

Paediatric MRI Research Ethics: The Priority Issues

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Abstract In this paper, we first briefly describe neuroimaging technology, our reasons for studying magnetic resonance imaging (MRI) technology, and then provide a discussion of what we have identified as priority issues for paediatric MRI research. We examine the issues of respectful involvement of children in the consent process as well as privacy and confidentiality for this group of MRI research participants. In addition, we explore the implications of unexpected findings for paediatric MRI research participants. Finally, we explore the ethical issues concerning advances in functional MRI. This paper

aims to provide a clear description of priority paediatric MRI research ethics issues to make some preliminary recommendations regarding next steps.

Keywords Magnetic resonance imaging · Paediatrics · Informed consent · Privacy · Confidentiality

Neuroimaging Technology

Tremendous technological strides in the field of biomedical imaging over the past few decades have resulted in advances in non-invasive disease detection, and are now making substantial contributions to our understanding of underlying anatomy and physiology in normal and disease-related conditions. Nowhere has the impact of this technology been more dramatic than the neurosciences, where neuroimaging holds the apparent promise of not only assisting with the effective and timely detection of diseases involving the central nervous system, but also of “prob[ing] into our deepest thoughts” [1] and greatly expanding our knowledge of the neural basis of human cognition [2], personality and emotion [3] as well as disorders like addiction. Although it is difficult to predict the scope of influence of these technological developments, neuroimaging is also likely to challenge established conceptions of free will, consciousness, rational decision-making, and individuality [1].

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The neuroimaging workhorses of today consist of a variety of modalities, including computed tomography (CT), single-photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), electroencephalography (EEG), and magnetoencephalography (MEG). It exceeds the scope of the paper to describe the details of these methodologies; generally, they allow imaging of brain structure, chemistry and function. They also make possible imaging and quantification of treatment effects, provide the means to monitor the effects of disease, and precisely delineate brain areas affected by insult [4].

In this paper, we focus on paediatric MRI research. We centre on MRI research because, over the past 20 years, MRI has become established as a “superior modality for morphological and anatomical imaging” [5] and, more recently, functional magnetic resonance imaging (fMRI) research has been used to provide increasingly higher resolution maps of functional regions in the brain. We focus on children because, as one American scholar comments, “neuroimaging pediatric patients is accompanied by all the ethical dilemmas associated with neuroimaging in adults, magnified exponentially” [6].

To date, there has not been adequate debate with respect to the ethical issues surrounding MRI research involving children. This is noteworthy in light of the interests at stake. The existing literature is far richer in questions than answers. Thus, a stronger foundation needs to be constructed upon which sound policy decisions, clinical guidelines and best practices, and research protocols can be built in the neuroimaging field.

Priority Ethical Issues

Technological progress in neuroimaging raises optimism about our ability to combat neurological disease and to obtain insights into the mysteries of human cognition; however, at the same time, it raises serious ethical questions. In this paper we will examine consent issues in paediatric MRI and related privacy and confidentiality concerns. We will also explore special issues with respect to unexpected findings and the implications of these findings for paediatric research participants. In the final section, we deal with ethical issues arising out of fMRI with reference to the paediatric population. These are all issues that we

believe require urgent attention by those engaged in conducting and overseeing paediatric MRI research.

Consent

The Consent Dilemma of Research Involving Children

The application of the general competence requirement to research involving minors (i.e., persons under the legislated age of majority) can raise difficult issues. If understood narrowly as requiring the consent of all minor participants, as opposed to allowing voluntary and informed consent to be provided by appropriate substitute decision-makers in those instances where the minor lacks the requisite decisional capacity, then many minors with serious and debilitating health conditions could be excluded from research [7]. Thus, in the name of protecting minors from inappropriate involvement or exploitation in research, they may be excluded from the benefits of research [8, 9] and put at more health risk than consenting adults. Children could become “therapeutic orphans” who are deprived of the benefits of scientific advances.

The issues pertaining to consent, as described above, are particularly acute in paediatric MRI research. First, because many neurologically compromised children will be important research participants from the scientific perspective, the ethical concerns regarding exploitation of children in research must remain high on the neuroimaging ethics agenda. Furthermore, some of the children who may suffer most from exclusion from research are the very children who are most vulnerable given their compromised neurological status (and concomitant vulnerability to discrimination).

Second, much of the neuroimaging research that might benefit children cannot be done on adult participants. The developing brain is quite distinct from the developed brain. The results of research involving adults cannot necessarily be extrapolated to children. When this has been done in the past, serious harm has accrued to the infant and child participants as demonstrated in research involving chloramphenicol and sulfa drugs in neonates and insulin regulation in children [10, 11]. Therefore, a considerable amount of research is needed in order to benefit children for

which adults cannot serve as alternatives. In particular, there is a specific need to establish normative values for new imaging research. MRI can improve visualization of structural findings and has the potential to highlight functional findings never before seen. In order to establish normative images, however large numbers of healthy children will need to be involved in research.

Third, it must be acknowledged that, precisely because the paediatric brain is in development, the effects on children of MR imaging techniques proven safe in adults are unknown. Uncertain risk is accompanied by potential benefits; sometimes the benefit is for individual child participants but often it is for children as a group. Justice demands that minors who do not have the required decisional capacity must not be automatically excluded from MRI research that possesses potential benefits for individual participants or for the larger group to which such individuals belong [12]. However, the appropriate boundaries for the inclusion and exclusion of children remain unclear. Paediatric MRI research requires much more careful deliberation and clear articulation of these boundaries.

Surrogate Decision-making

Parents have both the right and the responsibility to make clinical decisions for their children (those who are not mature minors). In doing so, they act as surrogates and are required to utilize the best interests of the child as the basis for their decision-making. The standard for research decision-making has also evolved into parental consent/permission and child assent. However, the basis for surrogate decision-making is complicated in the research context. Some research may have the potential to benefit the participants but much research has no such potential – it is designed to gain generalizable knowledge that may benefit others in the future.

And so it must be asked, can or should parents be able to give consent/permission for participation in research that has no potential benefit for the child? Is it possible to understand best interests as encompassing benefits to others? There are those who would answer no to this question; alternatively, others argue there is a benefit to children in learning altruism [13]. In terms of the test that surrogates must employ before reaching a decision, it may be appropriate to

explore whether the best interests test should be the required basis for surrogate decision-making in paediatric research. It is essential to neuroimaging ethics for these questions to be answered as, for example, much research is needed to establish normative values and yet the establishment of normative data requires the involvement of children for whom the research will have no direct medical benefit.

Paediatric MRI research introduces additional challenges to the legitimacy of some parental permissions/consents. In addition to the inherent difficulties of understanding the nature of research and its risks, there can be a powerful “therapeutic misconception” [14–16]. Parents of ill or vulnerable children, such as those with neurological conditions, may agree to research in the mistaken belief that it will provide benefits to their child even when researchers have carefully described the purpose of research as non-therapeutic. This is a crucial consideration with new technologies such as MRI precisely because they are often only available in specific centres focusing on severe and complex conditions which exacerbate parental vulnerability to therapeutic misconception. Efforts should be made to better understand the phenomenon of therapeutic misconception and to develop ways to manage the threats to voluntariness that can arise in the neuroethics research context. These efforts will need to involve philosophical reflection as well as the development of best practice guidelines.

Privacy and Confidentiality

A number of privacy and confidentiality issues can arise in the context of paediatric MRI research. A variety of situations may arise in which researchers need to be attentive to the potential for the disclosure of personal information about children. First, in the context of enrollment of potential participants, personal information will need to be requested and tests may need to be performed to ensure the safety of participants as well as to determine whether any exclusion criteria are met. For example, researchers must ascertain whether potential participants have tattoos or piercings and whether they might be pregnant. If a parent/guardian is present at the time of enrollment, the child may be placed in the position of having to disclose information that he or she wishes to keep from his or her parent/guardian.

Moreover, third parties may have an interest in the results of MRI scans. For example, insurance companies, motor vehicle licensing bodies, and schools might have an interest in the results of MRI scans even when undertaken for research purposes. In addition, other researchers might have an interest in accessing stored data or images from previous clinical or research MRIs for research purposes. And yet, the MRI research participants may well have an interest in restricting the use and disclosure of their MRI results.

A lack of clear direction is evident in legal and ethical guidelines/policy statements on the issue of the protection of privacy during the process of enrollment in research. And yet, as noted above, significant privacy interests can be affected through the enrollment process. Children may well desire to keep information about body piercings, tattoos, or pregnancies from their parents.

Where the parents have decision-making authority regarding the participation of their children in research, the researcher should provide all information necessary to exercise that authority. The researcher should, however, be careful to not elicit personal information from the child that the parent does not need to have in order to make a determination about participation [17]. This can perhaps best be achieved through providing an opportunity for the child to discuss personal information with the researcher separate from the parent.

Where the parents do not have decision-making authority with respect to the participation of their children in research (e.g., the child is a mature minor or has reached the legal age of consent to participation in jurisdictions where there is such an age), the minor ought to have a privacy right that is respected and protected. This means that researchers should ensure that the minor is not asked for personal information or given test results in the presence of parents without the prior consent of the minor (where that consent has also been sought in the absence of the parents).

It is not known to what extent such precautionary privacy-protective steps as described above are taken in many paediatric MRI research settings. Therefore, in order to educate researchers about the law and ethics with respect to this issue and to promote the protection of privacy and confidentiality in this arena, it would be helpful to have best practices developed with respect to privacy and enrollment processes.

Unexpected Findings

Detecting an unexpected pathology (or imaging artifact) known as unexpected findings, is a serious issue in MRI research and may significantly impact the welfare of research participants [1]. Psychological harm may result if the treatment options for the incidentally-discovered condition are limited [18] and this can complicate the informed consent process. These considerations may lead to a number of critical questions. For example, how are the risks of MRI technologies explained in the clinical and research contexts? How should they be described? What guidelines should be put in place to assess the decision-making ability of persons with brain disorders affecting their capacity to reason about clinical or research MRI? Who can authorize the participation of research of individuals with loss of or diminished capacity? What are the specific concerns for the paediatric population?

Unexpected findings on neuroimaging research scans are not as rare as one might think. Retrospective reviews of the MRI scans of healthy children and adults who participated as controls in neuroimaging research have revealed unexpected findings in approximately one-fifth to one-half of scans, with 1–2% meriting urgent or immediate medical referral [19–22]. The only study to date which has focused on unexpected findings in healthy children found abnormalities in 47 of 225 scans, with 17 meriting routine medical referral and one urgent medical referral [21]. Unexpected findings can change the lives of research participants in profound ways, and they can have a disturbing effect on researchers who are unprepared to deal with them [23, 24]. Therefore, far from being a hypothetical concern, unexpected findings represent an important practical and ethical challenge to neuroimaging researchers.

In the small but rapidly growing literature on the subject, unexpected findings are commonly categorized according to the need for medical referral, based on the scheme introduced by Bryan et al. [25]: (1) no referral required; (2) routine referral required; (3) urgent referral required; (4) immediate referral required. Findings for which no referral is required include common physiological changes, like chronic inflammation of the nasal passages and paranasal sinuses. Findings in this category also include so-called normal variants. These are minor anatomical

variations that occur in a fraction of the population and are without functional significance. Minor asymmetries in the cerebrospinal fluid spaces are a good example. Participants can expect little benefit from the discovery of such findings. However, in the case of normal variants, some participants may feel harmed by the discovery of a normal variant if they are prone to worrying about deviations from “normal.” This may be particularly relevant to school age children and adolescents who may be concerned about “fitting in.”

Unexpected findings that require medical referral, on the other hand, have implications for a participant’s physical health as well as emotional well-being. For children, these findings could significantly affect their physical and psychological development. Yet, depending on the nature of the finding, there is the potential for benefit as well as harm associated with such a discovery. Some lesions, like tumours or aneurysms, may be treated with better success if they are detected fortuitously in a preclinical stage rather than in an advanced, symptomatic stage. Clearly, it would be wrong to deny participants any benefit they might derive from the unexpected detection of a treatable lesion. On the other hand, it is important to recognize the potential for serious harm, given that the unexpected detection of a lesion may lead to anxiety, further tests, unpleasant treatments and associated complications. This is particularly regrettable when a lesion proves untreatable, or when a lesion proves to be harmless only after extensive, invasive evaluation. Another risk that should not be overlooked is the effect of an unexpected finding on a participant’s insurability [23]. Review of the literature on unexpected findings in neuroimaging studies shows that the insurance industry does take an interest in such findings [26, 27].

Undoubtedly, both participants and researchers would benefit from a proactive, standardized approach to the detection and management of unexpected abnormalities on MRI research scans. REBs would also benefit from the existence of clear guidelines, since they cannot be expected to resolve these issues anew for each MRI research proposal submitted for ethical review. In the future, the ability of neuroscientists, radiologists and bioethicists to deal effectively with unexpected findings on MRI scans from research studies will depend on their ability to find collaborative solutions to these questions.

Advances in Functional MRI

Advances in functional brain imaging technologies over the last two decades have led to exponential growth in the number of studies that provide insight into the working brain [28]. This, in turn, has generated a variety of ethical concerns about the emerging applications of these technologies in both paediatric and adult populations alike. Many experts have stressed the importance of tempering enthusiasm and exercising caution when it comes to interpreting what amounts to deceptively intriguing but greatly oversimplified windows into brain function [28, 29].

The potential for misuse of fMRI data poses unique concerns for the paediatric population. As in other medical fields utilizing “high-tech” modalities, the applications of fMRI may overstep the science. In the study of behavioural genetics, there is ample indication that new technologies are being used despite the insufficient scientific proof for their validity [30]. This eagerness to use technologies before they have been scientifically validated could also impact paediatric fMRI. With respect to education, certain institutions would likely be interested in studies that claim to demonstrate associations between functional brain maps and learning abilities. The potential would exist for functional neuroimages to be used inappropriately to categorize students and deny educational prospects. Some foresee the possible use of neuroimaging “scores” to screen students for admission into educational programs [5]. Beyond education, brain profiling could be misused in other areas, such as, criminal law. The current challenge is to begin developing policies that will guide the use of functional imaging methods for applications that have the potential to infringe on privacy and personhood.

Very little attention has been paid to the ethical issues surrounding functional brain imaging in paediatric populations. This is largely due to the fact that there are considerably fewer paediatric functional imaging studies. Therefore, it is difficult to make predictions about the effects of functional neuroimaging technologies in the paediatric population beyond analogies with issues that occur in adults. However, the ethical dilemmas associated with functional imaging in children are magnified due to interactions between the ever-changing background of development, the variability of brain function, and the methodological limitations of functional imaging

technologies [6]. In the context of neonatal care, fMRI research may provide insight into the likelihood of brain dysfunction in later life and open the door to grave ethical questions about withholding or withdrawing medical support from certain infants [31]. The plasticity of the immature brain increases the margin of error of such forecasts, thereby compounding an already difficult situation [31].

Consider, for example, the potential for misinterpretation of what ‘activation’ actually conveys in terms of brain function. In the case of functional neuroimaging, it may be even more challenging to convey the scientific reality in a manner that will be understood or accepted by a child. This point is especially pertinent when considering the difficulties faced by researchers themselves in evaluating fMRI data. Interpretation of paediatric functional imaging results is complicated by difficulties in establishing good normative data. Hinton [6] reviewed some of the problems and pitfalls in determining what is ‘normal’ with respect to structural anatomy and development – the situation only gets more complex when characterizing functional anatomy.

Despite caveats like these, there is promise in the application of a technology like fMRI for understanding the functional organization of the developing brain. For instance, it is possible to examine speech perception in infants [32] or dyslexia and reading impairments in children [33]. Research studies have begun to highlight ethical issues specific to children. Konrad et al. [34] and others have investigated whether children with attention deficit hyperactivity disorder (ADHD) differ from controls in terms of brain activation during attention-dependent tasks. Yet, should decisions about medication be guided by differences in readings of fMRIs? Understanding the neurobiology of disorders like ADHD is critically important. Nonetheless, to date, brain-based profiling could lead to over-interpretation of functional images, influencing all of the conclusions that may follow.

While the situation for paediatric functional imaging is similar to that of adults, far more care must be taken in terms of the complexity of interpreting brain activation findings within a developmental context. Regardless, functional imaging applications in paediatric populations are beginning to emerge. A close examination of the ethical issues will help ensure the proper application of functional brain imaging in paediatric and other populations.

Conclusions

On the basis of this review, we conclude that there is much work to be done in the area of paediatric MRI research ethics. Further clarification as to the role of children and surrogates in the consent process is needed. The neuropathology of the developing brain is believed to be quite distinct from that of the developed brain. However, valuable investigations into the differences may be hindered if issues on consent for paediatric research participation are not addressed.

Second, steps need to be taken in MRI research settings to assure privacy for children. Investigators and clinicians must be educated in the issues surrounding privacy and confidentiality for young research participants. These issues figure most prominently at times of enrollment and disclosure of research results. Best practices could help alleviate any confusion, although it is appreciated that the sea of privacy legislation, renders this a most arduous task.

Third, unexpected findings represent an important ethical challenge to researchers. The disclosure of unexpected findings requires the establishment of guidelines detailing the best course of action. Presently, very little information is available concerning the common practice of paediatric MRI research groups. Working through issues such as reporting of unexpected findings and the classification of such findings would be beneficial to both participants and investigators.

Lastly, the extent of the limitations of fMRI needs to be conveyed by researchers and clinicians alike. Guidelines, based on these limitations, to restrict the use of fMRI in the diagnosis and prognosis of paediatric disorders need to be developed.

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