

New Mri Techniques For Imaging Neonates And Infants With Minimal Sedation

Qassim Hassan Albahrani, Ali Abdulhamid Alfaris, Itedal Yousef Al Butyan, Madinah Ali Albutayyan, Alaa Mohammed Mobarki, Hussam Aldeen Ibrahim Khawaji, Hassan Hussein Hakami, Ayat Adnan Albahrani, Fatimah Younis Ali Almohammedsaleh, Zainab Yousef Albutyan, Hind Yousef Albutyan, Ahmed Ali Humedi, Mashael Shalash Alshammari, Sokaina Yousef Al Butyan, Abdullah Mohammed Swaileh Al Otaibi

Abstract

Magnetic resonance imaging (MRI) is a secure technique for examining the human brain. Nevertheless, a standard magnetic resonance (MR) scan is very susceptible to motion and necessitates the individual to remain still during the process, posing a significant obstacle for pediatric studies. Therefore, in a medical environment, sedation or general anesthesia is often used. In the context of study with healthy individuals, the use of anesthetics is not advisable due to ethical concerns and the possibility of causing long-term damage. In this article, we will discuss the procedures involved in preparing a kid for an MRI scan, as well as the specific techniques and instruments used throughout the scanning process to ensure a good outcome. In addition, we do a thorough assessment of how studies have documented the scanning process and the level of success achieved in scanning. We conducted a search of papers using specific topic headings in PubMed and found 86 research that used brain MRI in healthy individuals aged 0 to 6 years. Preparations for the scan were appropriately tailored to the subject's age. Infants and young children were scanned while they were sleeping, after feeding and swaddling. On the other hand, older children were scanned while they were awake. It was challenging to compare the efficiency of various processes due to the diverse reporting of the techniques utilized and the rates of success. According to this assessment, we suggest providing more comprehensive documentation of the scanning method in order to identify the specific aspects that influence the effectiveness of scanning. Over time, this might benefit the research area by obtaining data of superior quality, as well as aiding the clinical field in minimizing the reliance on anesthetics. In this section, we will provide the procedure used for scanning newborns aged 2 to 5 weeks in the FinnBrain Birth Cohort Study, as well as techniques for soothing neonates during the scans.

Keywords: *Magnetic resonance imaging (MRI), review, imaging neonates, infants, scanning.*

1. Introduction

Magnetic resonance imaging (MRI) is a safe and non-invasive technique used to evaluate the human brain during all stages of life. MRI, in contrast to computer tomography (CT) and X-ray, does not use ionizing radiation and offers exceptional differentiation of soft tissues (Lee et al., 2017). Therefore, it is very suitable for both clinical studies conducted with juvenile population and research settings with healthy people. Nevertheless, MRI is very susceptible to motion artifacts, necessitating the participant to maintain complete

stillness during the procedure. The scanner's acoustic noise may reach a maximum of 132 dB(A) (Foster et al., 2000), and the time it takes to gather data typically ranges from 15 to 60 minutes. The specific duration depends on the setup and the number of sequences being recorded. When doing clinical scans on young populations, it is common to provide mild sedation or general anesthesia in order to alleviate anxiety and minimize movement (Royal and Road, 2000).

Due to ethical concerns, such as the potential dangers associated with anesthesia, sedation is not often seen as a viable choice for neuroimaging studies involving individuals who are in good health (Edwards and Arthurs, 2011). Nevertheless, even those who are unable to cooperate during the scan may still be scanned without any movement while in a state of natural slumber. However, this approach presents significant difficulties when it comes to preparing for the scan. Notwithstanding these obstacles, MRI has a significant position in the realm of pediatric neuroimaging research (Zhang et al., 2019). The latest study examines the difficulties encountered in pediatric MRI and discusses several technical advancements that have the potential to enhance the success rate in the future (Barkovich et al., 2019).

There has been a significant growth in neuroimaging studies employing MRI as a way of imaging in healthy newborns. At the same time, this study area has extended to include other disciplines of science, such as psychology, logopedics, and social sciences. The human brain undergoes rapid development and increases in size during the first two years after birth (Knickmeyer et al., 2008), making it highly susceptible to many environmental factors (Pulli et al., 2018). Several studies have been conducted to examine normal development in healthy individuals, at-risk populations, and clinical populations, among others (Bompard et al., 2014; Li et al., 2014c; Deoni et al., 2015; Hazlett et al., 2012; Dean et al., 2014b; Grewen et al., 2014; Donald et al., 2015; Langer et al., 2015; Monk et al., 2015; Ou et al., 2015; Qiu et al., 2015, 2013b; Chang et al., 2016; Jha et al., 2016; Salzwedel et al., 2016; Karmacharya et al., 2018; Moran et al., 2019). In order to reduce the impact of environmental factors after birth, researchers have often focused on imaging infants as soon as possible after delivery, usually during the first few weeks of life. Infants tend to sleep a lot shortly after delivery, making this time period particularly ideal for doing imaging procedures (Galland et al., 2012). However, there are other obstacles that arise when it comes to recruiting participants and scheduling imaging sessions without disrupting parents' daily routines. In addition, pediatric scanning necessitates specialized knowledge due to the infrequent occurrence of these scans in both clinical and research environments.

In the past, several publications have specifically emphasized the use of non-sedation scanning techniques for newborns and young children. The primary determinant influencing the choice of preparatory methods is the age of the participants and their developmental requirements. Mathur et al. (2008) have provided instructions for doing brain MRI on newborn intensive care unit (NICU) patients without the need of sedation. Arthurs et al. (2012) conducted a review on ways to prevent sedation in newborn imaging. They specifically addressed problems related to physiological changes, equipment compatibility, and acoustic noise. The primary method used with newborns is the practice of feeding and wrapping, also known as feed and sleep, feed and swaddle, or feed and bundle. This approach is mostly utilized for babies who are under 3 months of age (Antonov et al., 2017). A specialized vacuum fixation immobilizer is often used to securely wrap the newborn using the feed and wrap approach. The use of a vacuum immobilizer is a secure and economical method that eliminates the need for anesthetic (Golan et al., 2011).

A retrospective questionnaire study conducted by Heller et al. (2017) shown that the predominant method for doing newborn MRI in NICUs in the United States was the feed and swaddle strategy (64%), while other NICUs generally relied on sedation or general anesthesia to facilitate the scans. The aforementioned research demonstrated a predictable

decrease in the efficacy of obtaining high-quality data in the feed and swaddle group as compared to the sedation and general anesthesia groups. Additionally, as time progresses beyond the first months after delivery, the method of feeding and swaddling becomes less successful, and doing scans without anesthesia becomes more challenging. Dean et al. (2014a) provided a detailed plan for doing brain scans on young, healthy children below the age of four while they are in a natural state of sleep without the need of sedation. A total of 384 MRI datasets were obtained from 220 healthy patients in a longitudinal research, with a success rate of 97%. The scans were arranged during the late hours, and in some instances, the individuals were intentionally deprived of sleep.

Additional research have documented methods for doing scans on children, particularly those above the age of 4, while they are awake (Raschle et al., 2009; De Bie et al., 2010). For instance, Raschle et al. (2009) presented comprehensive principles emphasizing comfort, suitability, and motivation (CAM). Additionally, a detailed procedure accompanied by a video report was provided for conducting pediatric neuroimaging sessions with young children. For individuals in this particular age range, the use of MRI compatible weighted blankets might be beneficial in reducing movement while undergoing MRI scans (Horien et al., 2020).

While efforts are made to minimize motion, there is still a chance of little, unintentional movements occurring throughout the acquisition process. Motion artifacts may occur and diminish the quality of MRI data even from simple bodily functions such as heart beats, breathing, or blinking. Motion, regardless of its kind, poses difficulties and is a matter of concern in both clinical and scientific imaging. In order to enhance the accuracy of the data, a variety of techniques have been created to reduce or rectify motion (Zaitsev et al., 2015). Methods may be categorized into prospective and retrospective methods, each including a range of methodologies. Prospective strategies use a real-time correction method (Brown et al., 2010), while retrospective techniques alter data throughout the reconstruction process (Loktyushin et al., 2013). Both techniques have been used in brain imaging (Godenschweger et al., 2016). Nevertheless, every technique has its constraints, and so far, no individual technique has the ability to entirely eradicate motion artifacts. Therefore, it is essential to minimize the motion (Reuter et al., 2015).

The main objective of this study was to examine the reporting of scanning techniques and success rates in previous research, which has not been addressed in previous reviews on this topic. We allocate a certain portion of our work to our own established protocols, which we anticipate will facilitate future data gathering. The primary objective of this systematic review is to provide a comprehensive overview of the methodologies employed for scanning subjects aged 0-6 years in an MRI scanner. Specifically, the review will focus on studies published within the past 9 years, with particular attention given to the procedures involved in preparing a child for an MRI scan. Additionally, the review will examine the techniques and tools utilized during the scanning process to ensure a successful outcome.

We specifically examined studies done on individuals who were healthy and born at full term, since research involving preterm people typically includes clinical considerations. The text provides explanations of the scanning operations and a concise overview of the frequently used approaches. In addition, we analyzed the effectiveness of the scans and, conversely, explored the causes of the unsuccessful scans. The second objective was to provide techniques for doing scans on newborns and young children without the need for anesthesia. In order to enhance the sample sizes and improve the quality of data, as well as minimize the occurrence of drop-outs in the follow-up scans, it is crucial to possess a thorough understanding of these methodologies. In the future, these techniques may also be used in clinical settings to minimize the need for sedation during MRI procedures. Lastly, we provide the newborn magnetic resonance (MR) techniques used in the Neuroimaging Lab of the FinnBrain Birth Cohort Study (finnbrain.fi).

2. Data analysis

According to the analyzed research, it seems that the age of 4 years is the most often observed age at which scanning is initiated while the kid is awake. During this particular stage of development, it is customary to use various techniques such as a simulated scanner and behavioral training to adequately prepare children for MRI procedures. Furthermore, a recently developed technology using Virtual Reality (VR) has introduced a novel strategy for preparing youngsters for MRI scans, in addition to the well-established techniques (Ashmore et al., 2019). The use of a training procedure using a simulated scanner resulted in a success rate of 88% (53/60) for structural MRI and 64% (23/36) for functional MRI in a sample of children aged 4-7 years (De Bie et al., 2010). In a study conducted by Cavarocchi et al. (2018), it was shown that 83% (162 out of 195) of pediatric patients aged 4 to 14 years had successful outcomes after undergoing a training procedure using a mock scanner. Additionally, there was an overall reduction of 30% in the need for sedation.

The study by Carter et al. (2010) suggests that the mock scanner is particularly efficient when used with children aged 3 to 8 years. Regrettably, the cost of fake scanners is somewhat high, hence restricting their accessibility. Nevertheless, there is empirical support indicating that using an inexpensive play tunnel that replicates the conditions of an MRI environment might serve as a valuable substitute (Barnea-Goraly et al., 2014). The researchers They et al. (2014) have created a behavioral training method called the 'submarine protocol' to help toddlers be ready for scanning. Once the youngster finished the necessary chores to get better acquainted with challenging parts of MRI, they were prepared for the 'submarine voyage'. The methodology has been used to get sophisticated MRI methods (DTI, fMRI) in normally developing youngsters aged 5 and 6, with a completion rate of 95% (72 out of 76) for the whole 35-minute scan.

A recent study by Runge et al. (2018) achieved a success rate of 95% in children aged 4-6 utilizing a combination of strategies. These strategies included an interactive app, a trained pediatric staff, a children's lounge equipped with a toy scanner, and a child-friendly multimedia environment in the MRI room. Remarkably, a meta-analysis conducted by Li et al. (2019) found that pre-MRI training, which included the use of materials such as booklets, audio recordings, videos, toy models, or mock scanners, did not lead to any improvements in data quality, sedative use, or scanning success rate. Authors hypothesized that a potential explanation might be that training amplifies anxiety and terror in youngsters. Nevertheless, the number of studies conducted was restricted ($n = 5$) and the sample sizes were modest. Consequently, more investigations are required to validate the results. Overall, it is difficult to directly compare success rates among research. Therefore, it is necessary to conduct a controlled study in the future to investigate the specific impacts of various strategies. Significantly, there is a notable absence of objective and standardized standards for determining what qualifies as high-quality data, as well as the amount to which it might be enhanced by post-processing.

In order to enhance comfort and guarantee safety throughout the scanning process, it is essential to effectively perform noise attenuation. According to this study, the most often used techniques for ear protection were earplugs (made of wax, foam, or silicon), soft shell earmuffs, standard ear protectors, or a combination of these. Soundproofing bore liners or foam inserts were not often used. The integration of many strategies has been shown to be more efficacious than using a single strategy in isolation (Tocchio et al., 2015). In order to provide adequate noise reduction during MRI scanning in newborns, Nordell et al. (2009) proposed the use of dental putty inserted into the outer ear canal, earmuffs placed over both ears, and an acoustic hood made of dampening material placed over the infant.

Passive noise control technologies, despite their effectiveness, are hindered by drawbacks like discomfort, difficulties with fitting, and, notably, inadequate noise reduction in some situations. Hence, in order to carry out scanning in a quieter manner,

active techniques such as quiet sequences and quiet coils have been devised (McJury and Shellock, 2000). Unlike other approaches that aim to decrease or remove the auditory disturbance, a novel acquisition technique called MR Fingerprinting-Music has been created to enhance the auditory experience by simulating music (Ma et al., 2016). As far as we know, there is a lack of research demonstrating the efficacy of the procedure in youngsters.

It is well recognized that movement during the process of obtaining images may result in picture artifacts, which can render the data worthless. According to the research examined, mobility was the primary cause for excluding data. Nevertheless, the precise impact of motion on the system is not well understood and sometimes not accounted for. This may be a challenge, particularly in research settings, as variables of interest such as age, sex, or illness are often associated with both the degree of head motion and structural alterations. Head movement during MRI scanning has been shown to affect measurements of gray matter volume and thickness (Reuter et al., 2015). As supported by prior research and current study, swaddling or wrapping are the most often used methods to limit movement during baby scanning. These procedures are simple, inexpensive, and readily accessible, but regrettably ineffective in later age cohorts. In addition, specialized vacuum immobilizer mats, cushions, and foam pads were used to ensure the stability of the body and head posture. Adolescents often have the capacity to see movies or television programs while learning, which has been shown to decrease the amount of head movement.

In a recent study, Greene et al. (2018) expanded on their previous work by doing tests that included both movies and real-time visual head motion input. Both approaches effectively decreased movement, however, it is worth noting that there was no synergistic impact seen when the methods were combined. In addition, these approaches may provide challenges during fMRI imaging, since they might potentially impact the functional results (Greene et al., 2018). In order to enhance adherence and reduce mental effort during functional imaging, a movie paradigm called Inscapes was used (Vanderwal et al., 2015). Nevertheless, physical techniques of head restraint, movies, or behavioral measures are unable of entirely eliminating motion. Consequently, motion correction is still necessary afterwards in all circumstances. These methods are particularly important when using high field MRI systems, such 7 Tesla scanners, since they produce louder acoustic noise, take longer to acquire images, and are more susceptible to motion artifacts (Stucht et al., 2015; Keuken et al., 2018).

3. Conclusion

To summarize, doing brain MRI scans on newborns and young children without sedation is difficult, but with proper preparation, it is possible to carry out. This overview illustrates the several methods for preparing a kid for scanning, managing noise reduction, and restricting mobility. Ultimately, this research demonstrates that the scanning techniques are often insufficiently documented. To optimize scanning success rates and identify the most effective preparatory procedures, we suggest providing a more comprehensive report of the operation. Over time, it could be feasible to use the most effective scanning techniques in the clinical context and decrease the need for anesthesia in pediatric neuroimaging, particularly in non-urgent situations.

References

1. Antonov, N. K., Ruzal-Shapiro, C. B., Morel, K. D., Millar, W. S., Kashyap, S., Lauren, C. T., et al. (2017). Feed and Wrap MRI technique in infants. *Clin. Pediatrics* 56, 1095–1103. doi: 10.1177/0009922816677806

2. Arthurs, O. J., Edwards, A., Austin, T., Graves, M. J., and Lomas, D. J. (2012). The challenges of neonatal magnetic resonance imaging. *Pediatric Radiol.* 42, 1183–1194. doi: 10.1007/s00247-012-2430-2
3. Ashmore, J., Di Pietro, J., Williams, K., Stokes, E., Symons, A., Smith, M., et al. (2019). A free virtual reality experience to prepare pediatric patients for magnetic resonance imaging: cross-sectional questionnaire study. *JMIR Pediatrics Parent.* 2:e11684. doi: 10.2196/11684
4. Barkovich, M. J., Li, Y., Desikan, R. S., Barkovich, A. J., and Xu, D. (2019). Challenges in pediatric neuroimaging. *NeuroImage* 185, 793–801. doi: 10.1016/j.neuroimage.2018.04.044
5. Barnea-Goraly, N., Weinzimer, S. A., Ruedy, K. J., Mauras, N., Beck, R. W., Marzelli, M. J., et al. (2014). High success rates of sedation-free brain MRI scanning in young children using simple subject preparation protocols with and without a commercial mock scanner—the Diabetes Research in Children Network (DirecNet) experience. *Pediatr. Radiol.* 44, 181–186. doi: 10.1007/s00247-013-2798-7
6. Bompard, L., Xu, S., Styner, M., Paniagua, B., Ahn, M., Yuan, Y., et al. (2014). Multivariate longitudinal shape analysis of human lateral ventricles during the first twenty-four months of life. *PLoS One* 9:e108306. doi: 10.1371/journal.pone.0108306
7. Brown, T. T., Kuperman, J. M., Erhart, M., White, N. S., Roddey, J. C., Shankaranarayanan, A., et al. (2010). Prospective motion correction of high-resolution magnetic resonance imaging data in children. *NeuroImage* 53, 139–145. doi: 10.1016/j.neuroimage.2010.06.017
8. Carter, A. J., Greer, M. L. C., Gray, S. E., and Ware, R. S. (2010). Mock MRI: reducing the need for anaesthesia in children. *Pediatr. Radiol.* 40, 1368–1374. doi: 10.1007/s00247-010-1554-5
9. Cavarocchi, E., Pieroni, I., Serio, A., Velluto, L., Guarnieri, B., and Sorbi, S. (2018). Kitten scanner reduces the use of sedation in pediatric MRI. *J. Child Health Care* 23, 256–265. doi: 10.1177/1367493518788476
10. Chang, L., Oishi, K., Skranes, J., Buchthal, S., Cunningham, E., Yamakawa, R., et al. (2016). Sex-Specific alterations of white matter developmental trajectories in infants with prenatal exposure to methamphetamine and tobacco. *JAMA Psychiatry* 73, 1217–1227. doi: 10.1001/jamapsychiatry.2016.2794
11. De Bie, H. M. A., Boersma, M., Wattjes, M. P., Adriaanse, S., Vermeulen, R. J., Oostrom, K. J., et al. (2010). Preparing children with a mock scanner training protocol results in high quality structural and functional MRI scans. *Eur. J. Pediatr.* 169, 1079–1085. doi: 10.1007/s00431-010-1181-z
12. Dean, D. C., Dirks, H., O’Muircheartaigh, J., Walker, L., Jerskey, B. A., Lehman, K., et al. (2014a). Pediatric neuroimaging using magnetic resonance imaging during non-sedated sleep. *Pediatr. Radiol.* 44, 64–72. doi: 10.1007/s00247-013-2752-8
13. Dean, D. C., Jerskey, B. A., Chen, K., Protas, H., Thiyyagura, P., Roontiva, A., et al. (2014b). Brain differences in infants at differential genetic risk for late-onset alzheimer disease: a cross-sectional imaging study. *JAMA Neurol.* 71, 11–22. doi: 10.1001/jamaneurol.2013.4544
14. Deoni, S. C. L., Dean, D. C., Remer, J., Dirks, H., and O’Muircheartaigh, J. (2015). Cortical maturation and myelination in healthy toddlers and young children. *NeuroImage* 115, 147–161. doi: 10.1016/j.neuroimage.2015.04.058
15. Donald, K. A., Fouche, J. P., Roos, A., Koen, N., Howells, F. M., Riley, E. P., et al. (2015). Alcohol exposure in utero is associated with decreased gray matter volume in neonates. *Metab. Brain Dis.* 31, 81–91. doi: 10.1007/s11011-015-9771-0
16. Edwards, A. D., and Arthurs, O. J. (2011). Paediatric MRI under sedation: is it necessary? what is the evidence for the alternatives? *Pediatric Radiol.* 41, 1353–1364. doi: 10.1007/s00247-011-2147-7
17. Foster, J. R., Hall, D. A., Summerfield, A. Q., Palmer, A. R., and Bowtell, R. W. (2000). Sound-level measurements and calculations of safe noise dosage during EPI at 3 T. *J. Magn. Reson. Imag.* 12, 157–163. doi: 10.1002/1522-2586(200007)12:1<157::aid-jmri17>3.0.co;2-m
18. Galland, B. C., Taylor, B. J., Elder, D. E., and Herbison, P. (2012). Normal sleep patterns in infants and children: a systematic review of observational studies. *Sleep Med. Rev.* 16, 213–222. doi: 10.1016/j.smrv.2011.06.001

19. Godenschweger, F., Kägebein, U., Stucht, D., Yarach, U., Sciarra, A. R., Yakupov, R., et al. (2016). Motion correction in MRI of the brain. *Phys. Med. Biol.* 28, 1304–1314. doi: 10.1002/nbm.3369
20. Golan, A., Marco, R., Raz, H., and Shany, E. (2011). Imaging in the newborn: infant immobilizer obviates the need for anesthesia. *Israel Med. Assoc. J.* 13, 663–665.
21. Greene, D. J., Koller, J. M., Hampton, J. M., Wesevich, V., Van, A. N., Nguyen, A. L., et al. (2018). Behavioral interventions for reducing head motion during MRI scans in children. *NeuroImage* 171, 234–245. doi: 10.1016/j.neuroimage.2018.01.023
22. Grewen, K., Burchinal, M., Vachet, C., Gouttard, S., Gilmore, J. H., Lin, W., et al. (2014). Prenatal cocaine effects on brain structure in early infancy. *NeuroImage* 101, 114–123. doi: 10.1016/j.neuroimage.2014.06.070
23. Hazlett, H. C., Gu, H., McKinstry, R. C., Shaw, D. W. W., Botteron, K. N., Dager, S. R., et al. (2012). Brain volume findings in 6-month-old infants at high familial risk for autism. *Am. J. Psychiatry* 169, 601–608. doi: 10.1176/appi.ajp.2012.11091425
24. Heller, B. J., Yudkowitz, F. S., and Lipson, S. (2017). Can we reduce anesthesia exposure? neonatal brain MRI: swaddling vs. sedation, a national survey. *J. Clin. Anesthesia* 38, 119–122. doi: 10.1016/j.jclinane.2017.01.034
25. Horien, C., Fontenelle, S., Joseph, K., Powell, N., Nutor, C., Fortes, D., et al. (2020). Low-motion fMRI data can be obtained in pediatric participants undergoing a 60-minute scan protocol. *Sci. Rep.* 10:21855. doi: 10.1038/s41598-020-78885-z
26. Jha, S. C., Meltzer-Brody, S., Steiner, R. J., Cornea, E., Woolson, S., Ahn, M., et al. (2016). Antenatal depression, treatment with selective serotonin reuptake inhibitors, and neonatal brain structure: a propensity-matched cohort study. *Psychiatry Res. Neuroimaging* 253, 43–53. doi: 10.1016/j.psychres.2016.05.004
27. Karmacharya, S., Gagoski, B., Ning, L., Vyas, R., Cheng, H. H., Soul, J., et al. (2018). Advanced diffusion imaging for assessing normal white matter development in neonates and characterizing aberrant development in congenital heart disease. *NeuroImage: Clin.* 19, 360–373. doi: 10.1016/j.nicl.2018.04.032
28. Keuken, M. C., Isaacs, B. R., Trampel, R., van der Zwaag, W., and Forstmann, B. U. (2018). Visualizing the human subcortex using ultra-high field magnetic resonance imaging. *Brain Topography* 31, 513–545. doi: 10.1007/s10548-018-0638-7
29. Langer, N., Peysakhovich, B., Zuk, J., Drottar, M., Sliva, D. D., Smith, S., et al. (2015). White matter alterations in infants at risk for developmental Dyslexia. *Cereb. Cortex* 27, 1027–1036. doi: 10.1093/cercor/bhv281
30. Monk, C., Georgieff, M. K., Xu, D., Hao, X., Bansal, R., Gustafsson, H., et al. (2015). Maternal prenatal iron status and tissue organization in the neonatal brain. *Pediatr. Res.* 79, 482–488. doi: 10.1038/pr.2015.248
31. Moran, M. M., Gunn-Charlton, J. K., Walsh, J. M., Cheong, J. L. Y., Anderson, P. J., Doyle, L. W., et al. (2019). Associations of neonatal noncardiac surgery with brain structure and neurodevelopment: a prospective case-control study. *J. Pediatrics* 212, 93–101.e2. doi: 10.1016/j.jpeds.2019.05.050
32. Ou, X., Thakali, K. M., Shankar, K., Andres, A., and Badger, T. M. (2015). Maternal adiposity negatively influences infant brain white matter development. *Obesity* 23, 1047–1054. doi: 10.1002/oby.21055
33. Qiu, A., Tuan, T. A., Ong, M. L., Li, Y., Chen, H., Rifkin-Graboi, A., et al. (2015). COMT haplotypes modulate associations of antenatal maternal anxiety and neonatal cortical morphology. *Am. J. Psychiatry* 172, 163–172. doi: 10.1176/appi.ajp.2014.14030313
34. Salzwedel, A. P., Grewen, K. M., Goldman, B. D., and Gao, W. (2016). Thalamocortical functional connectivity and behavioral disruptions in neonates with prenatal cocaine exposure. *Neurotoxicol. Teratol.* 56, 16–25. doi: 10.1016/j.ntt.2016.05.009