which is not always the case. Using whole-brain imaging, studies have shown that even speech sound processing in infancy recruits a large network of brain regions (e.g., Bosseler et al., 2021), including bilateral frontal, auditory, and parietal cortices. Furthermore, the contribution of these different brain regions changes as a function of development and experience with language (e.g., Ferjan Ramírez, Ramírez, Clarke, Taulu, & Kuhl, 2017; Kuhl, Ramírez, Bosseler, Lin, & Imada, 2014).

Considerable advances in MEG analysis methods and hardware designs in recent years have helped to address the issues listed above (Chen et al., 2019; Kao & Zhang, 2019). There are several review articles that provide guidelines for adult MEG studies. Gross et al. (2013) provided detailed guidelines for general MEG data acquisition and analysis suitable for use with adults. Several articles include comprehensive reviews on basic MEG physiology, general acquisition, and analysis of MEG signals and clinical applications (Bagić et al., 2011; Bowyer, Zillgitt, Greenwald, & Lajiness-O'Neill, 2020; Hari et al., 2018; Pernet et al., 2020; Puce & Hämäläinen, 2017). Kao and Zhang (2019) and Chen et al. (2019) provided extensive reviews on infant paradigms and analyses for various protocols, and infant-specific systems and hardware. To date, there are no articles detailing methods specific to MEG measurements of awake infants.

In the current article, we will discuss the various challenges unique to imaging awake infants and young children with MEG, and share general best-practice guidelines for data collection, acquisition, and preprocessing. These guidelines have been developed and refined over the roughly two decades of collecting infant data at the University of Washington's Institute for Learning & Brain Sciences (I-LABS) MEG Center and at collaborating institutions. We believe these methods can serve as helpful general guidelines for other researchers, and also serve as a basis for further discussion and development as MEG technology and software are improved. While the data acquisition guidelines are specific to awake infant measurements, our

FIGURE 1 Digitization setup for use with the Polhemus device. Left panel: A toy-waver is engaging with an infant as a researcher digitizes the anatomical landmarks, head position indicator (HPI) coil locations, and additional head points. Top right panel: An infant wears a soft cap equipped with the HPI coils. Bottom right panel: A researcher places the foam halo on the infant's head before the infant is positioned under the MEG helmet

guidelines for data preprocessing and analysis can be applied to all infant protocols or any adult clinical populations where patients are unable to remain still during recordings. These improvements have the potential to yield insights into the dynamics of neural processes in the developing brain.

2 | DATA ACQUISITION FOR INFANT MEG

2.1 | Data acquisition: Background

For adults, the MEG data acquisition process typically involves a number of standard steps to obtain high-quality data (Gross et al., 2013) including system setup, experimental design, general acquisition setup, and preparation of the participant. We have adapted this process to accommodate for the technical and behavioral challenges that infants present. Most notably, infants have a limited time window while they are awake, alert, and compliant. A supplemental video demonstrating this process for infant data acquisition is available at https://youtu.be/WfKRQSjHOJ8.

2.2 | Data acquisition: Recommendations

Efficiency is critical when it comes to successful infant MEG data collection; however, it is important to strive for an environment that is not frantic or disruptive to an infant's calm, alert state. Here we provide recommendations for equipment, and suggest experimental design modifications to adult protocols. These equipment recommendations are made for use with a standard adult-sized MEG system with superconducting quantum interference device (SQUID) sensors, but can easily be modified for a system with optically pumped magnetometers (OPM) or an infant-sized helmet system.

2.2.1 | Equipment: Prior to data acquisition

Outside the magnetically shielded room (MSR), it is important to prepare equipment prior to the arrival of the family for head digitization and other processes. The digitization area can be set up with MEG-compatible toys and chairs for the infant and caregiver (Figure 1).

- Digitization device
  As is the case for adult participants, head digitization is important for accurate co-registration and subsequent source localization. When choosing a digitization method for infants, the tolerance level for movement and speed of the digitization process must be considered. Our lab uses the Polhemus FASTrak system (Polhemus, Colchester, VT), which includes a stylus, a receiver attached to a wooden chair, and a sensor placed on the participant's head. The sensor–receiver set will adequately account for participant movement, and manual digitization with the stylus can be done quickly by experienced personnel. For infants, we use a wooden highchair with an attachment for the receiver and the sensor is taped to the top of a soft cloth cap on the infant's head. In principle, other digitization devices may also be used, such as a 3D camera system.
- Digitization highchair
  Most participants ages 5 months or older are able to sit upright in a high chair with five-point VELCRO safety straps and with an adult nearby. However, any infant unable to support their head or sit upright can be held in the arms of a caregiver or research assistant.
- Head position indicator coils
  If a stationary sensor array (i.e., typical SQUID whole head system) is used, it is highly recommended to compensate for any movement of the head in reference to the sensors. Head position indicator (HPI) coils are used to continuously output sinusoidal signals that can be localized offline after the experiment to provide the head position (translation and rotation) relative to the MEG sensors with millisecond accuracy (Ahlfors & Ilmoniemi, 1989). These head

positions will later be used for continuous head movement compensation.

- Infant cap
  An elastic infant-sized cap can be used in order to serve two purposes: (a) for temporary placement of the Polhemus sensor during head digitization, and (b) to adhere the HPI coils to the infant without having to tape the coils directly onto the infant's skin/hair. A soft and stretchy cap that fits snugly onto the infant's head helps to avoid movement of the coils after digitization (Figure 1, top right panel), which is essential for further signal processing and analysis. We recommend having a wide variety of cap sizes to accommodate different head sizes. The cap is secured to the head using a soft VELCRO chin strap that can be easily adjusted. Additionally, pieces of soft medical tape can be used to secure the front of the cap to the infant's forehead to prevent the cap from sliding. Our caps also include holes for the ears to allow easy access to the anatomical points during digitization. The ear holes also ensure that the ears can be accessed throughout the appointment if insert earbuds are used.
- ECG/EOG electrodes
  Electrodes for electrocardiography (ECG) and electrooculography (EOG) should be used to measure fields from the eyes and heart if the infant will tolerate them, as it assists with later artifact removal. The electrodes are placed on the infant during the preparation process. Using pre-prepped disposable electrodes allows the placement to happen quickly. Using small electrodes made specifically for infants ensures that the electrode adhesive does not cause discomfort during application or removal.
- Toys
  Toys that entertain infants are essential equipment for the entire infant MEG process, including preparation. A large collection of toys appropriate to different stages of infant development can be set up for immediate access during digitization. All toys must be tested prior to use to ensure that they are nonferrous and do not interfere with MEG sensors. Examples of toys that can be used during the preparation process include: stacking cups, squishy bath toys, touch-and-feel board books, hand puppets, bubbles, masks, and balls.
- Foam halo
  We suggest placing a foam halo (Travis et al., 2011) around the infant's head after digitization (Figure 1, bottom right panel). This adds a layer of protection between the infant's head and the helmet. The halo can also help to reduce head movement during the MEG measurement.
- Run sheets
  Documenting important information throughout the MEG process on run sheets is critical for subsequent data analysis. Refer to Figure 2 in Section 2.3 for an example.

2.2.2 | Equipment: During data acquisition

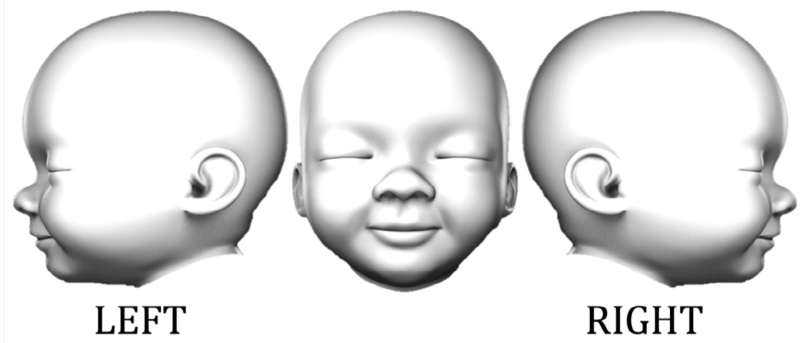
- MEG system
  Both pediatric and adult MEG systems may be used to acquire functional imaging data from infants. For a fixed sensor noise level, a pediatric-sized helmet allows for a higher SNR because the sensors in the helmet are closer to the sources of electrical activity in the infant's head. An adult helmet, on the other hand, allows for a certain degree of movement from infants during data collection while keeping them comfortable and engaged. The ability to move may reduce anxiety in infants who do not like to feel confined. For awake infant protocols, keeping the MEG in an upright position increases success rate and reduces attrition.
- Infant seat in MSR
  When using an adult system, the following adjustments can be made to the setup for upright infant measurements (Figure 3, top panel):
  - Placing an MEG-compatible infant car seat (with all metal components removed) on the seat of the standard MEG chair, positioned so that the top back of the car seat is level with the top of the standard chair.
  - Replacing all adjustable straps from the car seat with soft five-point double-sided VELCRO straps. The VELCRO straps must be long enough to reach over the torso to allow movement of the legs and arms, but keep the infant from falling out or slouching.
  - Adding an appropriately sized head rest to the top of the back of the car seat for head support.
  - Adding a booster cushion to the car seat ensures the infant is seated high enough that their head is positioned above the top of the seat. Having a variety of booster cushion sizes available is helpful to accommodate different ages and sizes.
  - Covering the seat with a soft blanket that can be removed and washed between participants.
  - Placing soft MEG-safe pillows around the sides of the seat for additional support and comfort.

- Toys
  A second set of toys can be set up in the MSR so that they are immediately accessible to the assistant during MEG measurements. Toys can be placed in bins on MEG-safe rolling carts so they can be easily transported as needed. Avoid toys that interfere with the specific study design, for example, toys that rattle or squeak during an auditory paradigm.
- Videos
  Infant-appropriate videos projected onto a screen in the MSR can be used to distract the infant during data acquisition.
- Video recording
  Video monitoring cameras inside the MSR give MEG researchers full view of the infant. We also recommend video recording the sessions using an MEG-safe video setup, which allows for coding behavior after data collection is complete.
- Additional seating in MSR
  An MEG-safe chair can be placed inside the MSR next to the MEG system so that the caregiver can be seated nearby, but out of sight from the infant. The area in front of the MEG system is left clear to easily access the infant as needed.

FIGURE 2 An example of an MEG session run sheet. Documentation of MEG data acquisition parameters, for example, the integrity of the HPI coils and digitization parameters (LPA, RPA). Sketch of an infant head model to document the location used for anatomical landmark digitization

Subject #: ____________________

cHPI accept: Y / N	# of coils accepted: /5	Record Average: Y / N	# Averages:
LPA: _____ RPA: _____	# of additional points: _____	EOG: _____	ECG: _____
MEG file name:			
Bad Channels:			Additional Staff:
Length of time? Triggers seen on acq ☐? # of epochs? EOG +ECG quality: ______?			Researcher: Tech(s):



Notes:____

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2.2.3 | "Toy-waving": The key to successful infant data acquisition

Researchers must be trained to help regulate an infant's mood and behavior during a data collection session. Having skillful professionals focused on reducing infant discomfort in an unfamiliar environment helps to reduce high attrition rates (Bell & Cuevas, 2012). Using toys to produce visual stimulation is a cornerstone of effective technique (Ballard et al., 2017; Hoerneke & Schoch, 2019). This practice of facilitating infant participation in research using toys will be referred to in this section as "toy-waving" (Werner Olsho, Koch, Halpin, & Carter, 1987).

The toy-waver's main goal is to maintain affect and arousal modulation, while ensuring that the infant's environment and position during the appointment complies with the experimental protocol (Kuhl, 1985). The target disposition for infant participants is a state of "pleased interest." Ideally the infant is highly attentive, neither laughing nor crying. Similarly, the ideal arousal level is calmness without drowsiness. Excited infants frequently wave their arms and kick their legs; a crying infant contracts muscles throughout the face, arms, and torso. In either state, the infant response causes muscle and movement artifacts in the MEG data. While efficient movement compensation methods are available, muscle artifacts, especially in the neck and head area, are problematic (Muthukumaraswamy, 2013). Depending on the experiment, a toy-waver can use auditory, visual, tactile, and social stimuli to engage or soothe the participant as needed. The toy-waver must rapidly assess participant preferences and in response, adjust their affect, proximity, and mode of stimulus presentation to evoke the desired infant response.

2.2.4 | Head digitization

The increased level of head movement makes the digitization process especially important for infants. Good representation of the head shape as well as accurate digitization of the cardinal points and HPI coils are essential for accurate source modeling. Once the infant cap is placed onto the head and fastened with the VELCRO strap, the toy-waver uses toys to engage and distract the infant. We suggest collecting a minimum of 200 additional points on the head surface to ensure a comprehensive representation of the head shape. In addition, documenting the precise location of the cardinal points is critical for proper co-registration and subsequent source localization.

External electrodes are placed on the infant at either the beginning or the end of the digitization process. Electrode placement is important in order to obtain a high-quality signal and to prevent the electrodes from being torn off during the measurement. We place two ECG electrodes on the infant to measure the electrical signal of the heart; one electrode placed on the chest slightly to the left of the sternum and the second electrode in a similar location on the back. We also place two EOG electrodes on the infant to measure the electrical signals produced by eye movements; one placed near the orbital rim slightly above the eye and the second placed slightly below the opposite eye. This electrode placement allows us to capture both blinks and saccades, while minimizing the number of electrodes that are used (Figure 3, bottom panel). As with many experimental design modifications directed to reduce infant attrition, researchers may choose to forgo the use of external electrodes if an infant will not tolerate them but would otherwise be successful.

FIGURE 3 Top panel: An infant seated under the MEG dewar in the infant car seat during data collection. Bottom panel: An infant seated in the MEG system showing the placement of the two EOG electrodes (red arrow)

2.2.5 | Infant data collection

Continuous head position tracking, channel saturation monitoring, and online averaging inform the researcher about the quality of the MEG measurement during data acquisition. Because infants can move erratically, continuous head position monitoring is necessary. Channels must be continuously monitored for sources of noise and for saturation. If too many channels become saturated through the course of the measurement, we determine and remove the source of noise before resuming data acquisition. This is important because the signal processing methods that are essential for successful infant data analysis, such as head movement compensation, suffer from channel saturation. Saturation is indicated by the sensor signals presenting as horizontal lines, and is in principle, straightforward to detect. However, continuous visual inspection of all channels in search of saturation is not feasible, and we therefore employ a specific saturation monitor that alerts the operator if too many channels become saturated (Nurminen, 2019).

2.3 | Data acquisition: Reporting

As with adult recordings (Gross et al., 2013), reporting for infant protocols is essential. Reports should include equipment diagrams and specifications with static information about the system setup and run sheets to document information about appointments, such as participant preparation, or details of the stimulus delivery. However, for infant data acquisition, a few extra items are worth reporting. Infant behavior during the MEG session, including periods of crying or excessive movement, should be documented in order to apply data-driven methods to suppress any residual artifacts in the data. Depending on the type of digitization method, it may be difficult to digitize points that are very close to the infant's eyes or ears (e.g., LPA/RPA), and therefore any deviations during digitization from the true locations should be documented on a run sheet and ideally also with a camera to ensure accurate co-registration between MEG data and the head model.

3 | DATA PREPROCESSING FOR INFANT MEG

3.1 | Data preprocessing: Background

Data preprocessing is necessary to suppress noise in the data which contaminates the brain signal of interest. The measured MEG signal is made up of a combination of brain activity, environmental interference (e.g., power lines, electronics), physiological interference (e.g., heart, eye blinks, other muscle activity), and sensor noise (e.g., transducer or electronic noise). Magnetic fields from the brain are extremely weak (Hämäläinen et al., 1993) and the amplitude of interfering signals is often orders of magnitude larger in comparison. With infants, several additional factors adversely affect the SNR. Infants can become fussy and irritable during data collection, resulting in fewer usable trials. Additionally, the smaller head size of infants can increase the distance of the head to the sensors, especially with adult-sized helmets, lowering the SNR. Furthermore, infants tend to move much more than adults inside the helmet, which can lead to a loss of spatial information and potentially result in inaccurate localization of the brain activity, unless properly compensated for (Larson & Taulu, 2017). Below we provide recommendations for noise suppression methods, and suggest parameters to optimize the SNR of infant data. A sample example script demonstrating these stages of analysis for a single participant's data from (Mittag, Larson, Clarke, Taulu, & Kuhl, 2021) is available at https://github.com/ilabsbrainteam/2022-Best-Practices-Infant-MEG.

3.2 | Data preprocessing: Recommendations

3.2.1 | Software

There are a number of packages available for MEG analysis. We use MNE-Python (Gramfort et al., 2013), an open-source Python software package for processing, visualizing, and analyzing human neurophysiological data, including MEG. Specifically for infant data, it contains implementations of the most recent advancements for signal quality enhancement using spatial filtering and movement compensation (M. Clarke, Larson, Tavabi, & Taulu, 2020; Helle et al., 2020).

3.2.2 | Visual inspection

Efficient signal processing is crucial for infant MEG. Modern automated signal processing methods efficiently achieve robust data quality even under very challenging data collection conditions. However, it is always good practice to visually inspect the data before and after applying preprocessing algorithms for artifacts, bad or flat channels, and bad segments. To ensure optimal data quality, we mark all bad channels or segments, and repair or remove these by subsequent processing methods. Any modifications to the data processing made on the basis of visual inspection should be explained in detail to ensure reproducibility.

3.2.3 | External noise suppression

SSS and its temporal extension, temporal signal space separation (tSSS) (Taulu & Hari, 2009; Taulu & Simola, 2006), are methods that compensate for external interference artifacts and are commonly used in MEG preprocessing. They are based on the vector spherical harmonic expansion of multichannel MEG signals under the quasi-static assumption of Maxwell's equations. While SSS is not effective against artifacts arising from sources very close to the sensors (roughly <50 cm), the tSSS method additionally suppresses the contribution of nearby artifact sources by utilizing temporal information. We recommend processing all infant data with tSSS because it is especially useful in cases where multiple people are moving close to the sensor array. When using tSSS with infant data, we recommend adjusting the following parameters based on the age and size of the participant: (a) correlation limit (CL), and (b) tSSS internal subspace. The effect of adjusting the tSSS correlation limit has been studied in detail (M. Clarke et al., 2020; Medvedovsky, Taulu, Bikmullina, Ahonen, & Paetau, 2009) and it is recommended that data with higher SNR use higher correlation limits, while data with lower SNR use lower correlation limits. The internal subspace truncation value for infant populations should be adjusted depending on the size and geometry of the sensor array. A value of 8 for the internal subspace has been recommended (Taulu & Kajola, 2005) and was optimized for adult-sized heads, while six generally yields higher SNR data for infants due to head size and distance from the sensors. The reduced truncation value is justified based on the analysis of the cumulative signal power for different source-to-sensor distances as outlined in Taulu and Kajola (2005).

3.2.4 | Movement compensation

Head movements in MEG distort the magnetic field distribution measured by the sensors (Medvedovsky, Taulu, Bikmullina, & Paetau, 2007). Head movements are common in infants and can result in large errors in source localization. However, head movement compensation can restore localization accuracy even if infant data is collected using adult-sized helmets (Larson & Taulu, 2017). During movement compensation, the time-varying position of the head with respect to the sensors is estimated and the data are transformed to "virtual sensor" locations corresponding to a target head position, specified by the user or software. The recommended target position is the time weighted-average position. This achieves an effect as if the head had remained in a static spatial relationship to the sensors during the MEG measurement.

3.2.5 | HPI coil SNR

Given that movement compensation is essential, the accuracy of head position information is very important. Continuously measuring each HPI coil's SNR and location in reference to the other coils during acquisition ensures that the coils are functioning properly and have not moved on the head. The SNR calculation is based on estimating the amplitudes of the individual HPI signals oscillating at precisely specified frequencies and comparing these amplitudes to the sensor noise level. If fewer than three coils were functional or if the coils moved or during portions of data collection, then it is necessary to remove those segments of data to avoid biasing source localization.

3.2.6 | Physiological noise suppression

Heart artifacts are prominent in infants and young children due to their small body size and the closer proximity of the heart to the sensor array. These artifacts are problematic when compensating for head movements because of the time-varying spatial relationship between the brain and the heart. Multivariate signal processing techniques such as independent component analysis (ICA) and principal component analysis (PCA) (Uusitalo & Ilmoniemi, 1997) can identify and spatially remove noise sources that arise from the body, such as cardiac or blink artifacts.

3.2.7 | Sensor noise suppression

Intrinsic sensor noise is weaker than environmental and physiological noise. However, in cases where the SNR tends to be low, which is typical of infant data, suppressing sensor noise can improve both the data quality and the detectability of the signals of interest. Oversampled temporal projection (OTP) can effectively suppress sensor noise in MEG data (Larson & Taulu, 2018) and can be used in combination with existing methods, such as tSSS (M. Clarke et al., 2020) or other noise suppression algorithms. Parameters of subsequent noise suppression algorithms (e.g., tSSS) may need to be adjusted after the application of OTP (refer to M. Clarke et al., 2020 for details).

4 | SOURCE RECONSTRUCTION FOR INFANT MEG

4.1 | Source reconstruction: Background

A growing number of MEG studies are focusing on source space analyses to directly assess neural generator activity as a function of development (Chen et al., 2019; Kao & Zhang, 2019). MEG source reconstruction consists of two components: computing a forward model that maps neural currents in the brain to MEG sensor values, and choosing a strategy for tackling the corresponding inverse problem that maps MEG data to brain currents. Modeling the sources in infant MEG data is generally the same as in adult data, but has unique challenges due to the immature structure of the infant brain and the lower SNR as compared to adults. Recommendations for infant source reconstruction center around strategies for achieving a high-quality representation of the source space based on anatomical MRI information and methods for minimizing source localization errors, despite low SNR data.

4.2 | Source reconstruction: Recommendations

4.2.1 | Forward modeling for infants

The forward model involves computing the magnetic fields at sensor locations for a given predefined set of source positions and orientations. The result of the forward model computation is a gain matrix, which is a data structure revealing the influence of each candidate source on every sensor in the helmet. The forward model is constructed from four essential elements: (a) a matrix describing the MEG instrumentation information (i.e., the position and sensor type), (b) a conductor model of the head (e.g., boundary element model [BEM] or finite element model [FEM]), (c) a transformation matrix describing the position of the head inside the MEG sensor array, and (d) the source matrix detailing the position and orientation of each candidate source of electromagnetic activity in the brain (in practice, elementary current dipoles). While the sensor geometry information is equally accurate for infant and adult source reconstruction, infant data poses unique challenges for creating an accurate conductor model, translation matrix, and source space model.

4.2.2 | Conductor model for infants

For EEG analysis, the conductor model for infant heads can be particularly complex to construct because in infants, the skull is not fully formed. Sutures and fontanels are highly variable across participants, which makes modeling of the electric conductivity profile difficult and participant-specific. While the electric potential distribution is susceptible to the details of the spatial profile of the electric conductivity in the head, the magnetic field pattern is not as significantly affected by changes in the conductivity geometry. Thus, the infant skull may be modeled as a homogenous conductor without significantly compromising source localization results (Lew et al., 2013). As with adults, the conductor model for infant MEG may be limited to a single homogenous layer, either formed from a sphere or the surface of the inner skull (using a BEM) as described by anatomical MRIs.

4.2.3 | Anatomical source models for infants

When anatomical data is used as a part of the forward model, whether derived from a template or individual MRIs, an additional process of MRI co-registration (of the MRI and head coordinate frames) must be performed (Chella et al., 2019). The resulting transformation matrix, together with estimated head-to-MEG transformation, establishes the proper geometrical relationship between the sources and the sensors.

When individual anatomical MRIs are available for infant participants, the co-registration process is much the same for infants as for adults. However, in addition to being expensive, individual MRIs for infants are typically much more difficult to obtain, so we recommend using suitable age-matched templates from O'Reilly, Larson, Richards, and Elsabbagh (2021), as they overcome many typical issues with infant source modeling (e.g., lack of surface and volumetric anatomical labels). Surfaces from anatomical templates should be warped to match the participant's head digitization. From there, a volumetric or surface source space can be constructed, as with adult data (Gross et al., 2013). In practice, this can be achieved in MNE-Python by using the "mne coreg" manual co-registration tool. In this way, the individual anatomy can be matched as closely as possible by the template. When using a surrogate MRI, free orientation sources should be used even for surface source space (dipoles along the gray–white matter cortical surface boundary) because the cortical folding of the surrogate is not precisely matched to that of the individual.

4.2.4 | Inverse modeling for infants

The inverse model combines measured MEG data with the forward model to estimate the amplitude of brain activity over time, while accounting for sensor noise structure. The steps for performing inverse calculations are largely the same for infants and adults; however, results must be checked when performing inverse calculations on infant data to determine that source localization errors due to low SNR or noise in the data are minimized. There are many potential inverse methods. Regardless of the source localization method, almost all are tested and validated on adult data, not infant data. Therefore, source estimation must be closely examined. Researchers should iteratively produce evidence of the quality of source reconstruction steps and then adjust to minimize errors as needed. Ideally, some sort of known ground truth for localization (e.g., primary auditory onset response in A1) can be used to validate a given approach.

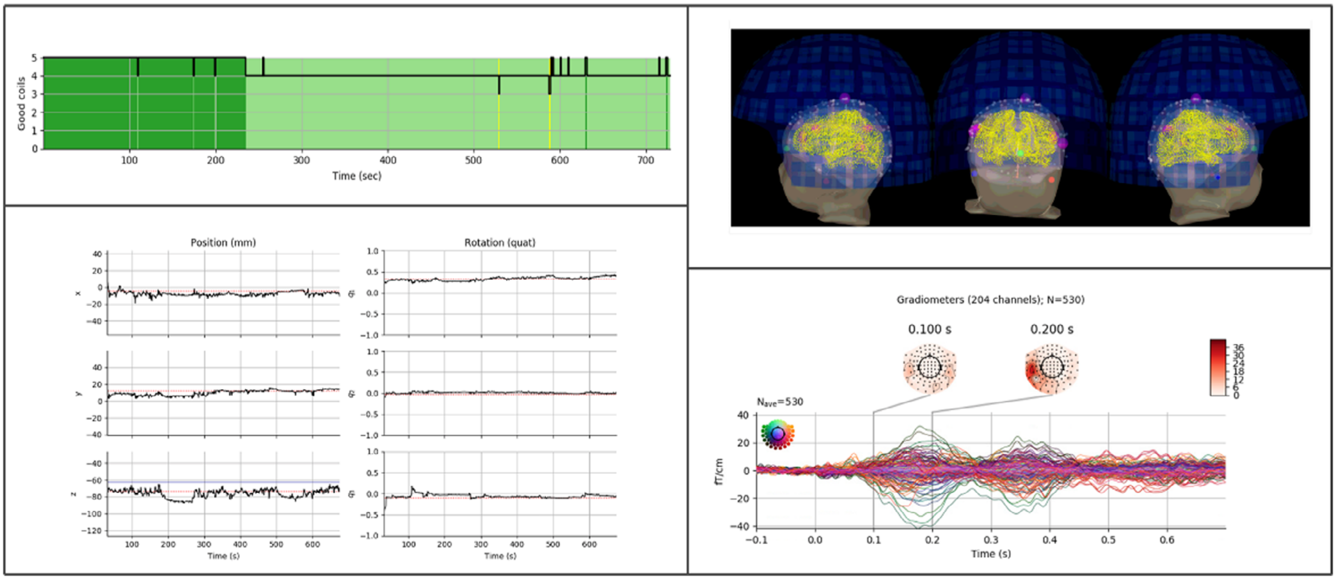

FIGURE 4 An example of plots from a QA report. Top left panel: Coil SNR as a function of time. Colors and y-axis represent the number of "good coils" out of 5. Bottom left panel: Head position deviation as a function of time. Translation shown on the left, rotation shown on the right. Top right panel: Co-registration alignment. Bottom right panel: Evoked response of auditory signal

4.3 | Data preprocessing and source reconstruction: Reporting

Automated data quality reports, produced upon completion of source estimation, are an essential tool for infant researchers. These reports allow rapid visual inspection of the data and the results of both preprocessing and source estimation (Figure 4). These reports allow for inspection of the co-registration alignment, source space, forward model, noise covariance, SNR, and source estimates.

5 | DISCUSSION

In this manuscript, we have discussed the various challenges with infant MEG and proposed some basic best-practice guidelines for data collection, acquisition, and analysis. Using these techniques, we are able to reliably obtain high-quality, robust infant brain data from our adult-sized SQUID system. The goal of this article is to allow our existing pipeline and practices to be used as a foundation for other laboratories to adapt and build upon, and to improve standards for MEG data collection, analysis, and reporting. These guidelines will surely change and adapt as exciting new advances in MEG technology and hardware emerge, including OPM sensors and infant-specific systems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Maggie D. Clarke contributed to writing, conception, design, investigation, methodology, and the supplementary video. Alexis N. Bosseler contributed to writing, investigation, methodology, and the supplementary video. Julia C. Mizrahi contributed to writing, investigation, methodology, and the supplementary video. Erica R. Peterson contributed to writing and investigation. Eric Larson contributed to review and editing and created the sample data pipeline and analysis. Andrew N. Meltzoff contributed to review and editing. Patricia K. Kuhl contributed to review and editing of the manuscript and the supplementary video. Samu Taulu contributed to writing, the conception, and design of the manuscript and provided supervision. All authors contributed to manuscript revision, read, and approved the submitted version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Maggie D. Clarke https://orcid.org/0000-0001-6198-0864
Eric Larson https://orcid.org/0000-0003-4782-5360
Andrew N. Meltzoff https://orcid.org/0000-0001-8683-0547

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