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Editorial perspective: Leaving the baby in the bathwater in neurodevelopmental research

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Challenges to the standard paradigm

'Natural behaviour is the language of the brain' (Miller et al., 2022). However, almost all attempts to uncover the brain mechanisms that underpin neurodevelopmental conditions do not measure natural behaviour at all. Instead, we measure brain activity while children watch identically repeated sequences of events on a screen in darkened rooms or sleep in a scanner. Through this, we attempt to identify an endogenous cause for the patterns of atypical interactions with people or environments that characterise their neurodevelopmental condition.

The core motivation for this approach is to reduce measurement noise and enable experimental control of extraneous variables (Holleman, Hooge, Kemner, & Hessels, 2020). Many have argued that to directly compare individuals we need to be able to measure differences in how they respond to identical stimuli, presented in identical settings. But when we remove the influence of children's everyday environment in order to measure their brain function within controlled settings, are we 'throwing the baby out with the bathwater'?

There are several ways in which taking children out of their everyday environments to measure brain activity might be problematic. The best-recognised of these is ecological validity: in attempting to dissect the neurocognitive mechanisms that underpin a real-world behaviour (such as gaze following in autism) we often simplify it (e.g. to a series of three static pictures), and then repeatedly present the same sequence (even though such exact replication virtually never happens in the real world). Researchers seldom report whether performance on such tasks corresponds to or indicates anything relevant to behaviour in the fast-flowing, complex real-world equivalent (Doebel, 2020). Although still pervasive, this problem is relatively well recognised, and well debated (Wass & Goupil, 2022).

In addition, there are two further core conceptual challenges to the experimenter-driven model that are often overlooked. The first concerns the choice of stimuli: who makes the decisions as to what is important to the child? In traditional lab-based tasks, researchers present children with standardised stimuli whose features have been chosen based on their own adult understanding of what is relevant for children. Stimuli often reflect neurotypical biases, and children with neurodevelopmental conditions are classified by the degree to which they show an 'atypical' response. However, specialisation of brain function may progress through changes in the way conceptual space is represented in the brain; and moving away from deficit-based perspectives in neurodevelopmental conditions requires us to understand how individual children encode the world, rather than how their responses differ from a neurotypical model. Both perspectives require us to move beyond individual experimenter-chosen stimuli towards approaches that take a child-led approach to deciding what is most developmentally relevant, over both short and long time-frames (Gui et al., 2022).

The second problem is also a deep-seated one. In experimental studies both the events themselves, and their exact timings, tend to be decided by the experimenter, and not the participant. But in the real world we *generate experiences through behaviours* (Wass & Goupil, 2022). As Dewey put it, "[w]hat we have is a circuit, not an arc or broken segment of a circle. [...] The motor response determines the stimulus, just as truly as sensory stimulus determines movement" (Dewey, 1896). From a modern perspective, evocative gene–environment correlations likely strongly contribute to the heritability of different developmental traits. For example, a recent meta-analysis revealed a heritability of parenting negativity or positivity of 23%, suggesting that parenting practices are in part shaped by genetically influenced characteristics of the child (Avinun & Knafo, 2014). If our models of brain function are built entirely on how the brain reacts to externally generated stimuli, we are failing to incorporate the role of those regions in generating experiences and this may lead our models of brain development to be significantly impoverished.

Solutions

Advances in computing, artificial intelligence and engineering have generated the tools and techniques required for a paradigm-shift in neurodevelopmental science. New technologies allow us to use miniature wearable devices to record large volumes of 'free interaction' data – where researchers simply visit children in their homes to attach devices at the start of a typical day, and then return in the evening to pick them up. New AI-augmented real-time analysis approaches allow us to generate a large space of experimental stimuli and map the stimulus that most engages a particular brain region or signal (Lorenz et al., 2018). Such methods provide the tools to capture brain and body function during child-led behaviour.

These new methods require new conceptual and analytic approaches to turn data into information, and to move beyond description of development to mechanism. Just like other 'Big Data' approaches, these new methods can in some ways be viewed as atheoretical (Mazzocchi, 2015). Rather than deciding for ourselves what we think is important, and designing an experiment to test our expectations, we are instead designing data collection and analytic procedures that will tell us what is important through observing patterns of association in the data. However, whilst naturalistic data can be mined using the tools of machine learning, it can also be selectively analysed using theoretically informed models as for any other kind of observational time-series data. One could, for example, test theoretical models by conducting hypothesis-driven tests on individual particular features of a naturalistic data-set, as we describe further in the examples below. Types of statistical approach used with longitudinal or other time-series data (including directed acyclic graphs, dynamic causal modelling, Granger causality, instrumental variable analysis) can be used to increase the strength of causal inference. Finally, real-time methods can be used to test theoretical frameworks by defining an experimental space that is organised across theoretically informed parameters (Gui et al., 2022).

Here, we review three worked examples (of stress processing, early activity level in ADHD and social brain development in autism) that illustrate these points. Our examples show how these new approaches may lead to new insights in neurodevelopment.

Stress

A core question in neurodevelopmental science is how early-life exposure to stressors (i.e. environmental factors which cause changes in the body's neural and endocrine stress systems) affects the development of later psychopathology (Koss & Gunnar, 2018). However, almost all previous research into the role of early-life exposure in causing later psychopathology is vulnerable to the limitations that we discussed at the start of this article. First, potential stressors are selected a priori and measured using 'static snapshot' approaches, such as questionnaires or clinical interviews. Second, when experimenters want to measure a stress response (i.e. how a child responds behaviourally, physiologically and neurally to environmental stressors) we typically do this by presenting an event (such as a caregiver freezing suddenly) repeatedly in a sequence which occurs non-contingently – i.e. irrespective of the child's own behaviour.

An alternative approach would be to shift away from lab- and questionnaire-based assessment towards an approach that involves recording large volumes of uncontrolled multimodal home recordings using wearable cameras, microphones and physiological monitors. How would this allow us to address these limitations? First, rather than deciding a priori what a stressor is, we can simply let the data do the talking. We can record multiple features of a child's audiovisual environment – from low-level factors (such as the volume, complexity and predictability of sensory information) through to higher-level factors (such as caregiver affect, expressed emotions, caregiver responsivity). We can regress them onto a child's physiological stress state to see which features of the environment are, on average, most predictive of a child's physiological stress state. Using multiple regressions on large multivariate datasets, we can control for the fact that different aspects of the environment will naturally tend to co-fluctuate.

We can then move beyond description using the data and knowledge that we have generated (e.g. the regression parameters that measure which of the environment measures we tracked is most predictive of a child's physiological state) to generate and test a Bayesian model that tries to forward-predict a child's physiological state based on known information about the environment. Having used similar methods to identify (e.g.) the optimal pattern of responsivity that helps a child to calm down – i.e. how a parent alters their own stress state and how they vocalise in response to child distress – we could then use these parameters to generate and test an algorithm that provides live advice to parents on how to respond to their child, based on the child's short-term stress state. Embedding this real-time intervention into naturalistic recording sessions allows us to conduct a rigorous test of our causal model.

But these naturalistic methods have important additional potential. As well as answering the question of 'what is a stressor?' by studying which aspects of the environment are *on average* most predictive of children's physiological stress states, we can also look at *individual differences* in how stress is caused between children. In other words, we can examine how the specific features of the environment that forward-predict a physiological stress response differ from child to child. These findings will, clearly, have direct and immediate new therapeutic potential.

Early activity level in ADHD

Naturalistic data collection allows us to determine *how we generate experiences through behaviours.*

Neurodevelopmental conditions like ADHD are often characterised by early changes in behaviour that precede more complex changes in cognitive and affective function (Sonuga-Barke & Halperin, 2010). For example, in ADHD early increases in activity level precede later changes in attention span, executive functioning and concentration and mental health difficulties (Goodwin et al., 2021). Critical to early intervention is an understanding of whether and how early activity level *causally* impacts a child's experiences, and the experience-dependent specialisation of their brain, but our understanding in this area is limited (Sonuga-Barke & Halperin, 2010).

Taking high density recording methods in real-world naturalistic settings would allow us to study how a child's interactions with the everyday environment (such as when and how they vocalise, where they look, how their parent responds, how their physical environment is structured, etc.) change as a function of activity level. These analyses can be conducted through data-driven approaches, but can also be theoretically informed. For example, we could test the hypothesis that microdynamic changes in physical activity 'interrupt' the development of real-world attentive brain states, on a moment-by-moment basis. If supported, this would point to causal pathways through which early atypical activity levels might cause later-emerging atypicalities in attention.

We can also test other theoretical perspectives on early child-environment interactions in ADHD. One example is the idea that dynamic dysregulatory 'metastatic' cascades might develop, in which an initial increase in child arousal might cause changes in how they interact with others (e.g., becoming more oppositional); which in turn changes how others interact with them (e.g., more expressed emotions); which in turn increases child arousal still further (Wass, 2021). This would, again, necessitate a hypothesis-driven approach – by asking, for example, whether a hyper-aroused child is more active and thus more likely to elicit negative parent feedback, which may in turn increase their hyper-arousal. Computational and embodied models can be used to test simple predictions about feedback loops between brain and environment, and targeted intervention studies can be employed to test causality. Although these and similar ideas have been discussed in the context of disorders such as ADHD and anxiety (Smith et al., 2021) they remain relatively under-explored in the research literature (Wass, 2021).

Early social brain development in autism

Differences in social behaviour are robustly observable by the second year of life in children with autism, but the brain mechanisms that underpin these differences remain elusive. Traditional approaches examine neural responses to one or two social stimuli (e.g., a face and a toy), with the assumption that progress in understanding autism will result from identifying how brain responses differ to a stimulus preferred by typically developing children. However, the deficit-based perspective implicit in this paradigm has come under criticism from both the neurodiversity movement (Manzini et al., 2021) and from its lack of translatable relevance. One solution is to shift our focus away from asking how an autistic child reacts differently to a single neurotypically designed stimulus towards identifying the stimulus that most engages that individual child. This strengths-based focus will give us new conceptual insight into brain organisation in autism, but also potentially yield more relevant information for the types of experience that might best promote learning opportunities for individual children.

We have recently developed neuroadaptive Bayesian optimisation for children (Gui et al., 2022), a technique in which a large space of experimental stimuli (organised based on either previous data or a theoretical framework) is efficiently searched for the stimulus that best elicits a particular brain response in an individual child. This approach removes the experimenter from the loop (being entirely based on real-time analysis of brain signals and using artificial intelligence to build a model of the stimulus space across which to search), allowing us to robustly probe the cognitive function of particular brain signals at the individual differences level. Coupling this approach with dense real-life behavioural data allows us to examine how model predictions relate to real-world interest patterns across the course of a day, and to test whether behavioural approach to an object or person is preceded by the neural signals predicted to be maximally sensitive to the approached stimulus. Further, theoretical questions can be addressed by determining where patterns of brain activity converge within the space for the majority of children; for example, whether direct gaze with positive emotion maximally elicits attention (Csibra & Gergely, 2009). Thus, these approaches can be combined to provide triangulated information on how the brain scaffolds motivated engagement with the environment.

Key challenges

Naturalistic rich data capture produces thousands of variables, and field-wide standards must be developed in areas such as minimising researcher flexibility, improving causal inference, and dealing with problems such as collinearity across data streams. Researchers and clinicians require appropriate training in the data management, statistical and analytic tools that will underpin this new field, and a culture of open material sharing must be built. Important issues like privacy and safeguarding must be carefully considered when potentially identifiable data from their child and people outside the family are captured, and this will impact appropriate methods for data sharing. Collaboration with industry will improve and democratise access to naturalistic data capture tools, which will allow collection from a diverse range of settings and populations. Finally, the incorporation of causally sensitive methods and real-time experimentation into naturalistic data collection approaches is an important area of development for the field.

Summary

Coupling new technologies with new conceptual and analytic frameworks places our field at the cusp of a paradigm shift. We must move away from experimental control through isolation and control, towards approaches that embrace the measurement and targeted analysis of complex, multivariate, naturalistic datasets. We must incorporate the role of brain networks in generating experience through behaviour in our conceptual models. Finally, we must delineate the child–environment interactions that are altered in neurodevelopmental conditions like autism and ADHD. To do this, we must venture outside the lab to measure children in their natural habitat – whether that be the kitchen, the playground – or the bath.

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