

Pediatric neuroimaging using magnetic resonance imaging during non-sedated sleep

Douglas C. Dean III · Holly Dirks · Jonathan O’Muircheartaigh · Lindsay Walker ·
Beth A. Jerskey · Katie Lehman · Michelle Han · Nicole Waskiewicz · Sean C. L. Deoni

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Abstract

Background Etiological studies of many neurological and psychiatric disorders are increasingly turning toward longitudinal investigations of infant brain development in order to discern predisposing structural and/or functional differences prior to the onset of overt clinical symptoms. While MRI provides a noninvasive window into the developing brain, MRI of infants and toddlers is challenging due to the modality’s extreme motion sensitivity and children’s difficulty in remaining still during image acquisition.

Objective Here, we outline a broad research protocol for successful MRI of children under 4 years of age during natural, non-sedated sleep.

Materials and methods All children were imaged during natural, non-sedated sleep. Active and passive measures to reduce acoustic noise were implemented to reduce the likelihood of the children waking up during acquisition. Foam cushions and vacuum immobilizers were used to limit intrascan motion artifacts.

Results More than 380 MRI datasets have been successfully acquired from 220 children younger than 4 years of age within the past 39 months. Implemented measures permitted children to remain asleep for the duration of the scan and allowed the data to be acquired with an overall 97% success rate.

Conclusion The proposed method greatly advances current pediatric imaging techniques and may be readily implemented in other research and clinical settings to facilitate and further improve pediatric neuroimaging.

Keywords Magnetic resonance imaging · Pediatric imaging · Brain development · Neurodevelopment · Sleep · Children

Introduction

MRI has become the modality of choice for neurological and psychiatric neuroimaging due to its exquisite anatomical tissue contrast, safety (i.e. no ionizing radiation), and the ability to investigate both anatomical structure and physiological function [1]. However, MRI is also sensitive to subject motion, which causes image blurring, ghosting and other artifacts that degrade image quality. Participants are often required to remain motionless for 40 min or longer, which can be a daunting task for subjects. For pediatric populations, including children younger than 4 years of age, this challenge is magnified by the loud noise of the scanner during image acquisition, and the intimidating “dark tunnel” that can quickly induce fear and anxiety [2]. In older children (older than 4), this anxiety can be alleviated through gradual pre-training in an “MRI-like” environment (i.e. a 0-Tesla MRI simulator or mock scanner) [3, 4]. Motion artifacts can also be reduced through visual feedback, in which cameras monitor the child’s head position and relay this information to the child as a movie or game throughout the scan [5]. Unfortunately, younger children can be less responsive to training as they may not fully comprehend or remember the instructions given to them, and such measures are unlikely to be successful in infants or toddlers. As the time interval between birth and 4 years of age is one of the most dynamic and vulnerable neurodevelopmental periods [6–9], the ability to longitudinally follow the developing brain is increasingly more important toward understanding

D. C. Dean III (✉) · H. Dirks · J. O’Muircheartaigh · L. Walker ·
K. Lehman · M. Han · N. Waskiewicz · S. C. L. Deoni
Advanced Baby Imaging Lab, School of Engineering,
Brown University, Providence, RI 02912, USA
e-mail: douglas_dean_iii@brown.edu

J. O’Muircheartaigh
Department of NeuroImaging Sciences, King’s College London,
Institute of Psychiatry, Delaware Crespigny Park, London, UK

B. A. Jerskey
Department of Human Behaviour and Psychiatry,
Warren Alpert Medical School, Brown University,
Providence, RI, USA

typical brain maturation as well as the etiology and pathogenesis of neurodevelopmental disorders.

Current clinical imaging practices of children younger than 4 years of age routinely involve the use of sedatives or general anesthetics to increase compliance and minimize intra-scan motion artifacts [10, 11]. While justifiable in a clinical setting, associated risks such as hypoxemia [12] and neurotoxic effects on development [13] make their use unethical in research settings that involve healthy children. Beyond ethical considerations, anesthesia also carries economic implications, requiring additional highly trained staff and monitoring equipment, beyond the drugs themselves [2].

In light of these considerations, research imaging of young children is typically performed during natural, non-sedated sleep [8, 14, 15]. Although this strategy eliminates risks associated with sedation, it can be challenging to get an infant or toddler to fall asleep in the novel environment of the MRI center, and to remain asleep throughout the MRI scan. Consequently, the majority of studies using this approach have focused on infants either at term age, or younger than 1 year of age, who can be fed, swaddled and imaged in relatively short succession [16–18], leaving a void between 1 and 4 years of age [19, 20]. This is particularly relevant when one considers that autism, attention deficit hyperactivity disorder and pediatric obsessive-compulsive disorder all behaviorally manifest during this period [20].

Improvements in imaging techniques and methodologies are therefore necessary to improve current pediatric neuro-imaging practices and increase the likelihood of acquiring high-quality MRI data. This includes the development of imaging techniques that provide more than just gray/white matter contrast, as well as approaches for transporting participants throughout the scanner environment, acoustic noise reduction, and minimizing parent and child anxiety. We sought to build upon prior work in this area to develop a novel methodology for performing MRI of young children (defined herein as 3 months through 4 years of age) during natural, non-sedated sleep. While developed predominantly for structural, functional and quantitative imaging of the brain in the research setting, these techniques may be adapted to be applied clinically. It is our hope that the outlined methods and ideas may serve as a guide to pediatric imaging that provides a safe, cost-effective and alternative method in imaging this important but understudied age range.

Materials and methods

Subjects

All participants in this study have been recruited as part of an ongoing longitudinal study investigating white matter maturation in healthy, typically developing children and its relationship

to behavioral development [21]. Parental consent was obtained in accordance with the Institutional Review Board of the host institution. Enrolled children met the inclusion/exclusion criteria of: uncomplicated singleton birth between 37 and 42 weeks' gestation with no physical MRI contraindications; no diagnosis of major psychiatric, depressive or learning disorders; no pre-existing neurological conditions or major head trauma and no exposure to illicit drugs during pregnancy.

Recruitment

Participants were recruited through a variety of methods, including: random phone calls to families in the surrounding area; informational brochures placed in the offices of pediatricians, gynecologists and obstetricians, daycare centers and preschools, radio advertisements and attendance of research team members at community events, such as local hospital-sponsored festivals. Interested parents were able to speak with a research assistant about the objective of the study and ask any questions. Information sessions were also offered to the parents, who could visit the MRI facility, meet with researchers and further discuss the study. These information sessions were especially helpful for parents who were initially hesitant of participating. If the parent was interested in participating in the study, the research assistant scheduled the MRI session in accordance with the parent's schedule as well as the child's normal sleeping patterns. Parents were informed that within a week of successful MRI acquisition, children would undergo a cognitive/behavioral assessment. Parents were also told that they would be reimbursed for their time, travel and participation in both portions of the study (MRI scan and cognitive/-behavioral assessment).

The majority of MRI sessions were scheduled in the evening hours around the child's bedtime. A few MRI scans were scheduled at naptimes for the youngest participants (under 6 months) if no other time was convenient for the parent. Upon scheduling the MRI session, parents were sent a confirmation email with the time and date of the MRI scan, directions to the MRI research facility and a phone number to call upon arrival. If transportation was needed, a taxi was provided.

Subject preparation and preparation of MRI facility prior to scan

Two to three days prior to the MRI scan, a researcher would remind/confirm the scheduled time and date with the parents. The researcher also suggested to the parents that they skip the child's nap and keep the child busy throughout the day to make them tired.

On the night of the scan and prior to the family arriving at the MRI facility, private rooms were set up at the MRI facility. These rooms were equipped with cribs and small beds, rocking chairs, diaper changing and bathing facilities, blankets and

small toys, allowing families to follow near-normal bedtime routines and to be as comfortable as possible (Fig. 1). The room's lighting could be adjusted with a dimmer switch. In addition to controlling the lighting of the private rooms, lighting around the facility was also dimmed to avoid disturbing the sleeping child when transporting them to the MRI suite.

Upon arrival, the family was met by a research assistant and guided through the study's consent and MRI screening form for each present family member. Having everyone fill out this form was a precautionary measure that allowed the researchers to know which family members were allowed into the MRI suite and which members had contraindications. The researcher also asked parents to remove any metal objects (i.e. keys, cell phones, wallets, belts) and then showed the family back to their private room. Once the child had fallen asleep, the researchers waited an additional 15–20 min to ensure the child was in a deep sleep.

Sound attenuation and reducing intra-scan motion

To ensure uninterrupted sleep during the scan, active and passive measures were implemented to reduce acoustic noise levels of the MRI acquisition. Active measures included modification of the imaging pulse sequences to reduce imaging gradient rise times and slew rates, and to soften sharp changes in the gradient pulses. The slew rate and maximum gradient amplitudes of the gradient coils were reduced to approximately 30% and 75% of their nominal values (approx. 15 mT/m/s and 30 mT/m, respectively). Passive measures included a removable sound-insulating foam insert (Ultra Barrier HD Composite; American Micro Industries, Chambersburg, PA, USA,) rated to reduce noise levels on the order of 20 dB (<http://www.soundprooffoam.com/pdf/Ultra-Barrier.pdf>) and electrodynamic headphones (MR Confon, Magdeburg, Germany) with embedded MiniMuff ear pads (Natus Medical Inc., San Carlos, CA, USA) (<http://www.natus.com>) provided a further 45 dB reduction (<http://www.mr-confon.de/en/products/headphones.html>) (Fig. 2).

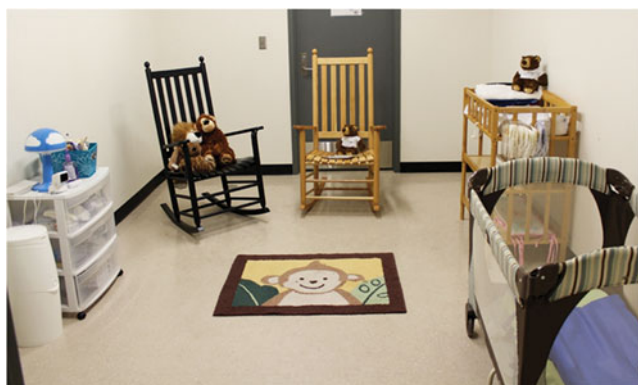


Fig. 1 Private sleeping room setup for an infant. Rooms are equipped with a crib (or bed in the case of an older child), rocking chairs, video baby monitor and snacks. Normal bedtime routines could be practiced so that children did not feel uncomfortable sleeping in a new environment



Fig. 2 MRI scanner with sound-insulating foam insert (Ultra Barrier HD Composite; American Micro Industries, Chambersburg, PA, USA) being installed into the bore of the scanner. Straps are used to hold the foam insert tight to the bore of the scanner. Noise reductions of up to 20 dB can be achieved

To reduce subtle body movement during the scan (i.e. movement from deep sleep breathing), appropriately sized MedVac vacuum immobilization bags (CFI Medical Solutions, Fenton, MI, USA) were used. These bags were placed under the infant or child before the patient fell asleep. Once asleep, the child was secured in the immobilizer (Fig. 3) and transferred from their crib or bed to a MRI compatible cart (Fig. 3). They were then moved from the private room to the scanner suite (Fig. 3). The child's head was carefully positioned into a 12-channel radio-frequency imaging head coil, electrodynamic headphones placed over the child's ears and the headphones and child were secured using memory foam cushions (Fig. 3). A pediatric pulse oximetry system was attached to the child's finger or toe to monitor the child during the scan. Finally, the child was landmarked, positioned to the center of the magnetic field and imaged (Fig. 3). A research assistant remained inside the scanning suite in case the child woke up during the scan. Parents were also invited to remain in the imaging suite during the scan.

Pediatric imaging and imaging protocols

All imaging was performed at a single imaging research facility equipped with a lone 3-T Siemens Tim Trio scanner (Siemens, Erlangen, Germany). Due to the wide age range investigated, a single imaging protocol was not suited for the current imaging study and, thus, five age-specific imaging protocols were developed [21]. Field of view (FOV) for these scanning protocols was determined by the mean head circumference while image matrix size was chosen such that $1.8 \times 1.8 \times 1.8 \text{ mm}^3$ isotropic voxel volumes were acquired. These templates also led to quicker image setup as scanning parameters (FOV, matrix size) did not need to be altered when adjusting the protocol series. Imaging times were additionally kept short (i.e. less than 30 min) to minimize the time of the scan and prevent the child from waking up

Fig. 3 Logistics of setting up for scanning of a sleeping child. **a** Children fall asleep either in crib or on bed. **b** Once asleep, children are buckled into a MedVac immobilizer and transferred to a MRI compatible cart. **c** Children are then wheeled into the MRI suite (**d**) and moved to the MRI scanner’s bed. **e** Electrodynamic headphones are carefully positioned onto children’s ears and held in place using memory foam cushions. **f** Children are then landmarked and moved to the center of the bore for scanning



before the scan was complete. Table 1 provides additional imaging parameters for these protocols.

Whole-brain, three-dimensional multicomponent driven equilibrium single pulse observation of T₁ and T₂ (mcDESPOT) imaging data was acquired [22]. The mcDESPOT imaging

protocol consists of 8 T₁-weighted spoiled gradient echo (SPGR, fast low angle shot [FLASH]) images, 2 inversion-prepared (IR)-SPGR images, and 16 T₁/T₂ balanced steady-state free precession (bSSFP, true fast imaging with steady state precession [TrueFISP]) images. SPGR and bSSFP images are acquired with

Table 1 Age-appropriate pediatric neuroimaging mcDESPOT protocols

Age group (months)	3–9	9–16	16–28	28–48
Acquisition time (min:sec)	18:22	18:42	21:38	24:20
Field of view (cm ³)	14×14×13	17×17×14.4	18×18×15	20×20×15
Unprotected dB ^a	54	62	69	74
SPGR TR/TE (ms)	12/5.8	12/5.9	12/5.4	11/5.2
SPGR flip angles (degrees)	2, 3, 4, 5, 7, 9, 11, 14	2, 3, 4, 5, 7, 9, 11, 14	2, 3, 4, 5, 7, 9, 11, 14	2, 3, 4, 5, 7, 9, 12, 16
IR-SPGR inversion time (ms)	600/950	600/900	500/850	500/800
bSSFP TR/TE (ms)	10/5	10.2/5.1	10/5	9.8/4.4
bSSFP flip angles (degrees)	9, 14, 20, 27, 34, 41, 56, 70	9, 14, 20, 27, 34, 41, 56, 70	9, 14, 20, 27, 34, 41, 56, 70	9, 14, 20, 27, 34, 41, 56, 70

^a Unprotected noise levels as measured at the front of the scanner bore

mcDESPOT multicomponent driven equilibrium single pulse observation of T₁ and T₂, dB decibels, SPGR spoiled gradient echo, TR repetition time, TE echo time, IR-SPGR inversion-prepared spoiled gradient echo, bSSFP balanced steady-state free precession

incremented flip angles and the bSSFP images are additionally acquired with 2 phase-cycling patterns (0° and 180°). A high-resolution anatomical T_1 -weighted image and resting-state functional magnetic resonance imaging data were additionally acquired [23, 24]. Priority was given in this order since we were predominately interested in assessing white matter maturation as measured by the myelin water fraction (MWF), a surrogate measure of myelin content [25, 26]. A scan was deemed successful if the mcDESPOT imaging data was successfully acquired.

If the child moved slightly while acquiring an SPGR, IR-SPGR or bSSFP image, that image was simply repeated. If the child woke up during the scan, scanning was immediately stopped and the child was brought out of the MRI scanner. Parents were allowed to comfort the child and try to have them fall back asleep. If parents thought the child would not return to sleep, they were encouraged to schedule another MRI session.

Longitudinal MRI scans

Due to the rapid brain development of children younger than 2 years of age [27] and differing rates of development between children younger and older than 2 years old [21, 27], families of children younger than 2 years of age were asked to return for an additional MRI scan every 6 months while families with children older than 2 years of age were asked to return each year. Families were contacted 1 month prior (5 months for children younger than 2 years, 11 months for children older than 2 years) to the desired date. If the parents agreed to the additional MRI scan, researchers inquired about any changes in the child's sleeping habits or patterns.

Results

Over the past 39 months (January 2010 to April 2013), 220 children younger than 4 years of age have been recruited to participate in the longitudinal study. Table 2 provides demographic information of these recruited study participants. Informational brochures placed in pediatricians' office have been the most effective strategy of recruitment, while placing random phone calls to families in the surrounding area has been the least effective tactic.

Table 2 Selected demographic information of recruited study participants

Characteristics	Males (129)	Females (91)
Gestational corrected age (initial scan, days)	594.4±455.1	519.9±429.5
Gestation duration (weeks)	39.5±1.2	39.5±1.3
Ethnicity (Hispanic/non-Hispanic/not reported)	25/82/22	15/67/9
Race (African American/Asian/Caucasian/mixed race/unknown or not reported)	11/1/74/20/23	7/2/61/10/11

The duration of a scanning visit was highly variable. If the child arrived asleep, the protocol could be completed in less than 1 h, including parental consent, MRI screening and safety questionnaires. Longer visits were due to the child having difficulty in falling asleep. The mean visit time was approximately 2 h, with a range from less than 1 h to more than 5 h.

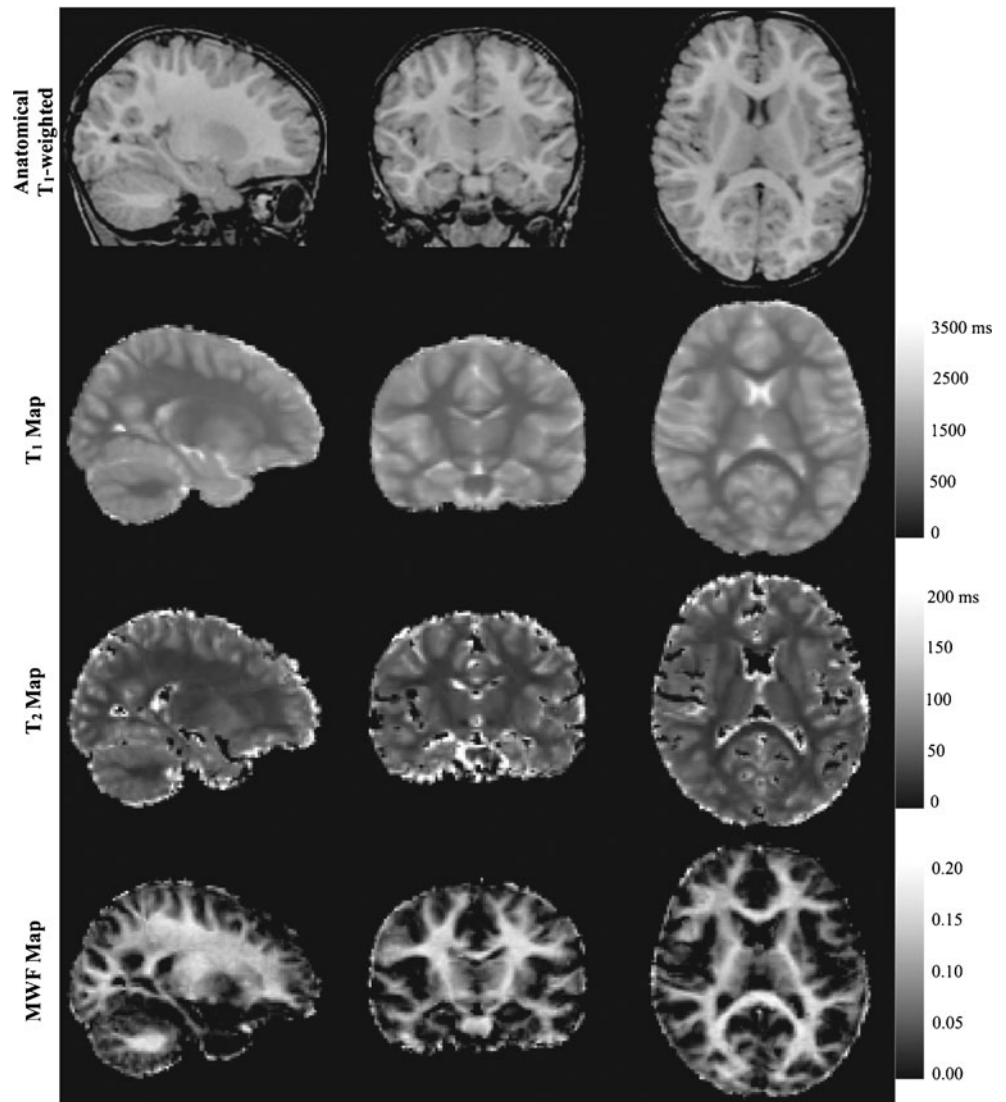
Sound attenuation measures were very effective at reducing the scanner acoustic noise. Reducing the slew rates and maximum gradient amplitude resulted in a sound reduction from 120 dB to approximately 85 dB (measured directly in front of the scanner bore). Further noise reductions were achieved with the passive measures (sound insulation conformed to scanner bore, electrodynamic headphones) with an overall estimated noise level of less than 60 dB. This decrease corresponds to an approximately 50% reduction in scanner noise, allowing research assistants and parents to remain in the scanner suite without ear protection as well as enabling the child to sleep comfortably throughout the acquisition.

Figure 4 shows a representative anatomical T_1 -weighted image as well as derived T_1 , T_2 and myelin water fraction maps. These images depict the typical quality of images acquired. Figure 5 illustrates both a representative dataset corrupted by motion artifact that would necessitate repeating. Success of scanning children during their first visit to the imaging facility was near 90%. A 100% success rate was achieved if the family returned for a second or third attempt. Of the 220 first-time scans, 9 datasets were deemed unusable due to image artifacts (i.e. intra-scan motion, off-resonance artifacts), yielding a 96% success rate of acquiring usable MRI data.

Longitudinal imaging

In addition to the initial MRI session, 164 children received at least one additional MRI scan. Children younger than 2 years of age were scanned at 6-month intervals; older children were imaged yearly. Table 3 provides a breakdown of the acquired longitudinal data. Figure 6 illustrates the overall attrition rate and number of active subjects throughout the longitudinal study separated by gender and divided into 2 age groups (3–24 months and 24–48 months). Larger attrition was observed in the children (both boys and girls) between 3 and 24 months old compared to those 24 to 48 months old. The main cause for children not returning

Fig. 4 Anatomical T₁-weighted and derived T₁, T₂, and myelin water fraction (MWF) maps from a representative 21-month-old depicting the quality of the acquired and calculated quantitative images. T₂ values were calculated in voxels with T₁ values below 3,500 ms



for follow-up MRI visits was the family relocating. In total, 384 pediatric MRI datasets have been successfully acquired from the 220 healthy and typically developing children between 3 months to 4 years of age. These study data correspond to an overall 97% success rate and represent one of the largest databases of multicomponent relaxometry imaging data in healthy children.

Discussion

Successful pediatric neuroimaging is essential to the study of healthy or typical neurodevelopment, as well as for understanding the early structural abnormalities associated with developmental disorders. Having an established routine of suitable preparation and child-friendly procedures increases

Fig. 5 Example of an inadequate scan that would necessitate either repeating or having the child return for a second visit. T₁-weighted SPGR images were acquired from a 3-month-old boy

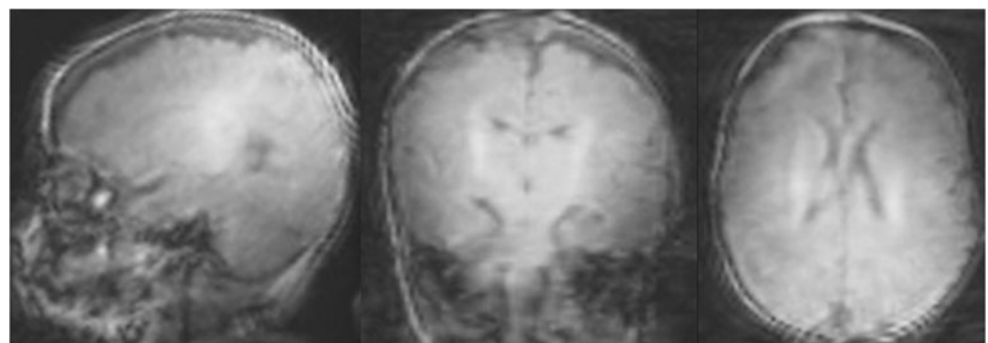


Table 3 Breakdown of acquired longitudinal data from study subjects

Age group	Gender	Initial scans	Follow-up #1 scans	Follow-up #2 scans	Follow-up #3 scans
3–24 months	Male	81	44	19	4
3–24 months	Female	67	39	14	6
24–48 months	Male	48	20	7	0
24–48 months	Female	24	9	2	0

the chance of obtaining high-quality images as well as positively influencing the experience of the participants and their families [4]. Although imaging children during non-sedated sleep has been previously described [8, 14, 15], the methodology outlined here addresses the common difficulties experienced in pediatric neuroimaging and provides a practical description for the acquisition of qualitative and quantitative structural imaging data of naturally sleeping children.

Silent but rapid imaging requires a delicate trade-off between imaging speed and noise. Separate image acquisition protocols for age subgroups (i.e. 3–9 months, 9–16 months, 16–28 months and 28–48 months) were designed with this trade-off in mind, with greater noise reduction in the youngest age groups and faster imaging in the older children. Imaging time for each age group was less than 30 min, while noise levels varied from less than 60 dB to 85 dB, allowing children undergoing the procedure to remain asleep. While changing the gradient slew rates and maximum amplitudes for these protocols allowed the imaging speed and noise levels to be modified, these factors did not affect the image quality or limit the desired image resolution for the current study.

Although imaging infants and toddlers asleep minimizes motion-related artifacts, these children are still apt to move

or even wake up. In these cases, scanning must be repeated. These issues are a greater concern with older children watching a movie or TV show. The pediatric MedVac immobilizers and foam cushions provide some restraint and help limit the children's mobility; however, they can be insufficient. Motion correction has been a very active area of research within the MR community, and advanced retrospective [28], prospective [29], and hybrid [30] techniques have been developed. Such methods could be used in conjunction with the outlined protocol to provide additional improvements of the data quality and increase efficiency of data acquisition.

The scanning success reported here compares favorably to other MRI research studies in young children [15, 19]. Causes for an unsuccessful scan were due to the child waking up during the scan, waking up during the transition to the scanner or not being able to fall asleep at the MRI facility. These scenarios were typically observed when scanning older children (2.5–4 years old) and were caused by their awareness and inability to fall asleep in the novel environment (i.e. MRI facility). Second- and third-attempt scans were often more successful because the child and parents were more familiar and comfortable with the setting and protocol.

The time of the family's arrival to the MRI facility to the time scanning actually took place was highly variable due to individual differences in sleeping patterns. Such irregular timing could make incorporating these procedures into a busy scanner schedule and/or clinical setting challenging; however, such flexibility is needed to acquire high-quality image data from naturally sleeping children. To reduce this variability, close communication with the parents regarding the child's sleeping schedule and patterns are helpful to anticipate an appropriate time to schedule the MRI scan. Nonetheless, the availability and flexibility of the scanning schedule must be carefully considered prior to imaging children during non-sedated sleep.

While the procedure outlined herein is based upon the mcDESPOT [22] imaging approach, many of the described modifications, including the use of a sound-insulating bore insert, headphones and immobilizers, can be adopted for other pulse sequences and imaging methods. Furthermore, these methods are not specific to neuroimaging and can equally be applied to imaging other body parts. Thus, they are of broad applicability and appeal. Combined, these

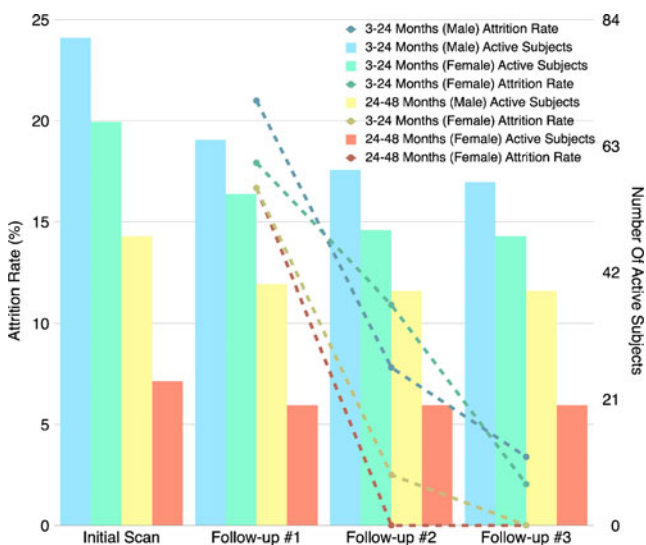


Fig. 6 Attrition rate and number of active study subjects enrolled in the longitudinal study. The number of active subjects included those whose MRI data has been acquired and subjects who are scheduled for a follow-up MRI scan. Attrition rates correspond to the attrition between follow-up visits

procedures require approximately 30 min of additional set-up and preparation time (in order to fasten the sound-insulating foam insert and arrange the private family rooms). However, selectively choosing only measures that are appropriate for an individual study's needs can shorten this time.

Conclusion

MRI acquisition during natural sleep provides an ethical alternative to the associated risks of using general anesthetics or sedatives and provides a valuable opportunity to investigate many open-ended questions about brain development. The methodology that we have outlined here addresses the major obstacles (acoustic noise, motion, length of time, etc.) that have limited pediatric neuroimaging research and greatly facilitates the advancement of pediatric MRI. The success rates that have been shown using the outlined method compares favorably to that of other multicentered pediatric imaging studies [19], while the amount of data collected within a short period of time (approx. 2.5 years) validates the methods' overall success. As the need and use of MRI for children continues to grow in research settings, it is hoped that the outlined methodology will not only help improve existing imaging protocols but will also provide a guide for future research to follow.

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Conflicts of interest None.

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