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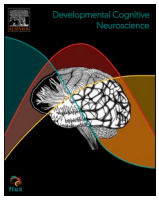

How will developmental neuroimaging contribute to the prediction of neurodevelopmental or psychiatric disorders? Challenges and opportunities

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ABSTRACT

Successful developmental neuroimaging efforts require interdisciplinary expertise to ground scientific questions in knowledge of human development, modify and create technologies and data processing pipelines suited to the young brain, and ensure research procedures meet the needs and protect the interests of young children and their caregivers. This paper brings together four interdisciplinary perspectives to tackle a set of questions that are central for the field to address as we imagine a future role for developmental neuroimaging in the prediction of neurodevelopmental or psychiatric disorders: 1) How do we generate a strong evidence base for causality and clinical relevance? 2) How do we ensure the integrity of the data and support fair and wide access? 3) How can these technologies be implemented in the clinic? 4) What are the ethical obligations for neuroimaging researchers working with infants and young children?

Developmental neuroimaging is a rapidly growing field, as exemplified by the recent launch of the Fetal, Infant, and Toddler Neuroimaging Group (FIT'NG), an academic society specifically designed to bring together researchers seeking to understand neurodevelopment in the first years of life (Pollatou et al., 2022). As technological and methodological advances have made it possible to measure brain structure and function more reliably—from pregnancy through the toddler years—there is an increased focus on how to use developmental neuroimaging to predict psychological, health, and behavioral outcomes later in life. As part of the FIT'NG 2023 meeting, an interdisciplinary panel was convened to discuss the role of developmental neuroimaging in the prediction of neurodevelopmental and psychiatric disorders. This paper is a report-out of a portion of the topics discussed by the panelists, highlighting pressing issues in the use of developmental neuroimaging as a predictive tool (Spann and Scheinost, 2024).

Here we describe a series of challenges and opportunities that must be met for developmental neuroimaging to play a role in clinical prediction. As an interdisciplinary group of co-authors, we address in four sections: 1) The importance of randomized control trials for infant MRI research, 2) FAIR (findable, accessible, interoperable, and reusable) data and cumulative science in developmental neuroimaging, 3) advances in developmental neuroimaging needed for clinical translation, and 4) ancillary care obligations in developmental neuroimaging research. Addressing these topics will lay the evidentiary foundation for the use of developmental neuroimaging, ensure the robustness and openness of the evidence, tackle the practicalities of implementation, and satisfy the unique ethical responsibilities that come with this new approach to clinical prediction and care.

1. The importance of randomized controlled trials for infant MRI research (Mary Dozier, psychologist)

When studying environmental effects on brain structure and functioning, researchers are often interested in making causal claims – in particular, they may want to ask whether environmental factors affect the developing brain. However, much of the research conducted thus far involving environmental effects on brain development has been correlational in nature. That is, most studies have investigated the effects of variables, such as prenatal risk or parental responsiveness, on differences in brain structure and functioning without experimentally manipulating the predictor variables. In such studies, one cannot make strong causal inferences even when statistically controlling for potential

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confounding variables (Miller and Chapman, 2001).

On the other hand, randomized controlled trials (RCTs) in which the relevant environmental variable (e.g., parental responsiveness) is manipulated allow one to make causal claims. We consider two examples here. First, the Bucharest Early Intervention Project (BEIP; King et al., 2023) manipulated the early caregiving environment by randomizing children from orphanages to care as usual or to specialized foster care, thus providing a vastly different environment for children randomized to one group versus the other. Second, a much more circumscribed intervention, Attachment and Biobehavioral Catch-up (ABC; Dozier et al., 2018) targeted parental responsiveness to infant cues very specifically through a brief home visiting program for parents involved in the child welfare system.

The BEIP and ABC studies provide evidence that the environment (neglect vs responsiveness) causally impacts brain development. Children randomized to foster care in the BEIP showed more mature brain functioning when assessed using electroencephalography (EEG) (e.g., Debnath et al., 2020), and more mature brain structure as seen in gray and white matter volume and cortical thickness (Sheridan et al., 2012, 2022) than children randomized to care as usual. Children randomized to receive the ABC home visiting intervention similarly showed more mature brain functioning when assessed through EEG (Bick et al., 2019) and more optimal patterns of brain structure and functioning when assessed through MRI than seen among children whose parents received the control program (Korom et al., 2024; Valadez et al., 2020, 2024).

Relatively few studies have examined effects of experience on children's brain development experimentally, and even fewer have examined effects on infants' brain development experimentally. One of the few exceptions, Milgrom et al. (2010) conducted a small experimental study examining effects of enhanced parenting on the brain development of infants born before 30 weeks gestational age (Milgrom et al., 2010). Diffusion tensor imaging (DTI) results revealed greater maturation and connectivity of white matter for the intervention group than for the control group, findings generally consistent with correlational studies reported in the literature (e.g., Rifkin-Graboi et al., 2015). We applaud these efforts and urge infant MRI researchers to feel the pull to ask their questions experimentally.

Questions have been raised about the ethics of randomizing young children to an experimental or control condition (e.g., Master and Fins, 2018). As researchers conducting randomized controlled trials, I and others (e.g., Zeanah et al., 2012) have made several points: 1) Typically the control condition does not deprive children of the treatment they would ordinarily receive (e.g., in the Bucharest Early Intervention Project, the principle of "noninterference" was employed with decisions about placements of children in the control group not affected by their participation in the research study); 2) Without the RCT, children from neither the experimental nor the control group would typically receive intervention beyond usual practice; and 3) It is usually unclear whether children in the experimental group are receiving a superior treatment until the completion of the RCT. Although natural experiments (e.g., implementing early intervention through telehealth as necessitated by the pandemic) are useful, they do not rule out confounds as thoroughly as do randomized controlled trials. For example, one would not know whether the differential effectiveness seen when implementing intervention through telehealth resulted from additional parental stress or some other factor associated with the pandemic. Therefore, if thoughtfully and carefully considered, we suggest that RCTs can provide important information regarding the effects of early experience on infants' brain development.

2. FAIR data and cumulative science in developmental neuroimaging (Rebecca Saxe, cognitive neuroscientist)

In neuroimaging studies of the brains of infants and toddlers, researchers are often limited by small and noisy datasets. These limitations are not the researchers' fault; collecting high quality developmental neuroimaging data is hard (Ellis et al., 2020). In particular, fMRI requires participants to lie completely still, in a dark, noisy, and unfamiliar environment, which is very challenging for infants or toddlers. However, analysing small and noisy datasets dramatically increases the risk of non-replicable and non-cumulative scientific claims (Boyce et al., 2023). Open science practices can help reduce these risks in developmental cognitive neuroscience (Gilmore et al., 2017; Niso et al., 2022).

Three key practices will increase the clinical impact of infant and toddler neuroimaging: preregistration of analysis plans, open data sharing, and testing generalizations.

First, researchers should pre-register their analysis plans (Nosek et al., 2018, 2019). For infant and toddler neuroimaging, this would mean committing in advance to sample sizes, power analyses, stopping criteria, preprocessing steps, thresholds for statistical claims, and correction for multiple comparisons (Pfeifer and Weston, 2020). Committing to analysis plans before seeing any data is the best way to limit experimenter degrees of freedom – the tendency to explore many paths of data analysis and (potentially unconsciously) choose the path that yields preferred results (Ellis, 2022).

Second, researchers should make infant and toddler neuroimaging data FAIR whenever possible. For example, the OpenNeuro repository is an excellent option (Markiewicz et al., 2021). There are three key benefits to data sharing, particularly when generating new data is difficult, expensive and rare as in our field. (i) The reproducibility and rigor of scientific claims can be directly confirmed. Critics can directly scrutinize the data, and claims that hold up to this scrutiny are more likely to be true. Anticipating scrutiny also makes the original researchers more careful and more likely to catch mistakes. To enhance scrutiny and reuse, the analysis code used to process neuroimaging data should be shared along with the data. (ii) The data can be reused to test different scientific hypotheses. Neuroimaging data in particular often allow for testing more than one hypothesis. When data are shared, researchers who don't have resources to generate their own data can nevertheless advance science by generating and testing hypotheses in shared data. Also, data collected by multiple groups can be aggregated to generate larger datasets with more statistical power. Combining multiple small datasets has repeatedly yielded novel discoveries in neuroscience that would have been impossible in any one of the datasets alone (Ferguson et al., 2014).

Sharing infant and toddler neuroimaging data does pose a challenge for privacy, which is particularly sensitive if these data could be used for predicting neurodevelopmental or psychiatric disorders (White et al., 2022). Parents may hesitate to consent to have their young child's brain in an open database, because of risks of stigma or insurance hikes (if a "pre-existing condition" were revealed). While deposited data are always anonymized, analyses suggest that it is possible to re-identify an individual adult directly from their brain images (Jwa et al., 2024; Jwa and Poldrack, 2022). Researchers who plan to share neuroimaging data from infants and toddlers should work with their institutional review boards, and develop a consent form that clearly articulates these potential risks.

An example of the benefits of data sharing is Richardson et al. (2018). In this project, 122 children aged 3–12 years watched the same 6-minute Pixar Short film, 'Partly Cloudy', while fMRI data were collected. The authors collected these data in order to test hypotheses about the cortical correlates of Theory of Mind development. Indeed, task-driven activity in right temporo-parietal junction was associated with both age and (separately) performance on a behavioural test of Theory of Mind (Richardson et al., 2018a). Yet these data were much more broadly useful, particularly given the unusual (at the time) inclusion of awake task data from three year olds. Since publication, this dataset has been downloaded more than 1500 times (Richardson et al., 2018b). At least thirteen published papers have reported re-analyses of this dataset to test distinct hypotheses about both other brain regions and other cognitive functions. In addition the dataset has been used in training courses for developmental neuroimaging analyses.

Finally, the most important practice to ensure that we make rigorous claims about links between infant and toddler neuroimaging data, and neurodevelopmental or psychiatric conditions, is that we explicitly test for generalization out of sample (Yarkoni, 2022). Minimally, all hypothesis about such links should formulated in one dataset, and tested in an independent dataset. That is, we need a robust practice of testing generalizations out of sample. Testing correlations between neuroimaging and phenotypic or clinical measures faces a major pitfall: because there are so many ways to analyse neuroimaging data, it is almost always possible to find some feature in the brain data that correlates with any other measure (Vul et al., 2008). Transparent preregistration and appropriate corrections for multiple comparisons can help, but the true standard of evidence, especially when children's health and family wellbeing are at stake, should always be an exact replication in a new sample. Until a replication is available, all claims from individual papers should be accepted only with caution. Funding agencies and journals should therefore be anxious to support and publish such replications. Explicitly considering generalization to an independent sample should also encourage researchers to consider other limitations on generalization, including whether the sampled population is representative of children at risk for neurodevelopmental or psychiatric conditions on demographic (e.g. race, geography, socioeconomic status) or clinical (e.g. severity) dimensions (Nketia et al., 2021).

Combined, these three practices of pre-registering analysis plans, sharing data, and testing the generalization of claims to independent datasets, will ensure that claims of links between infant and toddler neuroimaging and neurodevelopmental or psychiatric diagnoses are as rigorous as possible, generating cumulative progress.

3. Advances needed for clinical translation (Koraly Pérez-Edgar, developmental psychologist)

The last two decades have seen a remarkable increase in our ability to capture early neural development, beginning in utero and expanding into childhood and adolescence (Johnson and Haan, 2015). Relatively new technologies, such as magnetic resonance imaging (MRI) and functional near infrared spectroscopy (fNIRS), in addition to long-used techniques, such as EEG, have provided developmentally appropriate measures of underlying biological substrates that support observed patterns of behavior (Fox et al., 2006). Much of this work has occurred in parallel to another rich tradition examining individual and environmental factors that influence the rise of psychiatric difficulties in children, drawing from work in developmental psychopathology and clinical science (Cicchetti and Posner, 2005). Bridging this work is at the core of translating work from bench to bedside (Corlett and Schoenbaum, 2021). There is still much to be done to fully realize the potential of developmental neuroscience as a translational tool that can be used directly in a clinical setting (Ostlund et al., 2021). In this section we highlight three rough categories of concern that are most pressing at the moment, (1) the constructs, (2) the technologies, and (3) their integration in our current healthcare system.

First, researchers in developmental neuroscience and clinical science need to work in tandem to clearly and directly identify reliable biological markers associated with specific psychiatric disorders. This is an issue of both sensitivity and specificity and may be the largest initial barrier to moving forward with direct clinical application (Pfeifer and Allen, 2015). Developmental neuroscientists have done a wonderful job of outlining basic cognitive and affective processes that are associated with regions of interest in the brain, as well as distributed but interacting neural networks. For example, we know that deficits in decision making in children are associated with activity in the prefrontal cortex (Hartley and Somerville, 2015), and subsequently linked to neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) (Sonuga-Barke et al., 2016). In the same way, we know that variations in functional connectivity in systems involving the temporal-parietal junction (TPJ) are associated with both deficits in theory of mind and social cognition (Saxe and Kanwisher, 2004) as well as symptoms of autism spectrum disorders (Lombardo et al., 2011). However, these relations are not typically distinct to one or even a small subset of clinical presentations, and it is unclear how stable or robust any individual differences in these relations may be.

Within a clinical setting providers will need a direct link between a constrained set of neural markers, such as delta-beta coupling derived from EEG (Harrewijn et al., 2016) or BOLD levels in the striatum to reward (Delgado, 2007), and observable symptoms presented in the clinic, such as deficits in emotion regulation or disinhibited behavior. For example, a clinician suspicious that a child has type 1 diabetes will request a specific cluster of tests, including a random glucose test, a hemoglobin A1c test, a ketone test, and a type 1 diabetes autoantibodies test. The clinician will have a specific set of cutoffs that, together, indicate a formal diagnosis.

Unless a clinician can do the same when concerned with emerging symptoms of anxiety or the first signs of neurodevelopmental delay, they cannot reasonably use individual differences in a neuroimaging marker to generate a specific diagnosis. Neuroscience researchers and developmental scientists are now beginning to inch toward this goal. For example, the When2Worry project aims to modify robust developmental metrics associated with temperamental irritability to create risk profiles and then clinical norms predicting maladaptive profiles in young children to separate pre-clinical markers from the normal affective dysregulation and distress seen in toddlers and preschoolers (Smith et al., 2019). Similarly, researchers are using neural and behavioral markers to predict the effectiveness of cognitive behavioral therapy (Thai et al., 2024).

Second, imaging modalities must be refined and made amenable to use by a wide swath of providers, who come to their work with highly heterogeneous backgrounds in neuroscience (Reynolds et al., 2009). Clearly, we cannot presume that all children, their families, and their providers could easily access state-of-the-art MRI facilities. This may mean that in anticipation of clinical application we need to create multimodal assessments that build on a "chain" of technologies moving from the most expensive or least accessible down to the least expensive and most accessible. That is, a test that is amenable for use in a clinic would be linked back to a more resource-intensive measure used in the testing and norming process.

This approach is built on the premise not all children need to, or should have, a 3 T MRI to generate a clear diagnosis when we can more easily use electrophysiology or behavioral metrics in the clinic. However, we can leverage low Tesla scanners, as an entry point into pediatric clinical settings due to their portability, safety, and cost-effectiveness. Small portable MRIs operate at much lower magnetic fields (e.g., 0.064 Tesla), making it more suitable for bedside or clinic use. As such, we need to trade the need for deep structural and functional resolution in the norming phase for higher temporal resolution in the clinical phase. These in-clinic technologies, such as low Tesla MRI, EEG, and fNIRS, should be easy to implement through automated or pre-programmed processes that are informative and flexible for clinical use (as in the Type 1 diabetes example). Any neuroscience-based measures should provide easy to read metrics that the clinician can assess and compare to normative values. This final point will require large-scale studies in order to generate growth curves, similar to the height and weight charts familiar to anyone in a pediatrician's office. Until then, we must be very cautious in making individual assessments since within-study comparisons are often embedded in non-representative and selective samples. As one preliminary step, we can leverage available data to create risk profiles, prior to norming, as more richly discussed in other contributions to the current special issue.

Third, we need to consider the practical implications of how children will access this care, beyond simply generating diagnostic metrics and shrinking the technology to fit the clinic. In the context of the United States, we have strong interventions and treatments for a number of physical and psychiatric disorders that are simply inaccessible to a wide

swath of the population due to socioeconomic and geographic barriers (Kelleher et al., 1997). Thus, a multicomponent approach is needed to integrate neuroimaging-based technologies into our existing health care infrastructure. This includes first educating clinicians and providers in the use of these technologies through either built in curricula in medical schools and other places of training, or through continuing education processes (Arbuckle et al., 2020). We must then bring insurance and governmental entities into the conversation so that these technologies successfully advance through the approval process (e.g., Food and Drug Administration) and are then paid for through insurance.

As with many things in the US, economic barriers can create conditions under which treatments may as well not exist as they are wholly unavailable to many of the individuals who need them. Points one and two fall more comfortably within the domain of researchers conducting the science. However, for full implementation they will need to stretch themselves to engage in policy level conversations. If not, the hard work and ingenuity of scientists and clinicians will not generate actual tangible results for children and their families.

4. Ancillary care obligations in developmental neuroimaging research (Kate MacDuffie, PhD MA, pediatric bioethicist)

What do developmental neuroimaging researchers owe their participants? The amount of effort often required to collect useable data from infant/toddler participants is often herculean, and families typically participate in such research for limited financial incentives and no prospect of direct benefit. Typically, developmental neuroimaging studies do not share results with participants, aside from incidental anatomical findings identified in rare cases via radiologic review (Orme et al., 2010). The culture of many neuroimaging research groups is to cleanly separate research from clinical care, and attempt to avoid creating unrealistic expectations for participants about receiving any clinical benefit from the study (often referred to as the “therapeutic misconception”; Horng and Grady (2003). However, there is increasing recognition in other areas of neuroscience—implanted neural device trials, for example—that the lines between research and clinical activities are often blurrier than our current regulatory structures and ethical frameworks were designed to accommodate (Goering et al., 2024). Use of neuroimaging technologies to predict future behavioral and functional outcomes in infants and toddlers is an area in which the clear divisions between research and clinical care might exist in the minds of researchers, but may be blurrier for participating families, particularly those whose children are at elevated risk for developing a given disorder or condition. How should researchers who are using tools of developmental neuroimaging navigate this ethical complexity? Here, we explore the concept of ancillary care obligations as a useful frame for this challenge.

Ancillary care obligations, according to Belsky and Richardson (2004), is care that is provided to research participants that is beyond what is required to make a study scientifically valid and safe. The concept has been applied most frequently to research occurring in developing countries where access to medical treatments can be extremely limited—for example, HIV researchers who recruit participants in developing countries for an antiretroviral drug trial may be obligated to continue to provide access to drugs for HIV-positive participants even after conclusion of the trial (Goering et al., 2024). Belsky and Richardson propose that the strength of ancillary obligation depends on at least four factors: 1) participants’ vulnerability, 2) participants’ uncompensated risks or burdens, 3) depth (intensity and duration) of the researcher-participant relationship, 4) participants’ dependence on the researchers.

How might these four factors be evaluated in developmental neuroimaging research? Let’s take two examples. First, a study using MRI to predict psychosis in ultra high-risk (UHR) adolescents (Andreou and Borgwardt, 2020) and second, a longitudinal study using MRI to predict autism in infants with a family history (Wolff and Piven, 2021).

In the UHR for psychosis example, 1) Are participants vulnerable? Yes they are, both because they are minors (and therefore unable to independently consent for research) and because they have subthreshold psychotic symptoms and/or functional decline (by definition of being UHR). 2) Are there uncompensated risks and burdens? This is a likely yes. Financial compensation for research participation is typically very low, often unethically so (Largent and Lynch, 2017), and thus it is likely that adolescents in such a trial are undercompensated (if directly compensated at all). In addition, the experience of an MRI scan can be anxiety inducing, perhaps particularly those with subthreshold psychiatric symptoms, and thus the burden for these adolescents of participating is high. 3) What is the depth of the relationship with researchers? In a one-time neuroimaging study, the intensity and duration of the relationship are both small and so the depth of relationship would be considered low. 4) What is the degree of dependence on researchers? The answer to this question largely depends upon the degree to which necessary healthcare is available to participants outside of the research context. In the case of UHR psychosis, the standard treatments of cognitive behavioral therapy with or without antipsychotic medication are clinically available (Morrison et al., 2020). So, provided that the participant lives in a geographic area and has the financial resources to access such treatments (both big "ifs"), then the dependence on researchers should be relatively low.

In the infants with family history of autism example, 1) Are participants vulnerable? Yes. Infants, even more so than adolescents cannot consent to participate in research. Moreover, the caregivers of infants in these studies also have some degree of vulnerability, given that they are likely to be worried about their child’s development (MacDuffie et al., 2020). 2) Are there uncompensated risks and burdens? Like above, it is likely this answer is yes, given the typical underpayment of research participants and the often high time/energy burden of participating in infant neuroimaging studies that may require late night visits to the scanner to capture infants in natural sleep. Also, in this case, it is the parent that is compensated, not the infant, and so all risks and burdens experienced by the infant are uncompensated. 3) What is the depth of the relationship with researchers? In a longitudinal study, a relationship between researchers and participants can develop over time, resulting in earned trust and a higher degree of ancillary care obligations. 4) What is the degree of dependence on researchers? As above, the degree of dependence depends upon the extent to which healthcare is available outside of the research context. Unlike sub-threshold psychosis, for infants likely to develop autism, there are no clinical interventions available (Grzadzinski et al., 2021), and thus far only one published RCT showing evidence that presymptomatic intervention may improve subsequent outcomes (Whitehouse et al., 2021). Therefore, the absence of available interventions for presymptomatic infants results in increased ancillary care obligations.

Exploring these questions in these two contexts reveals that for both studies, there is a degree of ancillary care obligations for researchers (higher for the autism than the psychosis example). How can these obligations be satisfied? Belsky and Richardson (2004) articulate the need to balance ancillary care obligations against the primary goal of research which is to advance scientific knowledge. Even for well-funded studies, resources are limited, and extensive expenditure of effort and money to support ancillary care obligations would detract from research progress. So a balance must be struck.

What should researchers in these two cases do? In the UHR adolescents case, researchers should assess whether participants are currently in treatment, and if not, assist them with finding appropriate treatment. However, it would not be the researcher’s obligation to provide the treatment directly. In the autism case, researchers could assess parental concerns about their child’s development and assist parents with finding appropriate therapies (e.g., speech and language therapy to address language delays) even if autism-specific therapies are not yet available. Even better, neuroimaging researchers could partner with intervention researchers to triage infants who show patterns predictive of autism on

MRI into a presymptomatic intervention trial, which would both satisfy ancillary care responsibilities and generate additional scientific knowledge about intervention efficacy that is necessary to move the field forward (Grzadzinski et al., 2021; MacDuffie et al., 2021).

5. Conclusion

The panel presentation at the 2023 FIT'NG Conference asked panelists from a number of disciplines to consider the opportunities and challenges of moving neuroimaging technologies, particularly with the youngest patients, into a clinical realm. Here, four of the participants briefly introduce important considerations. 1) How do we generate a strong evidence base for causality and clinical relevance? 2) How do we ensure the integrity of the data and support fair and wide access? 3) How can these technologies be implemented in the clinic? 4) What are the ethical obligations that come with the use of clinical neuroimaging with infants and young children? The points raised here call for an integrated and sustained partnership across multiple domains, given the complexity and interdependence of these concerns. Scientific societies such as FIT'NG play an important role in bringing together experts for these interdisciplinary conversations.

CRediT authorship contribution statement

Kate MacDuffie: Writing – review & editing, Writing – original draft; **Rebecca Saxe:** Writing – review & editing, Writing – original draft; **Mary Dozier:** Writing – review & editing, Writing – original draft; **Koraly Perez-Edgar:** Writing – review & editing, Writing – original draft.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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