Practical Aspects of Running Developmental Studies in the MEG

Elizabeth W. Pang

Division of Neurology/Department of Paediatrics, Hospital for Sick Children/University of Toronto

Abstract

Developmental neuroimaging studies offer a unique opportunity to gain insight into the underpinnings of various cognitive functions by examining age-related changes in brain structure and function. There is an increasing body of neuroimaging literature discussing issues related to testing children in developmental studies [8]. These deal with fMRI developmental studies and discuss methods [31], data interpretation [40], and theoretical approaches [26]. There has not yet been an equivalent discussion for MEG developmental studies. This paper will address issues specific to data acquisition, analysis, and interpretation for MEG developmental studies.

Keywords

magnetoencephalography (MEG); children; development; source localization

Introduction

Magnetoencephalography (MEG) is a neuroimaging modality that records the tiny magnetic fields generated by neuronal conduction. It offers excellent spatial localization as well as high temporal resolution of neural events. MEG is gaining credibility in the clinical setting as a pre-surgical functional mapping tool (for reviews, see [48–49]) and is establishing itself as a valuable tool for cognitive neuroscience studies (for a review, see [20]). Similar to other popular non-invasive functional neuroimaging modalities (i.e., fMRI and EEG/ERP), MEG has no harmful effects, no side effects, and no long-term detrimental effects. All of these non-invasive modalities are ideal tools for use in research involving healthy populations and are particularly attractive for use in developmental studies and in longitudinal developmental studies.

While these neuroimaging modalities have their relative advantages and disadvantages, the choice of modality upon dependent on the researcher, the availability of the appropriate equipment, and the question being asked. However, regardless of the modality, there is a critical need to do developmental studies, as these offer a unique opportunity to gain insight into the underpinnings of various cognitive functions by relating (or correlating) changes in brain structure to changes in brain function, cognition and behavior [8]. As well, studies of typically developing populations offer a baseline for examining the effect of disease states on the developing neural network. Furthermore, it is only through the use of longitudinal

developmental studies that researchers will finally have the potential to disentangle cause and effect interactions between maturational and disease processes.

While numerous developmental studies have used electrophysiological techniques (namely, EEG and event-related potentials; for reviews, see [1,38,43]), structural MRI (for reviews, see [29,42]), and functional MRI (for examples, see [15,50]), the use of MEG offers the unprecedented opportunity to apply its exquisite spatio-temporal resolution to examining the complexities and intricacies of typical development and, as a consequence, atypical development. The availability of whole head MEG systems, with more than 300 recording sensors, attests to the maturity of MEG instrumentation. Recent advances in source estimation and signal processing (for a review, see [18]) attest to the growing interest and investment in MEG analysis methods and applications. A PubMed search with magnetoencephalography as the keyword showed 2 English publications in 1985; 103 in 1995; and 374 in 2005; however, the same search using magnetoencephalography + children as keywords revealed 0 in 1985; 6 in 1995; and 40 in 2005. Though MEG studies in children are fewer, they show a much steeper trajectory; clearly, there is interest in using MEG to examine topics within the field of developmental neuroscience.

There is now a solid body of neuroimaging literature discussing issues related to testing children in developmental studies. Some of these issues are common across neuroimaging modalities and pertinent to MEG researchers embarking on developmental research. In this regard, the reader is referred to early discussions on practical aspects for acquiring fMRI data in large developmental studies [4,13,27], and more recent discussions on methods [31], interpretation [40], and theoretical approaches [26] to developmental fMRI work. As well, there are guidelines for ERP studies involving children [37,53]. Within the autism research literature, discussions regarding age matching versus performance matching are important to consider if one is interested in testing clinical or developmental groups and comparing brain structure with age, function or behavior [3, 23]. Finally, the reader is referred to a paper discussing the ethics of neuroimaging studies in children [21].

While ethical concerns are uniform across all non-invasive neuroimaging modalities, studies of vulnerable populations (i.e., children and clinical groups) place additional onus on the researcher and merits a brief summary here. Hinton [21] highlights the fact that a child's understanding and capacity to give consent follows a developmental trajectory, but this is neither steady nor predictable; the researcher must maintain ethical guidelines that are dynamic and appropriate for the individual child. In addition to the commonly discussed ethical concerns of obtaining consent and assent, and assessing risk, Hinton also discusses the ethics of comparing pediatric data to adult norms which may result in misinterpretations and the misapplication of data due to the wrong labeling of correlations and associations as causes. These are important issues that require consideration prior to analyzing and interpreting developmental studies.

Another concern that is common to all neuroimaging modalities but would merit a brief discussion here is the presumption that hardware designed for adult use is directly applicable to use in children – particularly young children. Byars et al. [4] raised the issue that children had difficulty pressing the buttons on their response pad as these were designed for adult-

sized hands. They eventually resolved this by using a pneumatic ball for their studies. A more recent, and very innovative, solution has been the implementation of an eye tracking device to capture subject responses [19]. These authors suggest that this solution is particularly effective for “special populations” including children – this solution holds good potential and merits further testing by other groups. Another hardware issue for MEG is the adult sized sensor helmet, which is not ideal for small heads. This is discussed more extensively in a later section. There have been attempts to develop smaller custom sized helmets [24,54], but these are not commonly available. However, the hope is that as more groups pursue developmental studies and highlight the need for new pediatric developments, this will spur commercial developments and industry to invest in developing hardware that is child-appropriate.

Having touched upon matters common to all neuroimaging modalities, this paper will now focus on topics specific to the use of MEG to acquire data in children and to conduct large-scale developmental studies. In particular, the issues, confounds, and caveats around MEG data acquisition, data analysis, and data interpretation will be discussed.

MEG data acquisition for developmental studies

The ideal data acquisition session would include all of the following factors: collection of clean data with high signal and low noise, high performance and attention on all tasks by the subject, and the entire session completed in as short a time as possible. This ideal situation is attainable in children but requires planning and the researcher giving *a priori* consideration to technical, subject and task factors that impact data acquisition.

Technical factors

The biggest challenge to obtaining clean data in young children is movement artifact. While voluntary movement artifacts (muscle and blinks) are a challenge not unique to MEG, and fMRI solutions to both train the subject and immobilize the head [4] are applicable to MEG, there are some physiological movement artifacts that are problematic. Since young children have shorter necks, their hearts and lungs are closer to the MEG sensors; furthermore, the cardiorespiratory cycle is more dynamic in children with higher cardiac and respiratory rates; these factors compound to introduce frequent and large motion artifacts. Post-hoc signal processing techniques aimed at deriving a set of components to explain ocular artifact [39], head movements [55], or other artefacts [52] have been developed, but they do not seem to be widely used, and have not yet been validated in paediatric populations.

The shorter necks in children present a second technical problem. The MEG helmet, designed for adult neck lengths and head, is not optimal for children. Their shorter necks and smaller heads mean that most of the surface of their heads is distant from the MEG sensors. Since magnetic signals decrease as a function of distance, this is a serious challenge. Positioning the head so that the region of interest is closest to the sensors is an effective strategy [12,32]; however, this requires that one have an *a priori* expectation of the sites of interest and, that these neural sites are proximal to each other.

In adolescents, the biggest technical challenge is unidentified magnetic artifact. The standard MRI exclusions of dental braces and appliances are effective at excluding subjects whose data would clearly be contaminated by magnetic artifact. We also screen for tattoos [28]; however, we still find that the increasing prevalence and younger use of dermal and intradermal pigment (i.e., permanent cosmetics) have led to surprises and ultimately loss of MEG data. In our female teenage cohort, we have a 50% data loss statistic due to unidentified magnetic artifact. Even compliance with standard MRI recommendations [44] to remove all cosmetics 24 hours prior to coming into the lab, we suspect that a microscopic residue remains on the skin, and, if this contains metallic pigment, it will contaminate the MEG data. However, it is impossible to predict when this will happen. A related problem is the use of coloured contact lenses in our myopic subjects; we have had instances where the lens pigment has contained a metallic additive. Though relatively innocuous to MRI, residual eye makeup and contact lenses can introduce artifacts that overwhelm the MEG neural data. While some source analysis techniques can separate dental artifact from neural signal [7], or the application of a high-pass filter might remove some slow wave drift, the artifacts just described are particularly troublesome since the eyes are adjacent to the prefrontal and orbitofrontal lobes, regions of great interest in the teen brain, but difficult to separate *post hoc*. We have not yet found a solution to this costly and significant problem.

Subject factors

With regard to subject factors, MEG offers a unique benefit relative to fMRI. Byars and colleagues [4] report that anxiety and claustrophobia are significant concerns in the fMRI, especially for young children. These factors are less concerning in the MEG, as children report that the quieter MEG environment is more comfortable and less anxiety-producing. However, it is still essential to ensure that young children have adequate time to acclimatize, prepare, train and become familiar with the task and testing environment. Additionally, different children with different personalities will require different amounts of time.

Counterbalancing of hand response is standard practice in adult subjects; however, young subjects have a difficult time responding frequently with their non-dominant hand and often will switch subconsciously to their preferred hand. The literature shows that, although hand preference appears as early as 3 years of age, it is not well-integrated until 8–9 years of age [14]. Unlike fMRI block designs, accuracy and trial-by-trial reaction times can be captured in the MEG, thus maintaining a consistent and accurate response is important. Therefore, it may be that counterbalancing is not possible, or some accommodation must be made, when testing young children.

The selection of age range for a given study is an important topic. The lower age limit must be anchored in behavioural data demonstrating that the neural processes in question are emerging in that age group; although in reality, the lower range is often determined by whether children can cooperate for testing in the MEG environment. The upper age limit should be determined, partially by behavioural data (i.e., the upper limit is greater than the age of competence on task), and mostly by the brain region of interest. It is known that brain regions mature at different rates, and some regions are not mature until well into young adulthood [5,16]. If the cognitive processes of interest are subsumed in these brain regions,

then the age range of the developmental study must include older subjects. Alternatively, studies addressing research questions pertaining to a process or neural area known to mature early would make better use of neuroimaging resources by having a younger upper limit.

Finally, even with children of the same age, there are tremendous differences in abilities and skills. The study must incorporate some objective measure of task difficulty and performance, so that these can be taken into account when making between-subject and/or between-group comparisons; if this step is omitted, one runs the danger of not capturing development but rather effort, attention, task ability, or cognitive strategy. This is discussed further in the next section.

Task factors

Concomitant with subject factors are issues of paradigm and task design. Given the MEG's exquisite timing properties, it is tempting to create fast-paced, complicated paradigms aimed at answering complex questions while maintaining the subject's interest. However, a task that works superbly for adults may not be directly translatable to children. Tasks designed to maintain arousal and alertness in a healthy adult, would probably engender frustration and resignation in a young participant. Thus, constructing a task for use along the developmental continuum is challenging; however, if one wants to track the development of neural substrates underlying one specific cognitive function, then both task and performance must be equivalent across the age groups.

Having said this, there is also good reason to support the counter argument that the same tasks should not be used in the youngest and oldest groups so as to avoid floor and ceiling effects. An adult completing an excessively easy task may require fewer neural nodes to be active in the network, show smaller activations of the same nodes, or require additional nodes to maintain attention and interest. On the other hand, a young child completing a frustratingly difficult task may: produce insufficient numbers of correct trials for analyses, show fewer nodes or smaller activations reflecting their inability to do the task, or show more nodes and larger activations reflecting a compensatory strategy or additional effort invested in the task. Possible solutions are to develop child friendly versions of traditional neuropsychological tasks that will engage the child while probing the same processes as the adult versions, or, develop paradigms with adaptive pacing so that subjects can work through the task at their own speed.

Again, the advantage of MEG over fMRI is its excellent temporal resolution. The benefit of using MEG in developmental studies is that one important marker of maturation is the speeding of latencies and response times. Creative theory-driven task designs, and the use of image subtractions or task contrasts, can dissociate specific neural components and track their maturation relative to other components within the neural network.

MEG data analyses for developmental studies

Dependent variables from MEG data

MEG evoked data are usually studied in the time domain and dependent variables such as peak latency, interpeak latency and amplitude/magnetic field strength or power can be

measured and compared. These variables can be extracted from either sensor or source space. MEG induced data are usually studied in the frequency domain and dependent variables such as synchrony/desynchrony, and phase measures, such as coherence and connectivity, can be examined.

Incorporating age as an independent variable in MEG analyses

Typically, there are two strategies for incorporating age as an independent variable for statistical testing. One is to divide the entire age continuum into smaller, equally spaced ranges and acquire equal numbers of subjects within each range. This allows statistical testing using analysis of variance tests with age as a between-groups measure. Further, a control and clinical group could be acquired, and the control/clinical contrast can be incorporated as another between-subjects factor. There are several limitations to this approach. One is the presumption that effect size is homogenous across age groups. ERP data has demonstrated that sensory evoked potentials (for example, the visual evoked potential) are largest in infants and decrease in amplitude with maturity [10]; however, cognitive ERP components (for example, the P300) are smaller in children and increase with age [25]. From these studies, we know that these changes are non-linear and we can therefore presume that effect sizes in the MEG are also not homogeneous across age groups. A second limitation of this approach is the relatively arbitrary creation of sub-groups by specifying an age range. For example, if ages 2–4 years are selected as an age range, then it is not clear that a 3 year 11 month old child is very different from a 4 year 1 month old child, yet they would be in different groups while a 2 year 1 month old would be in the same group as the former. Although this is a standard and accepted practice, it is clear that there are inherent problems.

The second common data analysis strategy, using age as a variable in a regression analysis, also has advantages and disadvantages. The advantage is that age is treated as a continuous variable, which is more accurate. However, the disadvantage is that attempts to fit brain changes onto a line are over-simplified. Both cellular [35] and structural MRI [5,16] studies demonstrate that brain changes have periods of overgrowth and pruning following, mostly likely, a third- or fourth-order polynomial equation rather than a linear or curvilinear course. Attempting to fit a regression line to this function would result in missing brief windows of growth and regression.

Determining statistical thresholds for MEG data

With source estimation images, it is important to identify source locations that have activity significantly greater than noise. In MEG, unlike fMRI, there is no generally accepted method for setting statistical thresholds; however, a strategy that is increasingly used is permutation testing [6]. Permutation testing requires that combinations of active and control segments for the two populations are combined to create a null distribution. It then sets a threshold by computing the probability that a source exists at the identified location by identifying voxels with low probability of being a false positive. Gaillard and colleagues [13], in discussing fMRI data, caution that the application of adult thresholds to children's data may be overly conservative, as children have poorer signal-to-noise ratios and thus may need lower activation thresholds. More recent work has demonstrated that neural activity is

more variable, that is, “noisy”, in children [33,34]; another factor contributing to the poorer signal-to-noise ratio. This strongly suggests that separate thresholds for the adult and child groups need to be computed.

MEG data interpretation for developmental studies

The MEG dataset is dense and offers many dimensions for analyses. When compounded with the richness inherent to examining development, the numbers of possibilities for characterizing and interpreting age-related impact increase considerably. Again, there are many ways to analyze, and therefore, interpret MEG data. However, in keeping with the focus of this paper, this section will concentrate on the anatomical and neurophysiological developments that can impact observed results and describe situations where a researcher unfamiliar with these developmental changes could wrongly impute an interpretation.

Anatomical changes with development

There are many anatomical changes that happen with age but the two that have the most impact on MEG recordings are changes in head size and morphological changes in brain structure.

With regard to head size, the need for child-sized MEG helmets was raised in an earlier section of this paper. The implication of having a smaller head size will now be discussed. As magnetic field strength falls off with the square of the distance from the sensor, and most MEG helmets are designed to fit 90% of adult heads, despite the fact that a 5–7 year old child’s head may be only 10% smaller than an adult’s [13], there can still be a discrepancy of several centimeters from the head surface to the sensor. This distance means that the signal acquired at the sensor is much smaller in the child than in the adult. Immediately, this affects the signal-to-noise ratio and the measurements of power and global field strength. Thus, between-group comparisons (i.e., adults versus children) looking at absolute differences in power, for example, should be interpreted with caution. Instead, it would be better to incorporate a control or baseline task comparison within groups, so that power changes are assessed as proportional changes within age. This will account for the difference in baseline recordings. A second implication of having a smaller head size is that cortical structures are closer together, and often active at the same time. Since equivalent current dipole modeling has difficulty with spatially proximal sources [36] and beamformer analyses have difficulties with temporally correlated sources (although recent advances in source suppression modeling are addressing this issue, see [41]), these difficulties are exacerbated when studying the pediatric brain.

The second significant anatomical development involves morphological changes of the brain. This includes both changes in sulcal structure and folding, as well as changes in cortical thickness. With regards to the former, due to a property of magnetic fields, MEG data are best acquired when the neuronal population is oriented tangentially in the brain, that is, on the walls of the sulci. MEG recordings are “blind” to generators in a radial orientation; that is, MEG cannot see radial sources on the cortical surface. One important maturational change is the increase in sulcal folding and sulcal depth with age; thus, MEG signal strength

improvements may not necessarily be a function of age or development but simply, location on the sulcus and the physics of magnetic fields.

Related to changes in sulcal structures are changes in cortical thickness. High resolution MRI has shown nonlinear changes in cortical gray matter, with a pre-adolescent increase followed by a post-adolescent decrease. These cortical gray matter changes are regionally specific with developmental curves for the frontal and parietal lobe peaking at about age 12 and for the temporal lobe at about age 16; whereas cortical gray matter continues to increase in the occipital lobe through age 20 [15,29,45,47,57]. Further complicating this matter, it is now known that there are robust sex differences in the developmental trajectories for nearly all structures, with peak gray matter volumes generally occurring earlier for females with as much as a 2 year lag in males [9,30].

There are four immediate implications that arise from these combined structural changes. The first implication is with regards to warping pediatric data into standard adult MRI space to identify neural structures. The distortion from warping children's brains into either adult atlas (Montreal Neurological Institute, or, Talaraich & Tournoux [51]) will introduce an error from several millimeters to as much as a centimeter [13]. Choosing an appropriate pediatric atlas [11,56] and using it are essential. The second implication is with regards to grand averaging source localization data within a group of pediatric subjects. Given the changes in sulcal morphology and cortical density, it is critical to group subjects into small age ranges, possibly divided by gender, and then normalize onto age- and sex- matched templates. The third implication is the computation of head models for source localization. Some groups use a common head model for source localization and overlay their MEG results onto a template MRI. With adult data, this is an acceptable practice, but clearly, this is not acceptable for developmental studies. This creates a substantial increase in budgets for pediatric studies as individual MRIs must be obtained, but clearly, the benefits of overlaying functional data back onto accurate brain structures outweigh the costs of obtaining the MRI. The fourth implication is that changes in sulcal folding and cortical thickness may present inaccurate localizations and points to the potential need to include EEG investigations as a complementary modality to MEG. The combination of EEG, which can record radial sources on the cortical surface, and MEG, which can record within sulcal folds, would facilitate source localization and provide a complete picture of brain activity [1]. The impact of these implications is even more important in clinical pediatric populations where brain morphology and development are more atypical.

Neurophysiological changes with development

There are significant neurophysiological changes that happen with age. These include myelination, changes in synaptic density, and changes in the frequency content of the brain's oscillatory states.

Myelination in the brain is systematic, with primary sensory and motor areas myelinating first and progressing to parietal and frontal association areas; this process is not completed until young adulthood [2, 46, 58]. Myelination provides the bulk of regional brain size and establishes synaptic connections; and with the additional inputs of experience, exposure, learning, and maturity, it solidifies the neural network. Increased myelination represents

increased efficiency via shorter latencies and more consolidated networks. In the child's brain, immature myelination translates into less well formed, less efficient, and more widespread activations; thus, a more diffuse and smaller signal.

Myelination progresses in a linear fashion, while synaptic density in gray matter shows spurts and stops. The ratio of gray to white matter is greater in children than in adults [15] with gray matter synaptic density increasing and peaking between 4 to 8 years, then pruned with a second peak in the teenage years and further pruning to reach adult densities in late adolescence [17,22]. The MEG signal reflects the synchronized mass action of neurons, so with waxing and waning synaptic densities, the MEG signal (thus, SNR) is affected; possibly resulting in source mislocalization. With the changes in both myelination and synaptic density, MEG's millisecond temporal resolution is ideal for capturing the fine-tuning and increasing specialization of neural networks.

EEG frequency content also changes with age. Maturation is accompanied by a reduction in the low frequency components. The delta (< 4 Hz) and theta (4 to 7 Hz) bands predominate during early childhood; alpha (8 to 12 Hz) emerges in early childhood and increases into early adolescence; beta (13 to 30 Hz) continues to mature into adulthood, with beta and gamma (30 to 70 Hz) reflecting some attention and cognitive functions [1]. When making spectral comparisons between age groups, one needs to be wary of interpreting these known developmental changes as age-dependent task-related changes.

Summary: Reiterating the Need for MEG developmental studies

MEG methods can monitor brain processes in real time, capturing fast neural events and high-frequency oscillations, and permitting functional brain imaging at millisecond resolution through source analysis of high density maps. It can be used as a direct measure of the spatio-temporal dynamics of neural activation associated with a wide variety of cognitive processes and their development. Furthermore, due to its non-invasive nature, it can be used repeatedly without problems in longitudinal studies.

MEG holds great potential as a method for developmental studies; however, there are many processes interacting in the developing brain and body that impact MEG signal acquisition, analysis and interpretation. One needs to be aware of these and work towards finding strategies for addressing them.

In summary, while this paper has highlighted the need for MEG developmental studies, the real need is for multimodal neuroimaging studies where each modality compensates for the limitations of the other. With this complementary approach and the inclusion of cognitive and behavioural assessments, significant advances will be made in the field of developmental cognitive neuroscience, where complex questions of typical and atypical development can be addressed.

Acknowledgments

This work was supported by Canadian Institutes of Health Research (CIHR) MOP-81161. The author would like to thank Matt MacDonald and Travis Mills for comments on earlier versions of this manuscript. The author would also like to thank the many dedicated and determined research assistants, technologists, graduate students and post-docs

who have made developmental studies possible and successful in our institution. Finally, thanks to the many young participants and their families who volunteer for studies in the Sick Kids MEG lab. Without the gift of their time and energy, these studies would not be possible.

References

1. Banaschewski T, Brandeis D. Annotation: What electrical brain activity tells us about brain function that other techniques cannot tell us – a child psychiatric perspective. *Journal of Child Psychology and Psychiatry*. 2007; 48(5):415–435. [PubMed: 17501723]
2. Benes FM, Turtle M, Khan Y, Farol P. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. *Archives of General Psychiatry*. 1994; 51:477–484. [PubMed: 8192550]
3. Burack JA, Iarocci G, Flanagan TD, Bowler DM. On mosaics and melting pots: Conceptual considerations of comparison and matching strategies. *Journal of Autism and Developmental Disorders*. 2004; 34:65–73. [PubMed: 15098959]
4. Byars AW, Holland SK, Strawsburg RH, Bommer W, Dunn S, Schmithorst VJ, Plante E. Practical aspects of conducting large-scale functional magnetic resonance imaging studies in children. *Journal of Child Neurology*. 2002; 17:885–889. [PubMed: 12593460]
5. Caviness VS, Kennedy DN Jr, Richelme C, Rademacher J, Filipek PA. The human brain age 7–11 years: A volumetric analysis based on magnetic resonance images. *Cerebral Cortex*. 1996; 6:726–736. [PubMed: 8921207]
6. Chau W, McIntosh AR, Robinson SE, Schulz M, Pantev C. Improving permutation test power for group analysis of spatially filtered MEG data. *NeuroImage*. 2004; 23:983–996. [PubMed: 15528099]
7. Cheyne D, Bostan AC, Gaetz W, Pang EW. Event-related beamforming: A robust method for presurgical functional mapping using MEG. *Clinical Neurophysiology*. 2007; 118:1691–1704. [PubMed: 17587643]
8. Crone EA, Poldrack RA, Durston S. Challenges and methods in developmental neuroimaging. *Human Brain Mapping*. 2010; 31:835–837. [PubMed: 20496374]
9. De Bellis MD, Keshavan MS, Beers SR, Hall J, Frustaci K, Masalehdan A, Noll J, Boring AM. Sex differences in brain maturation during childhood and adolescence. *Cerebral Cortex*. 2001; 11:552–557. [PubMed: 11375916]
10. Dustman RE, Snyder EW. Life-span changes in visually evoked potentials at central scalp. *Neurobiology of Aging*. 1981; 2:303–308. [PubMed: 7335148]
11. Fonov V, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL. Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage*. 2011; 54:313–327. [PubMed: 20656036]
12. Gaetz W, Otsubo H, Pang EW. Magnetoencephalography for clinical paediatrics: The effect of head positioning on measurement of somatosensory evoked fields. *Clinical Neurophysiology*. 2008; 119:1923–1933. [PubMed: 18579439]
13. Gaillard WD, Grandin CB, Xu B. Developmental aspects of pediatric fMRI: Considerations for image acquisition, analysis and interpretation. *NeuroImage*. 2001; 13:239–249. [PubMed: 11162265]
14. Gesell A, Ames LB. The development of handedness. *Journal of Genetic Psychology*. 1947; 70:155–175. [PubMed: 20260602]
15. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*. 1999; 2:861–863. [PubMed: 10491603]
16. Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL. Quantitative magnetic resonance imaging of human brain development: ages 4–18. *Cerebral Cortex*. 1996; 6:551–560. [PubMed: 8670681]
17. Goldman-Rakic PS. Development of cortical circuitry and cognitive function. *Child Development*. 1987; 58:601–602. [PubMed: 3608641]
18. Handy, TC., editor. *Brain Signal Analysis – Advances in Neuroelectric and Neuromagnetic Methods*. Cambridge MA: MIT Press; 2009.

19. Hannula DF, Althoff RR, Warren DE, Riggs L, Cohen NJ, Ryan JD. Worth a glance: using eye movements to investigate the cognitive neuroscience of memory. *Frontiers in Human Neuroscience*. 2010; 4:166.doi: 10.3389/fnhum.2010.00166 [PubMed: 21151363]
20. Hari R, Parkkonen L, Nangini C. The brain in time: insights from neuromagnetic recordings. *Annals of the New York Academy of Sciences*. 2010; 1191:89–109. [PubMed: 20392277]
21. Hinton VJ. Ethics of neuroimaging in pediatric development. *Brain and Cognition*. 2002; 50:455–468. [PubMed: 12480490]
22. Huttenlocher PR. Synaptic density in human frontal cortex - Developmental changes and effects of aging. *Brain Research*. 1979; 163:195–205. [PubMed: 427544]
23. Jarrold C, Brock J. To match or not to match? Methodological issues in autism- related research. *Journal of Autism and Developmental Disorders*. 2004; 34:81–86. [PubMed: 15098961]
24. Johnson BW, Crain S, Thornton R, Tesan G, Reid M. Measurement of brain function in pre-school children using a custom sized whole-head MEG sensor array. *Clinical Neurophysiology*. 2010; 121:340–349. [PubMed: 19955015]
25. Johnstone SJ, Barry RJ, Anderson JW, Coyle SF. Age-related changes in child and adolescent event-related potential component morphology, amplitude and latency to standard and target stimuli in an auditory oddball task. *International Journal of Psychophysiology*. 1996; 24:223–238. [PubMed: 8993997]
26. Karmiloff-Smith A. Neuroimaging of the developing brain: Taking “developing” seriously. *Human Brain Mapping*. 2010; 31:934–941. [PubMed: 20496384]
27. Kotsoni E, Byrd D, Casey BJ. Special considerations for functional magnetic resonance imaging of pediatric populations. *Journal of Magnetic Resonance Imaging*. 2006; 23:877–886. [PubMed: 16649204]
28. Kreidstein ML, Giguere D, Freiberg A. MRI interaction with tattoo pigments: case report, pathophysiology and management. *Plastic & Reconstructive Surgery*. 1997; 99:1717–1720. [PubMed: 9145144]
29. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*. 2006; 30:718–729. [PubMed: 16887188]
30. Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, Blumenthal JD, Lerch J, Zijdenbos AP, Evans AC, Thompson PM, Giedd JN. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *NeuroImage*. 2007; 36:1065–1073. [PubMed: 17513132]
31. Luna B, Velanova K, Geier CF. Methodological approaches in developmental neuroimaging studies. *Human Brain Mapping*. 2010; 31:863–871. [PubMed: 20496377]
32. Marinkovic K, Cox B, Reid K, Halgren E. Head position in the MEG helmet affects the sensitivity to anterior sources. *Neurology and Clinical Neurophysiology*. 2004; 30:1–6.
33. McIntosh AR, Kovacevic N, Itier RJ. Increased brain signal variability accompanies lower behavioral variability in development. *PLoS Comput Biol*. 2008; 4(7):e1000106.doi: 10.1371/journal.pcbi.1000106 [PubMed: 18604265]
34. Misisic B, Mills T, Taylor MJ, McIntosh AR. Brain noise is task dependent and region specific. *Journal of Neurophysiology*. 2010; 104:2667–2676. [PubMed: 20844116]
35. Moore JK, Guan Y-L. Cytoarchitectural and axonal maturation in human auditory cortex. *Journal for the Association for Research in Otolaryngology*. 2001; 2:297–311.
36. Pang EW, Gaetz W, Otsubo H, Chuang S, Cheyne D. Localization of auditory N1 in children using MEG: Source modeling issues. *International Journal of Psychophysiology*. 2003; 51:27–35. [PubMed: 14629920]
37. Picton TW, Bentin S, Berg P, Donchin E, Hillyard SA, Johnson R Jr, Miller GA, Ritter W, Ruchkin DS, Rugg MD, Taylor MJ. Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology*. 2000; 37:127–152. [PubMed: 10731765]
38. Picton TW, Taylor MJ. Electrophysiological evaluation of human brain development. *Developmental Neuropsychology*. 2007; 31:249–278. [PubMed: 17559326]

39. Picton TW, van Roon P, Armilio ML, Berg P, Ille N, Scherg M. The correction of ocular artifacts: a topographic perspective. *Clinical Neurophysiology*. 2000; 111:53–65. [PubMed: 10656511]
40. Poldrack RA. Interpreting developmental changes in neuroimaging signals. *Human Brain Mapping*. 2010; 31:872–878. [PubMed: 20496378]
41. Quraan MA, Cheyne D. Reconstruction of correlated brain activity with adaptive spatial filters in MEG. *NeuroImage*. 2010; 49:2387–2400. [PubMed: 19850135]
42. Rivkin MJ. Developmental neuroimaging of children using magnetic resonance techniques. *Mental Retardation and Developmental Disabilities Research Reviews*. 2000; 6:68–80. [PubMed: 10899799]
43. Segalowitz SJ, Davies PL. Charting the maturation of the frontal lobe: An electrophysiological strategy. *Brain and Cognition*. 2004; 55:116–133. [PubMed: 15134847]
44. Smith FW, Crosher GA. Mascara - an unsuspected cause of magnetic resonance imaging artefact. *Magnetic Resonance Imaging*. 1985; 3:287–289. [PubMed: 4079676]
45. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AS. Mapping cortical change across the human lifespan. *Nature Neuroscience*. 2003; 6:309–315. [PubMed: 12548289]
46. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience*. 1999; 2:859–861. [PubMed: 10491602]
47. Sowell ER, Thompson PM, Rex DE, Kornsand DS, Jernigan TL, Toga AW. Mapping sulcal pattern asymmetry and local cortical surface gray matter distribution in vivo: maturation in perisylvian cortices. *Cortex*. 2002; 12:17–26.
48. Stefan H. Magnetic source imaging. *Revue Neurologique (Paris)*. 2009; 165:742–745.
49. Stufflebeam SM, Tanaka N, Ahlfors SP. Clinical applications of magnetoencephalography. *Human Brain Mapping*. 2009; 30:1813–1823. [PubMed: 19378272]
50. Szaflarski JP, Schmithorst VJ, Altaye M, Byars AW, Ret J, Plante E, Holland SK. A longitudinal functional magnetic resonance imaging study of language development in children 5 to 11 years old. *Annals of Neurology*. 2006; 59:796–807. [PubMed: 16498622]
51. Talarach, J., Tournoux, P. *Atlas of the Human Brain: 3-Dimensional Proportional System – An Approach to Cerebral Imaging*. New York NY: Thieme; 1988.
52. Taulu S, Hari R. Removal of magnetoencephalographic artifacts with temporal signal-space separation: demonstration with single-trial auditory-evoked responses. *Human Brain Mapping*. 2009; 30:1524–1534. [PubMed: 18661502]
53. Taylor JM, Baldeweg T. Application of EEG, ERP and intracranial recordings to the investigation of cognitive functions in children. *Developmental Science*. 2002; 5:318–334.
54. Tesan G, Johnon BW, Reid M, Thornton R, Crain S. Measurement of neuromagnetic brain function in pre-school children with custom sized MEG. *Journal of Visualized Experiments*. 2010; 36doi: 10.3791/1693
55. Wehner DT, Hämäläinen MS, Mody M, Ahlfors SP. Head movements of children in MEG: quantification effects on source estimation and compensation. *NeuroImage*. 2008; 40:541–550. [PubMed: 18252273]
56. Wilke M, Holland SK, Altaye M, Gaser C. Template-O-Matic: a toolbox for creating customized pediatric templates. *NeuroImage*. 2008; 41:903–913. [PubMed: 18424084]
57. Wilke M, Krägeloh-Mann I, Holland SK. Global and local development of gray and white matter volume in normal children and adolescents. *Experimental Brain Research*. 2007; 178:296–307. [PubMed: 17051378]
58. Yakovlev, PI., Lecours, AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A., editor. *Regional Development of the Brain in Early Life*. Oxford: Blackwell Scientific; 1967. p. 3-70.