Check for updates

The Journal of Child Psychology and Psychiatry

*Journal of Child Psychology and Psychiatry* 62:5 (2021), pp 631–634 doi:10.1111/jcpp.13416

# Commentary: Meeting the challenge of multidimensionality in neurodevelopmental disorders—reflections on Johnson et al. (2021)

**Laurie J. Hannigan,[1,2] and Alexandra Havdahl[1,2,3,4]**

[1]Nic Waals Institute, Lovisenberg Diaconal Hospital, Oslo, Norway; [2]Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, UK; [3]Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway; [4]PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway

> The existing modal analytic approach of looking for group differences in single markers between infants who do or don't meet criteria for later ASD (or other clinical outcomes) is beginning to limit our ability to break new ground in the study of neurodevelopmental disorders. (Johnson, Charman, Pickles, & Jones, 2021, p. 4)

The delivery may be measured, but this extract from the opening salvo of the 2021 Annual Research review by Johnson et al. carries the unmistakable sense of a gauntlet being thrown down. To researchers interested in uncovering the many converging aetiologies that underpin neurodevelopmental disorders, the message is simple: eschew the false comforts of reductionism. This means, the authors specify, not merely acknowledging the multifactorial nature of neurodevelopmental disorders on the one hand, while pragmatically pursuing approaches that address individual factors in isolation – implicitly assuming a simple additive model against which there is already ample evidence – on the other. Instead, they tell us the time has come to accept and embrace the challenge of understanding the *system*, with all its interactions, in proper developmental context. Were it asked to stand alone, such a rallying call might seem in equal parts self-evident and intractably aspirational. Fortunately, what follows from the authors is the expansion of a new framework that manages to ally pragmatism with progressiveness, impressively treading the line between conceptual solidity and practical utility to offer real prospects for progress in the field.

The authors make their case for the adoption of a new, systems neuroscience-inspired framework for prospectively studying the emergence of neurodevelopmental disorders in three stages. First, they set out the shortcomings of established approaches, citing the diminishing empirical returns of simplistic, single risk factor models as evidence that the field is in need of new ideas about how to structure its aetiological investigations. Next, the AMEND (Anterior Modifiers in the Emergence of Neurodevelopmental Disorders) framework is introduced, its key facets defined, and the existing evidence from across a range of disciplines that supports its essential distinctions and assumptions is appraised. Finally, Johnson et al. outline how the framework can be made empirically tractable. None of these steps are trivial, and a measure of success at each stage is crucial for the authors' ability to contribute to their stated goals of understanding the relationship between categories and dimensions with respect to neurodevelopmental disorders, identifying specific risk and protective factors, and indicating optimal routes for intervention.

Johnson and colleagues' call for an overhaul of the framework for researching the developmental emergence of conditions like autism spectrum disorder (autism) and ADHD is inspired by several well-established shortcomings of the existing literature. For instance, there is little that is controversial in their appraisal of the evidence that such conditions 'do not result from simple, mechanistic pathways'. The fruits of recent sampling-expanding efforts in molecular genetic discovery for autism (Grove et al., 2019) and ADHD (Demontis et al., 2019) have emphasized this – with the effects and expression of newly-discovered common variants no less diffuse, incremental, and probabilistic than in any complex trait so far studied. Even emerging evidence around the stronger effects of rare variants – which do seem to play a particularly important role in neurodevelopmental disorder aetiology (relative to that of other complex behavioural traits; Sullivan et al., 2018) – has primarily reinforced the picture of 'equifinality' presented by the authors. Given a broad acceptance within the field of the notion that neurodevelopmental disorders are multifactorial in origin, Johnson and colleagues' ensuing critique of reductionism (the assumption that 'a single underlying … component will be sufficient to explain or treat a given condition') may at first glance seem something of a *straw man* to be taken down in favour of their proposed changes. However, their position here is more nuanced. They are arguing that whether reductionist approaches are taken due to investigators' beliefs about the simple additivity of the true causal mechanisms or (more likely) as a result of pragmatic considerations, the outcome is the same.

Conflict of interest statement: No conflicts declared.

© 2021 The Authors. *Journal of Child Psychology and Psychiatry* published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health
This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

The hard truth embedded within this position is that continued acknowledgement of the limitations of reductionist approaches is insufficient. Put simply: if we want to make progress in identifying modifiable risk, protective and resilience factors for neurodevelopmental disorders, the authors argue, giving in to pragmatic concerns and merely paying lip service to the complexity of causal mechanisms is not going to cut it.

Having made a strong case for the need to *do better*, Johnson and colleagues proceed to start restocking our investigative toolkit. Breaking the empirical deadlock, they argue, requires an approach that acknowledges the primacy of the interactions *between* components in a system in determining system-wide outcomes. Their elegant and – given their later encouragement of the use of structural equation modelling – highly appropriate way of achieving this is by introducing an assumption in exchange for an additional degree-of-freedom. Specifically, they argue that making a distinction between markers of *early-stage processing* (reflecting brain systems controlling motor and sensory functions perinatally) and those pertaining to *neurocognitive modifiers* (that increasingly regulate the function and development of these systems after the first year of life) is the key to making the problem of multifactoriality in neurodevelopmental disorders truly tractable. The integrity of this distinction is a strong and – for the purposes of AMEND – crucial assumption, requiring a strong empirical rationale. Johnson and colleagues provide this, citing the extended development, relative developmental detachment from sensory and motor influences, and hierarchical superiority of the prefrontal cortex as evidence of its capacity to play 'a fundamental and increasing role in modifying the effects of lower-level sensory and motor systems on developmental trajectories'. As for the lower-level systems in question – their role is indicated by evidence of atypical sensory or motor processing in the perinatal period. Crucially, these are factors whose relative lack of sensitivity and specificity in predicting later neurodevelopmental diagnoses have so far rendered them of limited utility when considered in isolation. By reconceptualizing these early-life atypicalities as neurodevelopmental vulnerabilities that can be either compensated for or exacerbated by the action of the anterior modifier systems, AMEND neatly explains their limited predictive validity as *feature-not-bug*, and appropriately re-casts neurodevelopment as a dynamic, synergistic process in which interactions, rather than the components themselves, take centre-stage.

Johnson and colleagues are laudably explicit about the need for their framework to have empirical, as well as conceptual, validity. They offer researchers both general analytic and specific statistical guidance for implementing the AMEND framework to test hypotheses. Their advice to begin by identifying early-stage processing atypicalities in respect to both deviations from the norm *and* robust associations with neurodevelopmental outcomes of interest are good considerations that guard against the potential for multiplicity in a framework that emphasizes interactions. They also note that associations with known environmental or genetic factors linked to compromised neurodevelopment are, if not a prerequisite, at least a useful sanity check for putative early-stage processing deficits. Moreover, they suggest that direct investigations of perinatal sensorimotor processing among infants with conditions such as neurofibromatosis 1 or 22q11.2 deletion syndrome that can be diagnosed early in life may offer fertile ground for identifying candidate markers. Neurocognitive modifiers can then be identified, via their increasing influence on development after one year of age and their positive associations with neuro*typical* outcomes, and modelled as moderators. For this, the authors recommend structural equation modelling for its flexibility. Johnson et al. again demonstrate their awareness of the potential multiplicities thrown up by their framework, and in an important note on power, researchers are advised to weigh up the prevalence of the modifier, its correlation with the marker(s) of early-stage processing, and any grounds for dropping the main effect of the modifier in managing their Type 1 error rates. Finally, the authors reiterate their commendable insistence that we ought not to overlook the *developmental* dimension of the neurodevelopmental outcomes we study. To this end, they suggest making use of the data-reducing properties of latent growth and trajectory models to distil longitudinal information in ways that make it tractable within the AMEND framework.

Johnson and colleagues present us with both a stark challenge and a bold conceptual and methodological vision for meeting it. As is perhaps inherent in such boldness, some strong assumptions are made and some risks taken. First, the new framework is outlined partly as a response to poor sensitivity and specificity in the prediction of neurodevelopmental outcomes by established infant predictors. Despite acknowledging that measurement issues and stochasticity could provide simple alternate explanations for this phenomenon, the authors prefer a complex model which invokes interactions between components operating at different stages of the developmental process. This move against the gradient of parsimony is justified, quite reasonably, as a means to an end: it provides new, testable predictions that can be evaluated even in the absence of better-quality data. Yet even though the complexity of the basic aetiological model underpinning AMEND can be rationalized conceptually, it may still cause problems empirically. Johnson et al. provide pragmatic recommendations in terms of preserving power in the face of multiplicity – to which our own addition would be to encourage the

© 2021 The Authors. *Journal of Child Psychology and Psychiatry* published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health

kind of data-sharing and collaborative meta-analyses across different cohorts that has been successful in powering up genomic analyses over the past decade – but the fact remains that their model demands a stretching of statistical resources that represents an undeniable risk. On both of these issues, it could be argued that meeting biological complexity with its theoretical counterpart, in the form of the AMEND framework, is the step-change that the field needs at this time.

A more specific point of structural vulnerability in the AMEND framework is the necessary and central assumption concerning the delineability of early-stage atypicalities and later-stage modifiers. A convincing case for this is made, but rests somewhat heavily on the temporal division of the early years into pre- and post-12 months of age – a distinction that, at best, can only ever be heuristically correct. However, the authors do provide clear and easily applicable criteria for the definitions of both markers of early-stage processing and neurocognitive modifier systems. They also demonstrate appropriate wariness of potential circularities in definitions of modifier systems and the behavioural components of the neurodevelopmental disorders towards (or away from) which they may channel individuals' pre-existing vulnerabilities. However, the potential for circularities does remain, and the responsibility for following the authors' advice to avoid them is on the 'end-user'. Specifically, while neurocognitive modifiers may be 'designed to be identified at the brain and cognitive level' to ensure distinctiveness from core behavioural features of neurodevelopmental disorders, the nature of many of the prospective cohort samples in which the authors envisage the AMEND framework being deployed is such that *only* behavioural proxies for traits such as executive attention and social engagement are available. It will be important for the researchers analysing these samples to consider whether use of such measures to index modifiers in AMEND undermines the validity of the framework for their data.

As researchers working within psychiatric genetic epidemiology, we are interested in potential applications of the AMEND framework using genomic data. Johnson et al. correctly observe that current genome-wide association study (GWAS) based approaches, such as polygenic scores derived from case-control analyses of neurodevelopmental disorders, conflate genetic factors influencing risk via different processes (i.e., vulnerability and modification) in their conceptual pathway. We can think of a number of ways in which this situation could be addressed. Ongoing collection of brain-imaging data in genotyped samples and at scale will be relevant for distinguishing genetic variants associated with early sensorimotor processing and later neurocognitive modification. New approaches to decompose variance and covariance at a genomic level (Grotzinger et al., 2019), can also help make these distinctions even when direct measurement of one or other component is infeasible (see 'GWAS-by-subtraction'; Demange et al., 2021). Mendelian randomization (MR) offers methodological approaches to test the causal hypotheses arising from the application of the AMEND framework. Two possible MR methods that could be used to explore hypotheses within the AMEND framework are factorial MR and progression MR. First, factorial MR (Rees, Foley, & Burgess, 2020) can test for interactions between risk factors. In other words, factorial MR can estimate the effect of one risk factor (e.g., atypical early-stage processing) on an outcome (e.g., dimensional autism/ADHD symptoms) in the presence of a second risk or protective factor (e.g., neurocognitive modifiers). Overlap between the genetic propensities of the two factors (as is likely here) can be accommodated, as long as independent genetic variants are also available (Rees et al., 2020). Second, progression MR (Paternoster, Tilling, & Davey Smith, 2017) could be applied to understand whether neurocognitive modifiers causally affect symptoms or risk of neurodevelopmental disorders *within* individuals with atypical early-stage processing – though selecting this group could introduce collider bias which must be adjusted for (Mahmoud, Dudbridge, Smith, Munafo, & Tilling, 2020).

Overall, it is hard to imagine as forward-looking and comprehensive a framework as AMEND being presented with a greater sense of responsibility and pragmatism. The authors' commitment to outlining a framework that is conceptually sound enough to encompass evidence from across disorders and research domains and bold enough to resolve a well-articulated empirical impasse, while remaining methodologically accountable, is an impressive feat. It is also an act of service to the wider research community, and we share their hope that it motivates a new wave of discovery in the study of early neurodevelopment.

## Acknowledgements

The authors were supported by grants from the South-Eastern Norway Regional Health Authority (2018058, 2018059, 2020022) and the Research Council of Norway (274611, 288083). They would like to thank Dr Robyn Wootton for her input on an earlier draft. The authors have declared that they have no competing or potential conflicts of interest.

## Correspondence

Alexandra Havdahl, Nic Waals Institute, Lovisenberg Diaconal Hospital, Oslo, Norway; Email: alexandra.havdahl@psykologi.uio.no

© 2021 The Authors. *Journal of Child Psychology and Psychiatry* published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health

## References

Demange, P.A., Malanchini, M., Mallard, T.T., Biroli, P., Cox, S.R., Grotzinger, A.D., … & Nivard, M.G. (2021). Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction. *Nature Genetics*, *53*, 35–44.

Demontis, D., Walters, R.K., Martin, J., Mattheisen, M., Als, T.D., Agerbo, E., … & Neale, B.M. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*, *51*, 63–75.

Grotzinger, A.D., Rhemtulla, M., de Vlaming, R., Ritchie, S.J., Mallard, T.T., Hill, W.D., … & Tucker-Drob, E.M. (2019). Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nature Human Behaviour*, *3*, 513–525.

Grove, J., Ripke, S., Als, T.D., Mattheisen, M., Walters, R.K., Won, H., … & Børglum, A.D. (2019). Identification of common genetic risk variants for autism spectrum disorder. *Nature Genetics*, https://doi.org/10.1038/s41588-019-0344-8.

Johnson, M.H., Charman, T., Pickles, A., & Jones, E.J.H. (2021). Annual Research Review: Anterior Modifiers in the Emergence of Neurodevelopmental Disorders (AMEND)—a systems neuroscience approach to common developmental disorders. *Journal of Child Psychology and Psychiatry*, https://doi.org/10.1111/jcpp.13372.

Mahmoud, O., Dudbridge, F., Smith, G.D., Munafo, M., & Tilling, K. (2020). Slope-Hunter: A robust method for index-event bias correction in genome-wide association studies of subsequent traits. *bioRxiv*, https://doi.org/10.1101/2020.01.31.928077.

Paternoster, L., Tilling, K., & Davey Smith, G. (2017). Genetic epidemiology and Mendelian randomization for informing disease therapeutics: Conceptual and methodological challenges. *PLoS Genetics*, *13*, e1006944.

Rees, J.M.B., Foley, C.N., & Burgess, S. (2020). Factorial Mendelian randomization: Using genetic variants to assess interactions. *International Journal of Epidemiology*, *49*, 1147–1158.

Sullivan, P.F., Agrawal, A., Bulik, C.M., Andreassen, O.A., Børglum, A.D., Breen, G., … & Psychiatric Genomics Consortium. (2018). Psychiatric genomics: An update and an agenda. *American Journal of Psychiatry*, *175*, 15–27.

Accepted for publication: 1 March 2021

© 2021 The Authors. *Journal of Child Psychology and Psychiatry* published by John Wiley & Sons Ltd on behalf of Association for Child and Adolescent Mental Health