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Editorial: Transdiagnostic research: transitory or transformative?

Transdiagnostic is arguably one of the most 'in vogue' terms at the moment in child and adolescent psychiatry. A search for the word 'transdiagnostic' in *PubMed* shows an exponential increase over the last decade in medical research, with 2021 showing the highest ever use of this word. Within child and adolescent psychiatry, there are many reasons this word might be used. Conditions within child and adolescent psychiatry exist within a multi-dimensional space: they show high co-occurrence with each other; they share underlying brain and neurocognitive constructs, they share epidemiological risk factors, they share outcome pathways and they share treatments. In this editorial, I discuss transdiagnostic research, drawing on four impactful articles from the present issue of the *Journal of Child Psychology and Psychiatry*, and consider whether transdiagnostic research is likely, longer term, to be transitory or transformative.

What does transdiagnostic mean? A loosely constructed brief definition at this point in time might be: something that applies across specific diagnoses and unifies them. For longer discussions of transdiagnostic approaches to neurodevelopment and mental health, I refer the reader elsewhere (Astle, Holmes, Kievit, & Gathercole, 2022; Dalgleish, Black, Johnston, & Bevan, 2020; Sonuga-Barke, 2020). A search for the word 'transdiagnostic' in *PubMed* shows an exponential increase over the last decade, with 868 uses in titles or abstracts in 2021, the highest rate to date. In this brief editorial, I will discuss transdiagnostic research through drawing on four impactful articles from the present issue of the *Journal of Child Psychology and Psychiatry*.

I start with two papers investigating polygenic scores in community samples. Askeland et al. (2022) investigated which neurodevelopmental traits were associated with polygenic scores for autism, ADHD and schizophrenia. They worked with the Norwegian Mother, Father and Child Cohort Study (MoBa) on mother-rated scales of children's development from age 6 months to age 8 years. The rich cross-domain and cross-age trait data allowed multiple hypotheses to be tested within a single study. They found that the ADHD polygenic score was significantly associated with both inattention and hyperactivity traits from age 18 months up to age 8 years as well as with language difficulties at age 5 and 8 years. The autism polygenic score was associated with language difficulties at 18 months (though not at the later ages) and with motor difficulties at 3 years (but not at 6 or 18 months or 5 years). The autism polygenic score was associated with hyperactivity and inattention at age 8 years, in line with a large literature on genetic associations between autism and ADHD traits e.g., (Grove et al., 2019; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). It did not associate with repetitive behaviours or social communication at any ages. The schizophrenia polygenic score did not associate significantly with any of the traits.

By publishing all these analyses together, Askeland et al.'s paper encourages the reader to think transdiagnostically and to consider neurodevelopment broadly. This is closer to how child development actually operates (i.e. in a multi-domain and longitudinal space). If Askeland had split up their analyses and published their ADHD, ASD and schizophrenia polygenic score analyses separately, or published the results for each type of outcome separately (ADHD traits, autistic traits, motor development and so on), arguably these would have been less rich and less innovative papers.

To tackle multiple testing, Askeland et al. determined the number of effective tests by running a principal component analysis on their 25 neurodevelopmental outcome measures. The number of tests was decided based on the number of principal components that explained 80% of the variance. This number of tests was then applied in Bonferroni correction. In addition, they consider the effect sizes of results, regardless of significance. Overall, this seems a thoughtful and measured approach to correction for multiple testing.

A potential pitfall of some transdiagnostic research that aims to tackle multiple conditions or traits simultaneously might be a potential increase either in false positives or false negatives. Askeland et al.'s approach of including all the analyses together may have led to false negatives if an over-stringent correction had been applied. On the other hand, without sufficient correction, their present study, with so many tests run simultaneously, could have led to false positives even if objective effect sizes were small.

Next, I turn to Gidziela et al.'s (2022) study, which aimed to study how associations between behaviour problems and polygenic scores for neurodevelopmental and psychiatric conditions can be improved (i.e. increased in effect size). In a longitudinal genotyped cohort, the Twins Early Development Study, unrelated children were assessed on behaviour problems from age 2 to age 21. The outcome measures included total behaviour problems as well as internalising and externalising scores, all constructed from confirmatory factor analysis and

studied separately for childhood (ages 2–9 years), adolescence (ages 12–16 years) and adulthood (age 21). The authors showed that associations with polygenic scores were stronger when ratings on behaviour problems from different raters were combined as well as when data across ages were combined.

Importantly, and relevant to this editorial's theme on transdiagnostic research, Gidziela et al. found that models that included multiple polygenic scores together explained more variance in behaviour problems than individual polygenic scores for single conditions. By harnessing polygenic effects across conditions, this work gives us an improved sense of the overall scope of these gene–behaviour relationships in childhood.

The breadth of transdiagnostic research, such as the two studies mentioned above, can be awe-inspiring. A second potential pitfall of transdiagnostic research is delineating where exactly does the research start and end. Pre-registration helps with this, because the ambitions and end point of analyses is defined prior to data analysis. The Gidziela et al. paper pre-registered their hypotheses and analyses in Open Science Framework prior to accessing the data. This gives reviewers, editors and readers evidence of a time-stamped plan of analysis prior to data access.

Transdiagnostic research has also reached neuroscience, as demonstrated in the final two papers I focus on from this journal issue. Mewton et al. (2022) reported on the relationship between general and specific psychopathology in preadolescents (9–10-year-olds) and brain structure measured using MRI in a community cohort study, the Adolescent Brain and Cognitive Development study. Their variables for general psychopathology as well as externalising, internalising and thought disorder 'lower order' dimensions were derived from a higher-order model of psychopathology using confirmatory factor analysis (for a discussion of the p-factor model of psychopathology, see elsewhere (Caspi & Moffitt, 2018; Ronald, 2019).

Mewton et al. reported that lower global surface area and lower global cortical volume, though not cortical thickness, were both associated with general psychopathology. The externalising, internalising and thought disorder 'lower order' dimensions showed similar patterns of results as for general psychopathology. Furthermore, in regional analyses, the authors did not tend to find many specific associations between brain regions and lower order dimensions: most associations with cortical volume or surface area were present across multiple lower order dimensions or with the general psychopathology measure. The authors concluded that these brain structural associations were 'transdiagnostic markers' of general psychopathology because of the lack of specific associations with lower order psychopathology dimensions.

Indeed, claims of transdiagnostic relevance only stand up to scrutiny if researchers have ruled out that any findings are driven by associations with a single diagnosis or trait dimension. This was a strength of how the Mewton et al. study was conducted as well as the next paper I turn to, also within neuroscience, by Cañigueral et al. (2022). Cañigueral et al. also had a robust design to tackle specific versus transdiagnostic effects.

In Cañigueral et al.'s EEG study of attention in neurodevelopmental conditions, rather than ignoring the high co-occurrence of autism spectrum disorder (ASD) and ADHD, they make it central to their study design. ASD and ADHD both involve challenges with attention. Cañigueral et al. investigate whether ASD, when co-occurring with ADHD, involves an additive profile of atypical attention differences or if having both conditions leads to a distinct profile of attention, separate from either ADHD or ASD occurring alone.

Their results showed that children with ASD (either alone or with ADHD) showed greater post-stimulus N2 amplitude which was thought to reflect greater effortful attentional control. In contrast, children with ADHD (either alone or with ASD) showed reduced N2 and P3 amplitude; ADHD appeared to involve atypical integration of bottom up and top down attention, atypical attention allocation and attentional control. Cañigueral et al. conclude that children with a dual diagnosis show an additive profile of attentional signatures from both conditions.

In conclusion, given the high co-occurrence of conditions and their many shared facets, transdiagnostic research acts like glue that brings our field together. Does child and adolescent psychiatry need to shift itself towards conducting more transdiagnostic alongside condition-specific research?

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In this editorial, I've aimed to highlight some strengths in the approaches taken by the authors of the papers discussed here. Poorly planned and poorly conducted transdiagnostic research could easily lack direction, impact, hypothetical or theoretical grounding and be riddled with false positive (or false negative) results. Transdiagnostic research may end up transitory if it is poorly conducted, or if it is rebelled against because it is misunderstood as attempting to replace condition-specific research rather than complement it.

Despite the clear novelty and value of the above findings, one could argue that these four sets of authors sacrificed the potential impact of their work by making it transdiagnostic. I say this because transdiagnostic research can fall in the gaps of how

child and adolescent psychiatric research is currently organised, funded and communicated. Transdiagnostic research is a harder 'sell' at disorder-specific conferences, it may be missed and thus less likely to be cited by disorder-specific researchers or to impact policy documents for example, (*Policy paper: The national strategy for autistic children, young people and adults: 2021 to 2026*, 2021), it may not be read by clinicians with disorder expertise and, importantly for the authors' future funding success, it may be disregarded by disorder-specific funders.

Transdiagnostic research is transformative in the sense that it helps to reveal a part of the truth underlying child and adolescent psychiatry that single condition research misses and for that reason it is essential to our field. If the usage of 'transdiagnostic' in *PubMed* continues in its upward trajectory, transdiagnostic research is here to stay. It is time for our field to allow this type of work to share the stage with disorder-specific endeavours.

Angelica Ronald
Department of Psychological Sciences, Birkbeck, University of London, London, UK
E-mail: a.ronald@bbk.ac.uk

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