Essay

Involving children with neurodevelopmental disorders in biomedical research

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For the **prevalence of neurodevelopmental disorders** see https://www.cdc.gov/ncbddd/developmentaldisabilities/facts.html

In 2018, the US Center for Disease Control and Prevention reported that, among the general population of children in North America, 3–17% have been diagnosed with one or more neurodevelopmental disorders. New technologies and interventions afford improved quality of life for many of these children, but realising such benefits requires their participation in biomedical research. While children's rights to participation have been codified in the 1948 UN Declaration of Human Rights, the 1964 Declaration of Helsinki, and the 1989 UN Convention on the Rights of the Child, children with neurodevelopmental disorders in particular have historically been neglected from research and oftentimes from appropriate oversight.

A rights-based approach fosters inclusivity and respectful relationships in otherwise complex, asymmetric power relationships in research. Challenges that are affecting children ever increasingly today include the effect of neurotechnologies on the developing brain and social media use on researcher–participant relationships. We discuss these two challenges below and offer some solutions.

Wearable EEG-based neurotechnologies and mobile neurofeedback apps have been developed to help children with neurodevelopmental disorders—for example, to reduce anxiety as they start school. The development of this type of intervention requires data on brain state, cortisol levels, and executive functioning. The children may be identified for the study by staff; researchers obtain parent consent and child assent; and data are collected and archived for analysis to investigate learning trajectories.

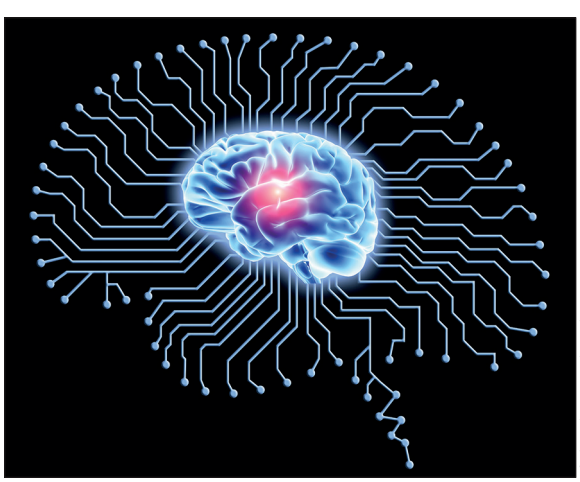
Many longstanding ethics questions broadly apply to this scenario. How can children with neurodevelopmental disorders who may not have the means to understand research really provide informed assent? How should archived data be managed as these children become adults? Should collateral effects or incidental findings of potential medical significance be communicated? What endpoints are needed to determine benefit to these children from the research?

The scenario, however, also introduces new research ethics questions. For example, how should researchers approach the consent-assent process when the long-term impact of the technology on the variable neuroanatomy and neuroplasticity of children with neurodevelopmental disorders is unknown? How might data that represent altered brain states impact identity and epistemic authority? What are the long-term obligations of researchers to the participant community to support the intervention as the technology evolves?

Additional considerations might arise when including children with neurodevelopmental disorders from remote or under-resourced regions of the world. The researchers must consider the cross-cultural generalisability of their work that embeds cultural and religious traditions into the science-based learning. Exposure of the children to multiple traumas and changing government policies on resource allocation may be factors. The researchers must build bridges with the children's community to ensure ongoing safety, gain trust, reduce power imbalances, and mitigate stigma.

The research may also become complicated when target enrolment involves children with developmental disorders associated with conditions that are resistant to drug therapy. For certain forms of epilepsy, for example, parents may access legalised cannabis for their children and be disinclined to stop its use. In this scenario, researchers are faced with the extra ethical challenges of unknown dose, purity, quality control, and potential substance–technology interaction effects.

Solutions to these complex scenarios start with technological innovation and research designs that can be modified in real-time to address different definitions of beneficial and adverse effects, appreciation of the diversity of brain data and individual trajectories of learning and maturing, and changing features of regulation over time. To this end, social and local concepts of brain disorders and the overall impact and legacy effects of research on children and their communities must be built-in features of new studies, especially when technology and biases from high-income countries are imposed on other traditional forms of discovery science and knowledge production. Value-sensitive technology development (VSTD), such as that proposed in systems engineering and human–computer interaction, is



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For more on the **Common Rule** see https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/index.html

one approach. In using VSTD, for example, children's values can influence the final design of the mobile neurofeedback app and a play-based intervention that is both age and culturally specific in the challenge described above, through participatory and cooperative design workshops. In other contexts, non-verbal children may offer their views through drawings and other hands-on means. VSTD thus embraces the early and ongoing contribution of diverse age groups, backgrounds, and professions of people both to attain common objectives and to reconcile disparate ones.

Flexible study designs can also better prioritise inclusivity and engagement over more traditional randomised controlled trials and effectiveness-oriented metrics such as performance outcomes. Bayesian trials or n-of-1 studies in which children are their own comparators open the door to smaller and possibly more informative trials. Other designs such as dose-extended, parent arm selection, placebo drop-out, and run-in trials may also minimise potential risks of involving children with neurodevelopmental disorders in research, especially where novel psychoactive drugs such as cannabinoids are involved. Through these approaches, technologies and interventions can be adapted throughout a trial to mitigate safety issues and manage collateral or incidental findings early on.

Participant recruitment is often a challenge in research of rare diseases, where researchers might have a relationship with nearly all members of the small, affected community through social media. The pressure from within the community to participate can sometimes be tangible in the online dialogue, but the relationship through the social network challenges the researcher's ability to protect the identity of the children in the recruitment, assent, and reporting process, as well as the confidentiality of their private health information.

Should the researcher leverage relationships with the families to recruit directly online? What strategies can be implemented to ethically recruit sufficient numbers of patients for the clinical trial? How does social media affect the research when participants or their families are in constant contact with the investigator, change the way that results are reported, or alter the disclosure of relationships or interests?

Alongside these questions, ethical concerns are heightened by the substantial ambiguity that exists around individual expectations and public sharing of information, and whether recruiting through social media shifts the classic role of participants as subjects to objects of research. The digital boundaries of private and public space are fluid, different types of social media sites exist, and levels of proficiency—especially among young and neurodevelopmentally diverse users—vary. Risks of harm from unclear or violated responsibility and insensitive language may be elevated particularly for affected children who are already stigmatised. Commercial or con artist bots, influencers, or trolls that may lurk in online research spaces can be indistinguishable from bona fide participants. The use of social media may result in affected families becoming unwitting recruiters for commercial interests or scientific quackery.

See **Online** for appendix

While social media remains largely uncharted territory for research ethics, there are some starting points for positive action. Posts about studies made on social media platforms—especially those with strict word limits—should provide links to websites that provide detailed study information, funding sources, contact information, disclosure of conflicts of interest, and screening processes. Responses to posts from participants must be monitored, and researchers should specify if responses will be used as data. Data management and protection plans are essential for data that reside on servers at researcher institutions, with third parties, and on participants' devices. The conditions for use of data from children should assure de-identification to maintain confidentiality while also allowing for future re-identification for later consent. Taken together, when this new open environment meets a population of children with brain disorders whose life course may be less predictable than those unaffected, raising the bar to an exceptional level of research professionalism is warranted.

The translation of biomedical research into real clinical benefit for children, particularly for those with developmental disorders involving the brain and whose autonomy is at greatest risk in society, will continue to be threatened if their exclusion from research persists. New research practices that transcend normative assumptions of ability and culture can mitigate this threat. Non-traditional study designs that engage the full participation–translation continuum can enhance the involvement of children with neurodevelopmental disorders, the strength of their voice, and the support of the communities that surround them. Modernising governance and oversight of research involving children with neurodevelopmental disorders in line with new study designs, data privacy, and procedural ethics systems such as the steps reflected in updates to the Common Rule is central to ensuring their dual right to participation and protection.

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