Research Article

A Review on progress in ADHD Disorder: From Characterization to Cause

Minakshi Verma[1], Sandeep Kumar Mishra[2*]

[1,2]Faculty of Pharmacy, Kalinga University, Raipur Chhattisgarh, 492101, India.

***Corresponding Author:**
Dr. Sandeep Kumar Mishra
Associate Professor
Faculty of Pharmacy, Kalinga University,
Village Kotni, Near Mantralaya, Raipur, 492101, Chhattisgarh, In
Email: skm15786@gmail.com

Abstract

The science of attention-deficit/hyperactivity disorder (ADHD) is motivated by a translational goal – the discovery and exploitation of knowledge about the nature of ADHD to the benefit of those individuals whose lives it affects. Over the past fifty years, scientific research has made enormous strides in characterizing the ADHD condition and in understanding its correlates and causes. However, the translation of these scientific insights into clinical benefits has been limited. In this review, we provide a selective and focused survey of the scientific field of ADHD, providing our personal perspectives on what constitutes the scientific consensus, important new leads to be highlighted, and the key outstanding questions to be addressed going forward. We cover two broad domains – clinical characterization and, risk factors, causal processes and neuro-biological pathways. Part one focuses on the developmental course of ADHD, co-occurring characteristics and conditions, and the functional impact of living with ADHD – including impairment, quality of life, and stigma. In part two, we explore genetic and environmental influences and putative mediating brain processes. In the final section, we reflect on the future of the ADHD construct in the light of crosscutting scientific themes and recent conceptual reformulations that cast ADHD traits as part of a broader spectrum of neurodivergence.

Keywords: ADHD; development; stigma; brain imaging; genetics.

Introduction:

Attention-deficit/hyperactivity disorder (ADHD), as currently formulated in diagnostic manuals (i.e., DSM-5 and ICD-11), represents the latest stage in a long history of attempts to characterize a cluster of overlapping early onset and persistent symptoms of hyperkinesis, inattention, and impulsiveness known to harm affected individual's lives through the functional impairment they create, both in the short and long term. These formulations describe, and thus implicitly conceptualize, ADHD as a singular, categorical entity with clear and definable boundaries both between disorder and nondisorder and between ADHD and other disorders, caused by dysfunction within the patient (Sonuga-Barke, 2020). This way of thinking about ADHD, although subject to minor adjustments in specific aspects of diagnostic criteria introduced following periodic review of available   unchanged for decades. However, during the same period

enormous strides have been made in our scientific understanding of ADHD that appear to challenge core elements of this conceptual model by highlighting, for instance, its dimensionality, causal heterogeneity, and genetic and neuro-biological overlap with other conditions (Posner, Polanczyk, & Sonuga-Barke, 2020); characteristics known to be shared with other psychiatric and neurodevelopmental conditions. These discoveries have led some to question how well the current diagnostic framework maps onto scientific findings about the underlying causal structure of the condition (e.g., Musser & Raiker, 2019). In this review, our goal is to take stock of the state of ADHD science; reviewing recent developments in light of past consensus while identifying key questions that need to be addressed going forward. The paper is presented individuals. In the second section, we examine risk factors, causal processes, and neurobiological pathways in terms of genetic architecture, environmental influences and brain structure, function, and chemistry.

The current work differs from previous reviews of ADHD science in a number of ways. In particular, in fulfilling our distinctive goal of characterizing prior consensus in the field while looking forward to the future, we wanted to allow the individual voices of the authors to be heard, encouraging a degree of subjectivity in the foci adopted, the interpretations made, and questions identified. To achieve this, each author was given responsibility for leading on a particular domain in which they had specialist experience (although to be honest, given the breadth of their experience, most authors could have led on most sections): Luis Rohde – charting development; Emily Simonoff and Stephen Becker – correlated characteristics and overlapping conditions; Sven Bolte€ – impact of living with ADHD; Barbara Franke – genes; Joel Nigg – environments; Xavier Castellanos and

in two major sections. The first focuses on the characterization of ADHD in terms of developmental course, correlated characteristics and traits and overlapping conditions available and its impact on the lives of affected scientific evidence, has remained fundamentally.

Disclosures.

Jeffrey Newcorn – brain; Edmund Sonuga-Barke – the future of the ADHD concept. Drafts of sections were circulated to be modified in the light of comments from fellow authors through a process coordinated and moderated by Sonuga-Barke. The final decision about the content of each section, however, always fell to the responsible authors. The paper is, therefore, neither a systematic review (though rigorously empirically grounded), nor a consensus statement (although there was a great deal of consensus). Through this novel approach, we hope to provoke debate and stimulate thinking about both past achievements in ADHD science and what are the most important next steps.

Characterization

Despite a number of important changes in successive DSM and ICD manuals, the diagnostic conception and formulation of ADHD have remained essentially unchanged for many decades – it is a categorical, childhood-onset neuro-developmental disorder marked by age-inappropriate, extreme and impairing levels of inattention,

and/or hyperactivity and impulsivity. In this section, we examine how well certain aspects of this formulation stand up in the light of evidence from recent studies and then frame key questions for future enquiry.

Charting the developmental course

In the fields of neurodevelopmental and mental health conditions, there is an increasing focus on early intervention and prevention. Understanding the course of a condition from its earliest manifestations is a prerequisite for the success of such approaches.

Prior consensus

ADHD has been traditionally conceptualized as a neurodevelopmental condition with an early childhood-onset and a steady course with limited remission (Posner et al., 2020). Longitudinal studies of child-to-adult ADHD developmental trajectories provide qualified support for this characterization while offering a more nuanced and complex view with regard to some aspects (Wootton et al., 2022). For most individuals diagnosed with ADHD, symptoms, and to some extent impairment, do indeed first appear in early childhood, even when their first formal diagnosis is later in life (Kieling et al., 2010). In fact, ADHD can be diagnosed reliably in the preschool period where hyperactivity and impulsivity tend to be the most prominent symptoms and some neurocognitive deficits associated with the disorder are already detectable (Shephard et al., 2022). Furthermore, although the overall observable symptom levels decline across the life course from childhood onwards in the general population (Wootton et al., 2022), the majority of individuals diagnosed with ADHD in childhood still have symptoms and/or impairments sufficient for a diagnosis in adolescence and early adulthood (Breda et al., 2021; Faraone, Biederman, & Mick, 2006). In fact, the Multimodal Treatment of ADHD (MTA) study, using data collected at multiple ages across development, suggested that full recovery/sustained remission during the period up to adulthood is rare, occurring in less than 10 % of ADHD individuals (Sibley et al., 2021).

Longitudinal studies have established that impulsivity and inattention are more persistent across development than hyperactivity both in the general population and in clinical samples (Willcutt et al., 2012). DSM presentations (inattentive vs hyperactive/impulsive) are not stable developmentally – reflecting more transient, time-limited manifestations of a fluctuating condition than real subtypes (Willcutt et al., 2012). If ADHD persists to early adulthood there appears to be a higher chance of further persistence into later life thereafter (Karam et al., 2015). Above and beyond core symptoms there are changes in the pattern of co-occurring mental health conditions as individuals grow. For instance, while in childhood oppositional defiant disorder (ODD) and conduct disorder (CD) are the most prevalent conditions co-occurring with ADHD, substance use and mood and anxiety disorders become more common co-occurrences in adulthood (Franke et al., 2018). The determinants of ADHD persistence have not been definitively established. A metaanalysis of childhood factors predicting ADHD persistence into adulthood found that symptom severity and co-occurrence with conduct disorder and major depressive disorder were statistically significant predictors (Caye et al., 2016). Genetic factors like ADHD family history and ADHD polygenic risk, although promising, need more investigation.

New leads

ADHD can be a late onset condition. The notion that ADHD is always a childhood-onset condition has been challenged by recent data from a range of countries (e.g., Caye, Sibley, Swanson, & Rohde, 2017; Sibley et al., 2018) suggesting that some individuals with an adolescent or early adult diagnosis have a late-onset variant of the condition; although there is a dispute on exact rates of lateonset ADHD, with estimates ranging from around 30% to 87% of those presenting with ADHD in adulthood (Breda et al., 2021). In-depth analysis suggests that individuals with the putative lateonset variant might differ from their

childhoodonset counterparts in important ways. They seem to have less severe symptoms and/or a lower genetic liability for ADHD and/or may have lived in more supportive families during childhood and/or have higher IQ - or a combination of these factors (Asherson & Agnew-Blais, 2019). However, this is another area that needs more research. These new data on late-onset ADHD suggest that clinicians should consider the possibility of an ADHD diagnosis in adulthood even if clinical thresholds for inattentive and/or hyperactive/impulsive symptoms and/or impairment have not been met in childhood. Symptom and impairment fluctuations across time are very common. The notion that childhood-onset ADHD is a persistent and stable condition has been challenged recently in a detailed analysis of its developmental trajectories. For instance, MTA naturalistic follow-up data demonstrated that over 60% of children with ADHD combined type had a fluctuating symptom course with, in clinical terminology, repeated periods of remission and recurrence – even when the former was conservatively defined as lack of (a) substantial ADHD symptoms, (b) impairment, and (c) treatment in the last six months (Sibley et al., 2021). It's been suggested that this uneven profile is the result of the interplay between timevarying environmental demands and underlying genetic vulnerability (Sibley et al., 2021).

The male-to-female sex ratio is increasingly more balanced with age. In childhood, approximately 2.5 and 4 times more males than females present with ADHD in population and/or clinical studies, respectively (Faraone et al., 2021). There is growing evidence that this ratio changes substantially as one moves through adolescence to adulthood with an increasingly large proportion of ADHD cases being female (Franke et al., 2018). This phenomenon, as it relates to clinical samples, is likely to be explained in part by referral bias (e.g., higher tendency to refer males in childhood due to hyperactivity and behavior problems, and a greater search for treatment

by females in adulthood). There are other hypotheses to be explored (see Hinshaw, Nguyen, O'Grady, & Rosenthal, 2022, for a summary). First, pubertyrelated changes in sex hormones may play a role (Hinshaw et al., 2022). Second, females might need a more severe presentation to receive an ADHD diagnosis in childhood due to diagnostic operationalization relying on samples composed mostly of boys, but, as severity is the main predictor of persistence, ADHD then tends to persist into adolescence and adulthood for them more than for males. Third, female children may be better able to mask impairment in childhood with this 'advantage' wearing off in adolescence and beyond. Fourth, males with ADHD might have more negative trajectories than females, for instance, more frequently ending up in prison or even dying prematurely.

Outstanding questions

Can we predict patterns of ADHD onset, persistence, and remission? Being able to prospectively predict the onset and persistence/remission of ADHD will facilitate a more personalized approach to intervention. One investigation in three population samples from the UK, Brazil, and the US recently provided evidence that a risk calculator using clinical and demographic data collected in childhood, like the Framingham Risk Calculator for cardiovascular disorders, might perform adequately in this regard (Caye et al., 2020). It remains to be determined which predictors will be most important in these models and whether clinical and/or demographics, pre- and/or perinatal, polygenic risk, and/ or early life determinants, and/or neuropsychological data will enhance their performance. It is also unclear whether prediction models generated in one sample will generalize to others. In this regard, the risk calculator mentioned above was assessed in a new sample (the Brazilian High-Risk cohort); it demonstrated adequate performance in its original format and showed that adding information about ADHD polygenic risk and prematurity did not improve accuracy (Lorenz et al., 2022).

Can we prevent the onset of ADHD through early intervention? If we can prospectively identify which young children will develop ADHD later in life, it may be possible to intervene early to reduce ADHD risk or ameliorate its impact. A recent meta-analysis provides promising evidence that targeting ADHDrelated precursors, such as deficient self-regulation or other executive function deficits, can reduce ADHD symptoms (Shephard et al., 2022). It remains unclear from this review; however, whether interventions can modify ADHD risk precursors (i.e., genuine prevention) or just reduce early manifestations of the condition itself (i.e., treatment).

What happens to ADHD in older adults? Currently, almost nothing is known about later life stages of ADHD developmental trajectories. Do symptoms and associated impairments progress, remain stable, or remit as people move into older age? A recent investigation using the Swedish Medical Registry suggested a strong and significant association between ADHD in adulthood and later dementia (Du Rietz et al., 2021). It may be particularly important to understand the clinical implications of the relationship between these two conditions, especially considering their phenotypic and neuropsychological overlap (Mendonca et al., 2021).

Can ADHD have positive outcomes? Longitudinal studies have largely focused on the negative impact of ADHD on individuals' lives. More recently the neurodiversity perspective has focused the research community's attention on strengths-based approaches (Sonuga-Barke & Thapar, 2021). This raises the question – Can people with ADHD find a productive niche in which they can excel during their development? This could involve, for instance, exploiting a creative ability to 'think out of the box' or the energy, drive and risk-taking required by successful entrepreneurs? Although initial findings remain controversial, a systematic review suggests positive traits may be related to ADHD traits (Hoogman, Stolte, Baas, & Kroesbergen, 2020).

Conceptualizing correlated characteristics and co-occurring conditions

Statistical studies have established that the defining symptoms of ADHD, inattention, and hyperactivity/ impulsivity, cluster with one another and are distinguishable from other dimensions of psychopathology (Willcutt et al., 2012). Nevertheless, there is substantial correlation between this ADHD symptom cluster and other psychological characteristics and traits, and co-occurrence with other neurodevelopmental and mental health conditions is common (Reale et al., 2017). This has raised questions about the status of these co-occurring elements. When should we extend the ADHD characterization to include these features, and when should we accept them as distinct but overlapping clinical phenomena?

Prior consensus

The two domains perhaps most often proposed for inclusion in a broader ADHD characterization are emotion regulation difficulties (ERD) and sluggish cognitive tempo (SCT) (Barkley, DuPaul, & McMurray, 1990; Lahey, Schaughency, Hynd, Carlson, & Nieves, 1987). ERD such as anger susceptibility/ irritability or low distress tolerance are present in an estimated 40–50% of children with ADHD, especially pronounced among the combined ADHD presentation, and associated with ADHD persistence (Faraone et al., 2019). The association with ADHD is not accounted for by co-occurring conditions such as ODD and anxiety (Nigg, Karalunas, Feczko, & Fair, 2020). SCT is a constellation of cognitive (e.g., excessive daydreaming, being 'lost in a fog') and motor (e.g., underactive, slow-moving) elements (Becker et al., 2016), with an international Work Group recently proposing to change the name of this set of symptoms to cognitive disengagement syndrome (CDS; Becker et al., 2022). These behaviors affect 25–40% of ADHD youth, especially those with combined or predominantly inattentive presentations (Barkley, 2013). SCT is empirically distinct from, though strongly

related to, ADHD symptoms, particularly inattention (Becker et al., 2016). Research examining the convergent and discriminant validity vis-a-vis SCT from ADHD has produced psychomet- rically strong and clinically useful instruments (Becker, 2021). Both ERD and SCT contribute to ADHD-related impairment (Becker et al., 2016; Faraone et al., 2019). ADHD-related ERD is associated with reduced quality of life (QoL), social impairment, and worse educational/occupational outcomes in children and adults (Faraone et al., 2019). SCT is associated with social withdrawal, internalizing symptoms (especially depression), and poorer functional outcomes (Becker et al., 2016). SCT and ERD, though statistically and clinically distinct entities, are often correlated (Becker et al., 2016). However, ERD cleaves specifically with hyperactivity/impulsivity (Faraone et al., 2019) and SCT with inattention (Becker et al., 2016).

A third domain, sleep problems, even if not meeting threshold for a sleep disorder, are also extremely common in people with ADHD, although less frequently proposed as part of an extended phenotype, despite 'restless sleep' being a symptom for the diagnosis in DSM-III. Children, adolescents, and adults with ADHD are more likely than their peers to obtain insufficient and/or poorer-quality sleep (Cortese, Faraone, Konofal, & Lecendreux, 2009; Dıaz-Roman, Mitchell, & Cortese, 2018). These effects are stronger for subjective measures (e.g., parent reports) than objective measures (e.g., polysomnography). Sleep problems in ADHD are associated with lower QoL, worse family functioning, and increased ODD and depression (Lunsford-Avery, Krystal, & Kollins, 2016). ERD is increased following sleep loss (Short, Booth, Omar, Ostlundh, & Arora, 2020). ERD and SCT are both correlated with poor sleep at night and daytime sleepiness (Fredrick, Yeaman, Yu, Langberg, & Becker, 2022; LunsfordAvery et al., 2016).

With regard to co-occurring conditions, 'pure' ADHD is the exception rather than the rule clinically. Population-based studies, accounting for potential ascertainment and referral bias in clinical samples, demonstrate substantially elevated rates of virtually all psychiatric and neurodevelopmental conditions in both children and adults with ADHD (Green, McGinity, Meltzer, Ford, & Goodman, 2005; Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010). Co-occurring ODD, anxiety, and depression are prominent in childhood (Wilens et al., 2002). Cooccurring autism also typically presents in early childhood although diagnosis can be delayed, possibly due to diagnostic overshadowing (Kentrou, de Veld, Mataw, & Begeer, 2019). Inattention is more strongly linked to withdrawal and depression, and hyperactivity-impulsivity is more often linked to behavioral conditions (Willcutt et al., 2012). Cooccurring conditions are in general associated with greater ADHD persistence in childhood (Riddle et al., 2013) and adulthood (Caye et al., 2016). After controlling for sex-specific population base rates, females with ADHD are more likely to have autism, intellectual disability, ODDD/CD and schizophrenia (Ottosen et al., 2019), suicidal behavior (Hinshaw et al., 2022; Ottosen et al., 2019), personality disorder (Ottosen et al., 2019), and substance abuse disorder (Biederman, Newcorn, & Sprich, 1991; Ottosen et al., 2019) but not anxiety and depression, which were similarly increased in females without ADHD as they were in those with ADHD. Overlap with physical conditions is also common but outside the scope of this review (see e.g., Galera et al., 2022). This high degree of overlap challenges current categorical diagnoses by highlighting the fuzzy boundaries of the conditions and the possibility of the distinct existence of what might be called hybrid disorders containing elements of different clinical domains.

There are a number of possible explanations for cooccurrence. First, overlap and ambiguity is common across the symptoms that define different diagnostic categories (e.g., difficulty concentrating diagnostic for ADHD, anxiety, and

depression, and 'interrupting others' may reflect ADHD impulsiveness or impaired social understanding autism). This creates problems, especially in research that relies on questionnaires or highly structured interviews, which may incorrectly assign symptoms. However, even in these cases, cooccurrences are not merely the result of overlapping symptom content as co-occurring conditions create more impairment (Mak et al., 2021). Second, twin and family studies illustrate shared genetic variance between ADHD and co-occurring conditions, especially autism (Miller et al., 2019; Polderman, Hoekstra, Posthuma, & Larsson, 2014) but also ODD (Thapar, Harrington, & McGuffin, 2001), anxiety, depression, and substance abuse (Chang, Lichtenstein, & Larsson, 2012). Molecular genetic studies also showed genetic variants shared between ADHD and other conditions including autism and depression (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Third, extreme environmental exposures including prenatal toxin exposures (e.g., alcohol) (Wozniak, Riley, &

Charness, 2019), prematurity (Sciberras, Mulraney, Silva, & Coghill, 2017), and severe psycho-social deprivation (Sonuga-Barke et al., 2017) increase shared risk for multiple neurodevelopmental conditions (e.g., autism, ADHD, and intellectual disability). Shared common postnatal factors, such as unsupportive parenting and peer relationship problems, may play a significant role in the development of cooccurring emotional conditions (Gustavson et al., 2021; Mikami & Hinshaw, 2006). Fourth, there may also be shared neuropsychological mediators. Deficient executive functions, common in ADHD (Willcutt, Doyle, Nigg, Pennington, & Pennington, 2005), are also observed in autism (Craig et al., 2016), depression (Fenesy & Lee, 2019), and anxiety (Nyberg et al., 2021), and they appear to drive its co-occurrence with autism (Lukito et al., 2017) and depression (Fenesy & Lee, 2019) in particular. Developmentally, cognitive

inflexibility is most prominent in young autistic children with other EF difficulties increasing with age, while inhibition problems are most prominent in young children with ADHD (Visser, Rommelse, Greven, & Buitelaar, 2016). Genetic factors account for some of these covariances (Brooker et al., 2020), though EF can be relatively state-dependent, improving with remission of depression (Biringer et al., 2005) and stimulant medication in ADHD (Coghill et al., 2014).

New leads

ERD may delineate a diagnostic subtype. Emotional impulsivity (fast-rising reactivity in response to events) and deficient emotion self-regulation may represent a specific ADHD ERD subtype (Martel, 2009). This has promise as a way of parsing ADHD heterogeneity, advancing clinical prediction and guiding intervention selection (Nigg, Karalunas, et al., 2020). The delineation of irritable, surgent, and mild temperament profiles further improves descriptions of ADHD heterogeneity (Karalunas, Gustafsson, Fair, Musser, & Nigg, 2019).

SCT appears to mediate ADHD-related academic difficulties. Longitudinal data show that SCT and ADHD inattention are differentially associated with lower achievement in reading and math, respectively (Becker, Burns, Leopold, Olson, & Willcutt, 2018). Perhaps related to this, SCT appears to represent a promising bridge between clinical science and mind wandering studies in cognitive psychology and neuroscience (Becker & Barkley, 2021).

Poor or insufficient sleep could play a causal role in ADHD. A sleep restriction/extension study found evidence that shortened sleep duration may cause increases in ADHD inattentive, but not hyperactive– impulsive symptoms, in adolescents with ADHD (Becker et al., 2019). These findings extend the work conducted with school-aged children, which found that insufficient sleep impacted attention, and to a lesser extent, ERD (Davidson, Rusak, Chambers, & Corkum, 2019).

ERD and SCT share risk factors and neural processes with sleep problems. Poor sleep and ADHD (Gregory, Agnew-Blais, Matthews, Moffitt, & Arseneault, 2017) and impulsivity and anger/frustration may have common genetic origins (Miadich et al., 2020). ADHD and sleep disturbances share deficits in arousal (Owens et al., 2013) and have common neural correlates, particularly in cognitive control and salience networks (Shen et al., 2020). In addition to the close link between them and sleep, circadian functions may be implicated in ADHD (Bijlenga, Vollebregt, Kooij, & Arns, 2019), ERD (Gruber & Cassoff, 2014) and SCT (Fredrick, Yeaman, et al., 2022).

Broader ADHD characteristics can help explain cooccurrence of ADHD and other conditions. ERD has trans-diagnostic relevance across emotional and behavioral psychopathologies (Aldao, Gee, De Los, & Seager, 2016). It is a common feature of depression and anxiety as well as ADHD (Mayer et al., 2022). There are behavior genetic correlations between ERD, ADHD, and mood (Merwood et al., 2014). Early irritability is associated with the ADHD polygenic risk score (Riglin et al., 2017). Longitudinal analyses in a population cohort suggest that both ADHD and autism-related ERD mediate risk for later depression (Eyre et al., 2019). SCT, associated with both ADHD and depression (Becker et al., 2016), predicts future adult depression (Smith, Zald, & Lahey, 2020), perhaps via negative peer processes (Fredrick, Langberg, & Becker, 2022). Sleep problems are linked to anxiety, depression, and ERD in children with ADHD, with bidirectional longitudinal associations (LunsfordAvery et al., 2016). Experimental data showing sleep restriction increases depression and SCT strengthens causal inference (Becker, Tamm, Epstein, & Beebe, 2020). Sleep disturbances may be mechanistically trans-diagnostic via their reciprocal relation and shared neurobiology with emotion dysregulation (Harvey, Murray, Chandler, & Soehner, 2011).

Gene–environment correlations can link ADHD to other conditions developmentally.

People with ADHD experience a multitude of negative environmental exposures that appear to drive some cooccurring conditions. In particular, maltreatment rates are elevated in ADHD, and these are linked to later aggression, anxiety, and depression (Craig, Bondi, O'Donnell, Pepler, & Weiss, 2020; Peleikis, Fredriksen, & Faraone, 2022). Both passive and evocative environmental correlations are implicated (e.g., Harold et al., 2013; Ratanatharathorn et al., 2021): Twin studies suggest that ADHD behaviors evoke negative responses, which drive later problems (Ohlsson Gotby, Lichtenstein, Langstrom,€ & Pettersson, 2018), while the association between maltreatment and maternal ADHD symptoms is consistent with a role for passive gene–environment correlation (Gul & Gurkan, 2018).

Outstanding questions

Should ERD and/or SCT be considered as part of the ADHD diagnostic criteria and/or as specifiers within ADHD? The evidence for ERD as a core feature of ADHD is growing and these features are informing models of dysregulation as an organizing framework that can inform nosology. With regard to the latter, ADHD has extensive heterogeneity, and features within the broader phenotype may be informative beyond the ADHD symptom dimensions and DSM-defined presentations (Nigg, Karalunas, et al., 2020). As mentioned above, this has been examined in relation to ERD with promising evidence emerging (Karalunas et al., 2019; Nigg, Karalunas, et al., 2020). Future studies need to extend these sorts of analyses to SCT and sleep problems.

Are ADHD presentations the same when they are accompanied by co-occurring conditions? Current diagnostic classifications, based as they are on external manifestations rather than underpinning pathophysiology, may be limited when applied to overlapping phenotypes. Future research exploring underpinning mechanisms will be required with deeper phenotyping of symptom profiles and

biomarkers to elucidate shared and specific risk factors that will contribute to more valid classification.

Are broader phenotype domains useful intervention targets? Recent findings highlight the potential value of developing ADHD-specific interventions that act by targeting SCT and ERD. For instance, interventions that aim to reduce proneness to anger, a highly relevant dimension of irritability, could reduce risk for later negative outcomes such as anxiety in individuals with ADHD (Karalunas et al., 2019). Further, it is important to assess if SCT and ERD predict treatment response to current evidence-based interventions for ADHD.

Does effective therapeutic control of ADHD have positive long-term effects on co-occurring conditions? Just as it has been challenging to discern the long-term effects of interventions on ADHD symptoms, it is unclear whether good control of ADHD reduces ongoing or later-onset co-occurring conditions. Understanding whether such treatment effects are mediated by improvement in ADHD symptoms is critical to decision-making about continuing treatment when ADHD symptoms are no longer impairing.

Which children with ADHD are resilient to adverse environmental exposure? While we know that children with ADHD are more likely to have adverse experiences that can lead to the development of cooccurring problems, less is understood about the processes that confer resilience to these experiences. As strong emotion regulation is linked to greater resilience in the general population, it is plausible that this may act as a protective feature in terms of reducing the risk for emotional problems.

Impact of living with ADHD

Traditionally researchers have focused their ADHD characterization, and clinicians their therapeutic efforts, primarily on core symptoms; inattention, hyperactivity, and impulsivity. However, in recent years a more holistic and person-centered focus on the impact of living with ADHD in terms of functional impairment, Quality of Life (QoL), and stigma has started to prevail.

Prior consensus

Impairment is a defining feature of ADHD and can be seen across multiple domains – emerging through the complex interplay between an individual's abilities-disabilities and the environmental context in which they live and operate. Impairment profiles vary significantly between individuals with ADHD, but core functional challenges are shared widely (Bolte et al.,€ 2018). Across cultures, ADHD negatively impacts peer and sibling relationships (Ros & Graziano, 2018). ADHD is associated with risky behaviors marked by higher rates of teenage pregnancy, gambling, and accidents and premature death (Shoham, Sonuga-Barke, Yaniv, & Pollak, 2021). Hyperactive–impulsive symptoms correlate with risk-taking, accidents, and social exclusion by peers, while inattentive symptoms correlate with low scholastic/vocational performance and low selfconfidence (Willcutt et al., 2012). Impairment persists into adulthood for more than half of cases (Song et al., 2021) and is aggravated by the presence of other neurodevelopmental and mental health conditions (Jangmo et al., 2021). Impairment may be underestimated in females during childhood (Mowlem, Agnew-Blais, Taylor, & Asherson, 2019) perhaps related to sex differences in profiles of cooccurring conditions (Rucklidge, 2010). Females may also make greater efforts to hide challenges and live up to social expectations (de Schipper et al., 2015).

QoL and, relatedly, well-being and life satisfaction, are substantially reduced in ADHD – although there is great inter-individual variation. In general, selfreported global QoL is reduced across life domains and over time compared to typically developing individuals, with both children (Jonsson et al., 2017) and adults affected (Lensing, Zeiner, Sandvik, & Opjordsmoen, 2015). QoL is affected more where co-occurring conditions are present (Klassen, Miller, & Fine, 2004). The effects of ADHD are comparable to those seen in serious

pediatric health conditions (Coghill & Hodgkins, 2016). Parents' and siblings' QoL is also reduced (Peasgood et al., 2021).

People with ADHD can experience prejudice, stereotyping, and discrimination due, often, to the diagnostic label. These forms of stigma, when internalized, can lead to a sense of alienation that reduces help seeking and lowers self-esteem (Clement et al., 2015). Fuelled by misconceptions about its causes and misinformation about medication (Hinshaw & Scheffler, 2014), ADHD stigmatization is common among family, public, and professionals (Lebowitz, 2016). ADHD-related stigma is more pronounced than in specific learning disabilities but less so than for bipolar disorder (Kaushik, Kostaki, & Kyriakopoulos, 2016). The use of biomedical terms by clinicians and scientists (e.g., disease, abnormality) for the experience of being different can be stigmatizing, although some terms, such as 'patient', are still more accepted in ADHD than in other neurodevelopmental conditions (e.g., Kenny et al., 2016).

New leads

Wholistic and person-centered assessment is increasingly seen as vital. Research and practice focused solely on symptoms is limiting, as it neglects the QoL as well as the performance and capacity of patients with ADHD and families. It also tends to focus attention on the individual, ignoring environmental influences, and constraints (Pellicano & den Houting, 2022). While DSM-5 and ICD-11 do not operationalize QoL, they have bolstered the importance of performance and impairment by introducing a mandatory impairment criterion for all conditions and recommending standardized scales for functional assessment based on the International Classification of Functioning. Recently, core sets of items tailored for detailed functional assessment in ADHD in research and practice have been developed, covering body functions, activities, participation, and environmental factors (Bolte et al.,€ 2018).

There is no clear-cut impairment threshold above which ADHD should be diagnosed. Arildskov, Sonuga-Barke, Thomsen, Virring, and Østergaard (2022) recently reported that although correlated with symptoms, there is no obvious threshold at which an increase above a certain level of symptoms leads to a disproportionate rise in impairment. Setting the level of impairment required for a diagnosis, therefore, appears to some extent arbitrary and based on social norms and the level of support needed. Setting those thresholds is a clinical decision and needs to be tailored to individuals given each person's history, unique skills, life challenges, and access to support and resources.

ADHD treatments increasingly focus on reducing impairment and improving quality of life. Reducing impairment, improving functioning and QoL should be the primary focus of future treatment trials (Coghill, Banaschewski, Soutullo, Cottingham, & Zuddas, 2017). Targeting symptom severity may be stigmatizing and/or less important for clients in terms of long-term social outcomes and wellbeing. For instance, it has been demonstrated that major drivers of impairment and low QoL in ADHD are sleep problems and mental health issues (Mulraney et al., 2017; Ahnemark et al., 2018). The European Medicines Agency guidance and national European healthcare authorities have started to recommend and reinforce such an approach (e.g., Swedish Board of Health and Welfare, 2019).

Outstanding questions

Is ADHD associated with personal strengths and societal benefits as suggested by the neurodiversity perspective? Neurodivergent people, like all people, can display both relative and absolute strengths (Pellicano & den Houting, 2022). Initial research has suggested that ADHD is perceived as being associated with specific strengths such as energy and drive, creativity, hyper-focus, and agreeableness (Hoogman et al., 2020; Sedgwick, Merwood, & Asherson, 2019), but the level of generalizability and specificity to ADHD per se remains unclear

(Groen et al., 2020). A refocusing on strength-based approaches to ADHD must be careful avoid opposition to treatment or research, in ways that do an injustice to severe impairment and overlooks instances of frank neural injury (e.g., in low birth-weight children, lead-exposed children with ADHD). While more research is needed in this area to clarify potential strengths and benefits associated with ADHD, a more balanced view on neurodivergent people, embracing positive psychology, and highlighting their value is required (Bolte, Law-€ son, Marschik, & Girdler, 2021). Related to this point – involvement of people with ADHD in the ADHD research process is increasingly seen as vital – allowing them to give advice and help shape the research process and order its priorities by providing essential insights into their experience of the condition.

Should interventions focus on removing barriers to functioning rather than 'normalizing' people with ADHD? ADHD interventions have traditionally focused on reducing an individual's symptoms. There has been comparably little research examining intervention approaches that focus on reducing impairment through reasonable environmental accomodations, although studies in the classroom setting so far show limited effects (Lovett & Nelson, 2021). However, there is a growing consensus that attempts at such accommodations across settings are not only ethically desirable but also potentially fruitful (Bolte et al.,€ 2021). More research is needed on how to ensure that they take account of the relative needs and strengths of individuals with ADHD and are balanced with the need to challenge the individual on an appropriate level to promote learning and increase their capacities to cope with environmental demands (Richardson et al., 2015). Importantly, the removal of barriers to functioning, and consolidating and developing facilitative environments should be carried out in conjunction with psychological and psychiatric interventions aiming to empower and increase well-being.

Does getting an ADHD diagnosis increase or reduce stigma? The effects of diagnostic labeling and diagnostic disclosure in mental health conditions are person-specific and have, therefore, commonly been studied anecdotally or using vignettebased experiments (O'Connor, Brassil, O'Sullivan, Seery, & Nearchou, 2022). In ADHD, knowledge relating to stigma is predominantly based on respondents who experience stigma associated with their own or their relatives' ADHD (Mueller, Fuermaier, Koerts, & Tucha, 2012). ADHD-related social stigma appears to vary from case to case, and labeling can either exacerbate, ameliorate, or not affect stigma. However, the limited available research indicates more rather than less social stigma is associated with receiving a diagnosis of ADHD, when evaluated by teachers and student peers, whereas receiving a diagnosis of autism, a common co-existing condition in ADHD, is associated with ameliorated stigma (O'Connor et al., 2022).

Are there sex/gender differences in ADHD-related stigma? Research has not yet consistently and systematically considered sex/gender effects across all aspects of ADHD (Hartung & Lefler, 2019). There are cultural influences on social stigma in mental health related to sex/gender, and these influence public attitudes about mental health (Holzinger, Floris, Schomerus, Carta, & Angermeyer, 2012). These and other factors may impact on sex/gender differences in social stigma associated with ADHD, but there is hardly any research conducted on this topic.

Risk factors and causal processes and pathways

From a translational perspective, science that deepens our understanding of the biological mechanisms and environmental processes that lead to the onset and development of neurodevelopmental and mental health conditions holds the key to more effective interventions to support individuals with such problems (Nigg, 2022). ADHD science has progressed our understanding of these matters enormously over recent decades, as

researchers have exploited more powerful models and methods made available by technological advances. Paradoxically, if anything, however, these advances can lead to the sense that we are farther than ever away from fully understanding ADHD. This is because they have revealed just how complex and heterogeneous are the genetic and environmental influences as well as the psychobiological processes involved in ADHD.

Genes

ADHD is a highly heritable condition (meaning individual variation is strongly related to genetic variation), although the inheritance of the condition (across generations) is complex, and familial transmission from generation to generation may not be easily discernible. Genetic research identifying the genes involved in ADHD can provide insights into ADHD-associated biological processes. Since the genetic make-up of a person is determined during conception, studying the genetics of ADHD can open a window into the molecular and cellular mechanisms that may contribute causally to these processes. Successes in collaborative, genome-wide genetic studies have led to new insights and new hypotheses about the nature of ADHD and its relationship with other conditions and traits. Although to date findings regarding individual genes are too small for clinical use and summary algorithms are still being studied, prospects for clinical intervention are appearing.

Prior consensus

Estimated heritability in general population twin samples is 74%. This estimate is similar for ADHD defined as a category or dimension, and the degree of heritability does not increase as symptom severity increases – confirming that it is best viewed as the extreme end of a continuous heritable trait. Heritability is similar for ADHD in children and adults (Faraone & Larsson, 2019). Despite its high heritability, ADHD has a complex, polygenic genetic component, with several-to-multiple genetic variants implicated in most affected individuals. As in other diseases with a similarly complex genetic make-up, most of the genetic variants involved play a very limited role in ADHD risk individually, and different combinations of genetic risk variants are present in different individuals with ADHD (Faraone & Larsson, 2019). To identify the genetic variants underlying polygenic conditions such as ADHD, collaborative genome-wide association study (GWAS) meta-analyses involving very large samples of cases and controls are required. For ADHD, the first report with data on around 20,000 people with ADHD and over 35,000 without identified 12 ADHD risk variants (of the single nucleotide polymorphism [SNP] type) (Demontis et al., 2019), and a more recent study with over 38,000 individuals with ADHD and nearly 187,000 unaffected individuals identified 27 genome-wide significant loci (Demontis et al., 2022). In all cases, each statistically significant SNP carried a very small risk individually; together, all studied SNPs, when aggregated, explained 25–30% of the total ADHD heritability estimated from twin studies. Other types of genetic variants, for example, rarer variants with potentially larger effects at the level of the individual identified through (rare) copy number variant (CNV) studies (e.g., Harich et al., 2020) and whole exome sequencing (WES) studies (e.g., Satterstrom et al., 2019), also seem to contribute to heritability. In addition to genetic factors, environmental factors are also involved in the etiology of ADHD, and it is likely that an interplay (involving both interaction and correlation) exists between genetic and environmental factors.

Genetic studies are helping to unravel the neurobiological pathways and (brain) substrates associated with ADHD. Based mainly on animal and pharmacological studies, in early genetic studies, researchers had hypothesized that genetic alterations controlling monoaminergic (especially dopaminergic) neurotransmission may underlie ADHD susceptibility (Faraone et al., 2015). More recently GWAS-based hypothesis-generating, datadriven analyses

of biological processes have confirmed the role of these neurotransmission-related genes (Cabana-Domınguez, Torrico, Reif, Fernandez- Castillo, & Cormand, 2022; Thapar et al., 2016) and implicated other brain-related processes – especially those linked to maturation, for example, in prenatal and early postnatal neurite outgrowth (Mooney et al., 2016; Poelmans, Pauls, Buitelaar, & Franke, 2011; Thapar et al., 2016). Combining GWAS with brain imaging data has helped identify common genetic aspects determining (adult) intracranial volume (Klein et al., 2019) and the surface area of cortex (Grasby et al., 2020). Bioinformatic enrichment analyses has implicated genes upregulated in fetal brain development (Demontis et al., 2022).

Genetic contributions to ADHD overlap with contributions to other psychiatric and neurodevelopmental conditions – with overlapping SNPs most prominent for major depression and autism spectrum disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) – and also rare genetic variants identified (Satterstrom et al., 2019). Biological overlap due to genetics has also been seen with neuroticism scores and IQ as well as with somatic traits and diseases (Demontis et al., 2019). These studies have provided insight into the causes of co-occurrences between ADHD and other health conditions (e.g., Mota et al., 2020).

New leads

There are different genetic contributions to childhood, persistent adult, and late-onset ADHD. Longitudinal twin studies have suggested that the genes associated with ADHD change from childhood to adolescence and adulthood: Less than half of the genetic factors involved in childhood may still play a role in adulthood (Chang, Lichtenstein, Asherson, & Larsson, 2013). GWAS analysis currently suggests 80% measured genetic overlap between children and adults with ADHD (Rovira et al., 2020), so future studies will need to clarify this discrepancy. The late-onset form of ADHD has not yet been studied sufficiently to assess its genetic contribution; conflicting results

are reported on whether the genetic contribution to this form is lower or similar to that of childhood-onset forms (Agnew-Blais et al., 2021; Riglin et al., 2022). A study on late-diagnosed ADHD suggested a lower genetic burden in adults with late-diagnosed ADHD than in those with persistent ADHD (Rajagopal et al., 2021).

There may be genetically-based sex differences in ADHD. A range of different study designs have tested the hypothesis that quantitative and/or qualitative sex differences in genetic factors may contribute to the differences between ADHD prevalence in males and females (Martin et al., 2018). A recent analysis combining epidemiological and genetic approaches suggested that the siblings of females with ADHD are at higher familial risk of ADHD than the siblings of affected male individuals; however, no increased burden of common-variant ADHD genetic risk was seen in females, and the genetic overlap of such ADHD risk variants was close to 100% (Martin et al., 2018).

Genetic association is not the same as causation. Molecular genetic studies are correlational. Experimental designs, for example, using cellular and animal models, postmortem material, and/or intervention studies, are required to bolster causal inference (Klein et al., 2017). Furthermore, statistical approaches, such as Mendelian Randomization, can help determine the direction of gene-related effects. Recent studies using this design found, for example, that genetic correlations observed between ADHD and lifetime cannabis use are indicative of ADHD being causal for cannabis use (Soler Artigas et al., 2020) and that genetic liability for ADHD affects educational attainment independently of general cognitive ability (Dardani et al., 2022).

Outstanding questions

Why are heritability estimates derived from behavioral and molecular genetic studies different? While the heritability of ADHD based on twin studies is 74% (Faraone & Larsson, 2019) genomewide studies of

common genetic variants so far only provide heritability estimates of 20–30% (Demontis et al., 2019). Additional ADHD twin heritability may be explained by rare genetic variants, as described above. Missing heritability may also be accounted for by potentially synergistic gene–environment and gene–gene interactions, which are incorporated in twin study heritability estimates alongside genetic main effects (Purcell, 2002). Understanding the extent of these contributions represents an important focus for future study, and it is to be expected that the implementation of whole genome sequencing technology in genetic analyses will capture additional variance over and above current methods.

Can genetics inform diagnostic/stratification (biomarkers) in clinically relevant ways? Genetic screening is commonly used in the clinic for some medical conditions in which a single genetic mutation is responsible for a major increase in risk. In ADHD, however, several-to-multiple genetic variants contribute to the disorder in most patients, and those seem to have only limited effect sizes. Even the rare variants linked to ADHD are not sufficiently predictive of case status to be clinically useful, although a recent finding showed the effects of such ADHD risk variants to be comparable to those associated with ASD risk (Satterstrom et al., 2019). Scores capturing polygenic risk burden derived from GWAS (called polygenic scores) are starting to be used in the clinic for other multifactorial diseases (such as breast cancer and cardiovascular disease; Khera et al., 2018). While not (yet) sufficiently diagnostic of conditions like ADHD (explaining about 3% of the variance in ADHD broadly defined; Li & He, 2021), these scores may have utility in the clinical toolbox, as part of risk algorithms in combination with other indicators, for parsing heterogeneity, and/or for targeting interventions. When talking about genetics, the possibility of prenatal screening for the risk of conditions like ADHD based on genetics needs mention, as some companies have been known to offer such services.

Beyond the fact that genetics is currently not informative for prenatal screening for ADHD, this obviously raises profound ethical and moral questions related to the selection (e.g., embryo selection), engineering out (e.g., gene editing), or other interventions upon identification of an embryo/fetus at risk of ADHD. These discussions are not unique to ADHD -- similar issues hold for other mental health conditions (ASD, bipolar disorder) and even basic traits (such as sex, height, IQ). Given the rapid developments in this field, it is vital that researchers, clinicians, people with ADHD, and ethicists/moral philosophers address these issues as a matter of urgency in order to put safeguards against such practices in place.

Do genetic effects underpin resilience as well as risk? So far, molecular genetic studies of ADHD have exclusively focused on identifying risk factors. However, it is becoming clearer that genetic factors may underpin resilience to risk exposure in people with psychiatric conditions (Hess et al., 2022; Hofgaard, Nes, & Røysamb, 2021; Maul et al., 2020). Understanding the interplay between genetic resilience and risk factors is an important priority for ADHD science going forward.

Environments

Genotype-environment coaction is axiomatic and foundational in contemporary developmental theory (Bronfenbrenner & Ceci, 1994) but specifying particular environmental effects in causal models is difficult. Indeed, it is necessary to distinguish a risk factor (i.e., correlated but not causal) from a mechanistic factor (i.e., plays a causal role). Risk factors associated with ADHD are important to clinical prediction, but mechanistic factors are important for potential prevention or treatment because they may be modifiable prevention/intervention targets. In this section, we first note key risk factors, then add cautions regarding the state of mechanistic research (which indicates that several risk factors do not appear to be causal). In particular, the existence of passive

correlation between genetic and environmental risk (rGE) makes it difficult to disentangle the causal role of genes and environments based purely on observational studies (Sonuga-Barke & Harold, 2018). This means that what looks like an environmental effect could be a genetic one. However, rGE can also be compatible with causal effects, in that environment can mediate genetic effects (genetic nurturance; Armstrong-Carter et al., 2020; Kong et al., 2018; de Zeeuw et al., 2020). Crucially, in the case of genetic nurturance, the environment is mediating the effect of the parental (nontransmitted) alleles – in the offspring, this is a purely environmental effect. This is distinct from the environment being correlated with transmitted alleles (i.e., confounded with genotype). Genetically informative designs for ADHD that have failed to find causal links have generally not considered the possibility of genetic nurturance. Thus, the causal status of environmental exposures often remains unclear except when direct experimental designs can be used, as illustrated below. However, given the large literature, environmental associations with ADHD cannot be ignored in explanatory accounts. Thus, although effects of individual exposures on ADHD tend to be statistically small, even these seemingly small effects may be important from a public health perspective and, clinically and conceptually, may accumulate to accentuate or add to genetic liability leading to ADHD, either in additive or multiplicative ways.

Prior consensus

Interest in the role of the environment in causal accounts of ADHD has ebbed and flowed over the last 50 years. Recent developments in ADHD genetics, especially the recognition of the challenge of 'missing heritability' has underscored the need to revisit this question. While few, if any, environmental effects are expected to be specific to ADHD, in as much as they invariably are related to general nervous system development, a consensus has now emerged that some understanding of

environmental context is necessary for developmental and causal accounts. Twin studies have previously established that direct effects on variation in ADHD are principally due to heritable factors (i.e., genetic variation), with the remainder explained by nonshared environment (exposures unique to each twin) or random error (Purcell, 2002). However, two kinds of genotype-environment interactions are not measured in the typical twin design. Of most interest is the interaction with shared environment (those shared by two twins), because these may often be due to common exposures not only in the family but that vary meaningfully in the population (such as dietary factors, pollutant exposures, or socioeconomic factors). These matter because if identified as causal, they may have potentially significant implications for public health prevention strategies.

With regard to specific risk factors, the massive literature was recently summarized in an umbrella review of meta-analyses; the authors judged the credibility of associations between ADHD and a range of different environmental exposures based on the p-value, size of sample, and homogeneity of findings. It identified nine associations as having high credibility (random effects $p < .000001$, or $p < .000001$, $n > 1,000$; Kim et al., 2020). Most of these were maternal pre- and perinatal factors including prepregnancy and pregnancy overweight and pregnancy hypertension, gestational hypertension, preeclampsia, acetaminophen use, and smoking. Two were child factors – childhood eczema and low serum vitamin D. However, all effects were modest in size (Odds Ratio(OR) < 2.0). Several other smaller associations were also deemed reliable ($p < .001$) including child blood lead level, child blood magnesium level, maternal stress during pregnancy, and maternal selective serotonin reuptake inhibitor (SSRI) exposure during pregnancy. A number of other associations, including preterm birth or low birthweight, low paternal education, and head trauma, had larger effect sizes (OR >2.0). However, these were judged to have

limited credibility based on small sample and/or low homogeneity of findings. Other literature suggests interesting but tentative initial findings regarding the role of traffic-related air pollution such as nitrous dioxide and small particulate matter (Donzelli, LlopisGonzalez, Llopis-Morales, Cioni, & Morales-Suarez- Varela, 2019), polyfluoroalkyls (Qu et al., 2021), and even more speculatively, manganese (particularly from soy-based baby formula; Crinella, 2012).

With regard to the adequacy of that review and the issue of causality, we note the following. The authors' requirement of study homogeneity to assign high credibility to an effect can be questioned given ADHD's expected etiological heterogeneity. Their reliance on meta-analyses also limited the comprehensiveness of their findings by ruling out compelling evidence from single large studies, causally informative studies (e.g., natural and quasi-experiments), and unusual cohorts. Considering those limitations, and taking account of more recent causally informative evidence, we can underscore the likely causal role of preterm birth/very low birth weight with a large effect size (OR >3.0) (Franz et al., 2018) as well as extremely rare but extreme institutional neglect in early life (Kennedy et al., 2016). While more causally-informed evaluation is needed, evidence is accumulating related to a continuum of psychosocial adversity (Gomez-Cano, Zapata-Ospina, ArcosBurgos, & Palacio-Ortiz, 2022) although such effects may be causally bidirectional.

Experimental evidence, while still limited, does lend support to a causal role of synthetic food additives in influencing ADHD symptoms in the population (McCann et al., 2007; Nigg, Lewis, Edinger, & Falk, 2012) although these would play only a minor role in ADHD itself. One causally informative study supported a role of common background lead exposure in ADHD (Nigg, Elmore, Natarajan, Friderici, & Nikolas, 2016) and a review of causally informative studies concluded that birth weight exerts a

causal effect on ADHD symptoms (Rice, Langley, Woodford, Davey Smith, & Thapar, 2018). That said, extreme environmental effects would provide a primary explanation of ADHD status only in a minority of cases. Other, less studied, common exposures appear to add to ADHD risk; if causal, they would have a substantial public health impact on ADHD. Important candidates here include neurotoxic pollutants notably organophosphates and organochlorine pesticides as well as the now discontinued (yet still environmentally present) polychlorinated biphenyls (Polanska, Jurewicz, & Hanke, 2013).

In contrast, it is crucial to note that for many ADHD risk factors, the association appears not to be causal but explained by genetic or familial confounds, or else is reverse causality due to evocative genotype-environment correlation. For example, a causal role has not been supported for maternal smoking (Haan et al., 2022; Rice et al., 2018) and maternal pregnancy weight gain (Musser et al., 2017). Child maltreatment had only a small causal association with ADHD symptoms in a population study that controlled for familial and genetic confounding (Dinkler et al., 2017) More studies of these kinds are needed to determine which risk factors mandate intervention. The moderator effect of environmental exposures on genetic liability or genetic effects remains poorly mapped, though some important examples have emerged. Perhaps the most obvious one, in which clarity has been building for decades, relates to parenting. While unlikely to be an important etiological factor in ADHD in and of itself (but see below under new directions and outstanding questions), parenting behaviors or styles likely moderate the course of development of individuals with ADHD – especially in terms of the development of complicating and co-occurring sources of impairment (Daley et al., 2018).

New leads

Polygenic risk scores are being used in gene x environment statistical interaction studies.

New insights into the statistical interplay between genotype and environment are emerging (Nigg, 2022). Polygenic risk scores from GWAS are being used to study the interplay between broad genomic liability and specific exposures although, albeit with limited success in identifying statistical interactions for many risk factors (Østergaard et al., 2020). Nevertheless, statistical interactions between ADHD polygenic risk and low birth weight (Rahman et al., 2021) and maternal depression (Chen et al., 2020) have been observed along with replicated interaction findings for maltreatment (He & Li, 2022; Ratanatharathorn et al., 2021). It is important to note that PRS's are not mechanistically informative, so these studies identify statistical dependencies that can be exploited for risk stratification and clinical prediction, but do not identify mechanistic or biological gene–environment interplay. Nonetheless, this type of work may open the door to advanced clinical prediction algorithms in which behavioral, psychosocial and genomic risk can be combined to form a total risk score with either additive or interactive effects.

Deeper understanding of the developmental role of gene–environment correlations. Understanding correlations between genotypic and environmental risk in ADHD (rGE), passive and evocative, continues to advance. More work is needed to examine genetic nurturance, which could reverse or amplify genetic liability (Garg et al., 2018). Crucially, the unknown frequency, timing, and magnitude of rGE effects in ADHD (like other disorders) leaves unresolved the mechanism behind many genetic and environmental exposure findings as well as some gene x environment findings. Thus, it will also be helpful to have direct mechanistic studies. For example, many risk factors appear to be consistent with an hypothesis of a common pathway to ADHD potentially involving metabolic syndrome or inflammation in pregnancy, including the clear association of ADHD with maternal obesity, hypertension and preeclampsia as

well (Kim et al., 2020). Studies that directly investigate, using experimental designs, the role of antiinflammatory interventions could evaluate a more complete mechanistic story. Epigenetics. Epigenetic effects are of keen interest and fascinating potential, though with important challenges (for extended discussion, see Cecil & Nigg, 2022), because they can relate to both environmental and genetic mechanisms, both of which are potentially useful practically (Dall'Aglio et al., 2018). However, it is important to recognize that epigenetic effects can also be stochastic (i.e., random) and that any findings require control for genetic effects (often overlooked in the epigenetics literature to date). It is also important to recognize the limitations of current methodologies for examining epigenetic effects on neural development in humans (Bakulski, Halladay, Hu, Mill, & Fallin, 2016; Cecil & Nigg, 2022). Large-scale studies of DNA methylation in ADHD are now beginning to be conducted (Mooney et al., 2020). The first replicated finding in this space is that infant perinatal DNA methylation is correlated with ADHD symptoms in early childhood, but those same methylation marks are not correlated cross-sectionally with ADHD symptoms (Neumann et al., 2020). It remains unclear to what extent this finding reflects genetic versus environmental influence on epigenetic mediators. However, it does suggest that early-life mechanisms likely cascade through development, consistent with recent developmental formulations of ADHD (Nigg, Sibley, Thapar, & Karalunas, 2020). New work on longitudinal change in ADHD and epigenetic markers, for example in peripheral tissue DNA methylation, will be an important focus of research in the coming years despite its challenges (Cecil & Nigg, 2022).

Outstanding questions

Which environmental effects are causal and which are explained by genetic correlations? As mentioned above, environmental effects are confounded with each other and with genetic risk. A new generation of causally

informative studies, aided by clever experimental and intervention designs as well as new methods in genetics, will be essential in distinguishing mechanistic effects of exposures from those are statistical risk factors but not causal.

Can the cumulative effect of multiple common exposures be harnessed clinically? Given the small effect size associated with most environmental (and genetic) risk factors, algorithms and models that aggregate and weight these risks will be essential for exploiting any translational potential they will have either for clinical prediction or, when causal, for prevention (but see the section on ethical concerns). Rapidly expanding efforts using machine learning algorithms also auger well for progress here. Alternatively, if shared mechanisms such as the aforementioned inflammation hypothesis are able to be verified, new risk biomarkers or intervention targets might emerge.

What role does early caregiving play in amplifying or dampening ADHD overall risk? Childhood caregiving has been much studied with evidence suggesting several aspects of caregiving can moderate the development and course of ADHD symptoms

(e.g., Claussen et al., 2022). While more genetically informative studies will be useful in that arena, a key gap in the literature related to very early life caregiving in ADHD. Early life prospective cohorts remain crucial to progress in the field of ADHD research. Genetically informative designs (Leppert et al., 2019) as well as experimental studies of parenting interventions will be crucial here.

What is the relationship between the ubiquitous use of digital devices and ADHD? The widespread use of screens and mobile devices in the modern world has created a fragmented, rapidly changing digital world where distraction (from the task in hand) is the rule rather than the exception. Children with ADHD may be, especially vulnerable to problematic use (Werling, Kuzhippallil, Emery, Walitza, & Drechsler, 2022). This

remains an area in need of more examination for child development in general and for ADHD risk, in particular, whether children with ADHD are more vulnerable to harmful effects (Sonuga-Barke & Kostyrka-Allchorne, in press).

Brains

Alterations in brain structure, function, and chemistry can be conceptualized as mediators of the pathways between originating genetic and environmental risks, ADHD onset and progression, and associated impairment. To that extent, they represent potential targets for the development of new interventions. Characterizing these alterations represents a key challenge in ADHD translational science. The advent of brain imaging has facilitated a more comprehensive understanding of ADHD, especially with regard to underlying neurobiology and mechanisms of treatment. However, the field has recently entered a period of flux as the recent addition of large-scale and well-powered neuroimaging analyses challenge some established findings. In parallel, the utility of ADHD neurochemistry studies has been constrained by the difficulty of translating findings from in vitro or animal studies to humans, and the failure of drugs, which target neurotransmitters known to indirectly impact catecholamine neurotransmission to produce improvement in ADHD symptoms in humans.

Prior consensus

The central role of catecholamine (e.g., dopamine (DA), norepinephrine (NE)) in ADHD pathophysiology was established by a plethora of research, including in vitro studies of receptor binding, animal models, and imaging of catecholamine receptors (Pliszka, 2005). D1 and alpha-2 receptors within prefrontal cortex circuits modulate attention and cognitive control, allowing differentiation of signal from noise (Arnsten, 2006). Striatal D2/D3 receptors and dopamine transporters (DAT) are directly or indirectly implicated in most core and associated features of ADHD, including motivation/reward, impulsive responding,

delay aversion, inhibition, attention, and learning (Dalley, Mar, Economidou, & Robbins, 2008). A variety of other neurotransmitters are involved in modulating arousal and attention linked to ADHD via their interaction with catecholamine (Pliszka, 2005), that is, glutamate (excitatory neurotransmitter inhibited by DA), acetylcholine (ACH), nicotine, GABA, and histamine-3. Serotonin (5-HT) is implicated in mood regulation (Sargin, Jeoung, Goodfellow, & Lambe, 2019) and impulse control (Dalley &

Roiser, 2012) but also contributes to executive function (Sargin et al., 2019).

Positron-emission tomography (PET) imaging has shown that striatal DA transporter (DAT) and postsynaptic DA receptor function is altered in ADHD (Fusar-Poli, Rubia, Rossi, Sartori, & Balottin, 2012), informing understanding of acute (Wilens, 2008) and chronic (Wang et al., 2013) mechanisms of stimulant medication. It has also documented the high density of limbic DAT and D2/D3 receptors in amygdala and hippocampus and their role in motivation (Volkow et al., 2011) and reward (Volkow et al., 2009). The widespread distribution of DAT and DA receptors across brain regions and functions, and the multiplicity of neurotransmitter systems and neural networks involved in modulation of catecholamine neurotransmission, has informed the conceptualization of ADHD as a broad and heterogeneous neuro-regulatory disorder (Pruim et al., 2019). NE is also central to ADHD pathophysiology and treatment. Like DA, NE has both direct and indirect effects (Berridge, 2001): Further, it is an important modulator of DA neurotransmission (Oades et al., 2005). NE-specific drugs (e.g., atomoxetine, alpha-2 agonists) are less effective at controlling symptoms than stimulants (Cortese et al., 2018), which have direct effects at both the DA and NE transporters. However, PET radioligand methodology for NE is less well developed (Moriguchi et al., 2017). Therefore, the full extent of NE regulation in ADHD and the neurobiological basis of

noradrenergic treatment have been harder to study.

The past 25 years have seen an explosion in research using MRI to examine the structural and functional basis of ADHD pathophysiology. These studies have elaborated the multiplicity of neural networks involved in ADHD and illustrated that it is a much more neurobiologically complex condition than previously thought. Most published MRI-based studies have reported ADHD-related alterations in either brain structure or function with some effects holding in meta-analytic reviews – however, overall these are variable and inconsistent. Meta-analyses of structural MRI studies confirmed reduced total brain volume (Valera, Faraone, Murray, & Seidman, 2007) and smaller localized gray matter volumes in regions including putamen/globus pallidus, caudate, and anterior cingulate cortex (ACC; EllisonWright, Ellison-Wright, & Bullmore, 2008; Nakao, Radua, Rubia, & Mataix-Cols, 2011). Fronto-cortical and subcortical correlates of deficits in timing (Hart, Radua, Mataix-Cols, & Rubia, 2012), inhibition, and attention (Rubia, Mataix-Cols, Radua, Hart, & Nakao, 2012) have been reported in fMRI metaanalyses. Analyses have increasingly moved to a more systems-science approach focusing on brain networks and circuits rather than particular regions. Meta-analysis identified ADHD-specific task-related hypoactivation in the frontoparietal network (FPN) and hyperactivation in the default mode network (DMN) and the visual and dorsal attention networks (Cortese et al., 2012) – broadly converging with the seminal hypothesis that behavioral dysregulations reflect insufficient segregation between the default mode and executive control networks (Sonuga-Barke & Castellanos, 2007).

Studies of resting-state fMRI (rfMRI) examine the functional organization of brain networks through their temporal correlations in blood oxygen leveldependent (BOLD) signal during task-free scans. Samea et al. (2019) performed an omnibus metaanalysis and found no reliable convergence when combining rfMRI, task-based fMRI and

voxel-based structural studies. In contrast, a meta-analysis by Gao et al. (2019) exclusively dedicated to rfMRI reported ADHD-related hyper-connectivity between FPN, DMN, and affective networks, and hypoconnectivity between the FPN and ventral attentional (VAN) and somatosensory networks (SSN). Applying multilevel kernel density analysis, Sutcubasi et al. (2020) reported reduced functional connectivity in the DMN and cognitive control networks and between them in child studies. In contrast, in broader whole-brain analyses, Cortese, Aoki, Itahashi, Castellanos, and Eickhoff (2021) found no evidence of ADHD-related alterations in brain functional connectivity. Studies of structural connectivity in white matter tracts have also provided inconsistent results. A meta-analysis of diffusion studies combining whole-brain voxel-and tract-based analyses reported lower fractional anisotropy (FA), a measure of white matter fiber organization, in two corpus callosal tracts as well the inferior frontooccipital fasciculus and left inferior longitudinal fasciculus – although the authors questioned the validity of the results as they mainly reflected studies that had not addressed head motion artifacts (Aoki, Cortese, & Castellanos, 2018).

New leads

Large-scale and reliable studies show substantially reduced ADHD-related structural alterations than previously reported. What was considered established ADHD brain science based on the metaanalysis of small scale, selective and under-powered studies has been challenged by findings from the Enhancing Neuro-Imaging Genetics through MetaAnalyses (ENIGMA) consortium studies in which sample aggregation yields analyses of individuallevel data in large data sets (~3,200 to ~4,200 participants). This has led to a recalibration of the scale of ADHD-related brain alterations with reliable but smaller effects found than previously reported (Cohen's d < 0.20). In childhood, ENIGMA has detected smaller total intracranial volume, total cortical surface area, and

volumes of subcortical nuclei, including amygdala and hippocampus, along with long implicated striatal regions (caudate, putamen, nucleus accumbens; Hoogman et al., 2017, 2019). No effects were seen in adult samples. Still smaller effects have been reported in the Adolescent Brain Cognitive Development study (ABCD; Casey et al., 2018) which recruited ~11,700 children at ages 9-to-10 years of age. A FreeSurfer analysis of brain structure, with careful control of movement artifacts, found no ADHD-related effects in cortical thickness or subcortical volumes (Bernanke et al., 2022). Estimated total intracranial volume and total cortical surface area were significantly smaller in children with ADHD versus healthy controls although the effect sizes were even smaller than in ENIGMA (d =0.08 for both). Small global differences were found in caudal ACC (d =0.12), middle temporal gyrus (d =0.07), postcentral gyrus (d- = 0.09), cuneus (d =0.08) and pericalcarine cortex (d =0.10). The authors noted that ADHD in the community ascertained ABCD sample is less severe than in studies that recruit clinical cases, which may account for the attenuation of effect sizes. Greater severity of motoric hyperactivity can also affect neuroimaging results, as excessive head motion during scans is the principal reason for loss of analyzable data. Overall, the ENIGMA and ABCD findings confirm the presence of structural differences in children with ADHD but highlight their subtlety.

Neurobiological heterogeneity may also contribute to the small effects observed – large studies combine groups of ADHD individuals who may have different neuro-structural profiles implicating different brain circuits and regions. Initial analyses using multivariate grouping statistics has been successful in identifying such sub-groups with ADHD-related effects greater in some of these than others (Li et al., 2021). In a similar vein, small ADHD-related differences were observed in analyses of three ABCD fMRI tasks, tapping working memory, inhibitory control, and reward

processing. During the working memory task, reduced activation in task-positive and reduced deactivation in task-negative (i.e., default mode) areas were correlated with CBCL Attention Problems scores (Owens et al., 2022). Those results were noted to be consistent with the aforementioned hypothesis implicating the interplay between the default mode and cognitive control networks (Sonuga-Barke & Castellanos, 2007).

Longitudinal fMRI studies reveal new insights into ADHD-related brain function. A pioneering longitudinal study of brain function with a substantial sample and improved MRI acquisition methods detected two types of trajectories in BOLD signal correlations (Vasa et al., 2020). Conservative trajectories, those that remained strong across the age range sampled, were characterized, by changes especially primary cortex, while disrupted trajectories involved associative networks and subcortical–cortical circuits that either strengthened or weakened with development. This suggests that complex developmental trajectories need to be considered in prospective longitudinal studies of ADHD brain function.

Dimensional perspectives may reveal unique insights. The ABCD rfMRI baseline data have also been examined dimensionally (Karcher, Michelini, Kotov, & Barch, 2021). Interestingly, both a general psychopathology factor and a neurodevelopmental factor, combining inattention, hyperactivity, impulsivity, clumsiness, and repetitive behaviors were found to be associated with reduced DMN connectivity (the latter having a stronger effect), with the neurodevelopmental factor also associated with stronger correlations between DMN and the cingulo-opercular (salience) network. Nevertheless, these and other brain-behavior relationships accounted for less than 1% of the variance.

Novel molecules are informing our understanding of heterogeneity across the broader ADHD phenotypes. Studies of the action of novel neuromoderators are providing new insights into the possible basis of heterogeneity in the broader ADHD phenotype. This may help with the identification of novel treatment targets for ADHD sub-groups. Recent attention has focused on orexins – arousalpromoting peptides, which arise in the hypothalamus and brainstem and project to the locus coeruleus, where they increase firing of noradrenergic neurons with knock-on effects on dopaminergic activity (Sakurai, Saito, & Yanagisawa, 2021). Orexins play a key role in modulating a range of ADHDimplicated processes; reward, attention, arousal, appetitive behavior, and sleep (Katzman & Katzman, 2022; Subramanian & Ravichandran, 2022; Villano et al., 2017). Medication-na€ıve children with ADHD have been found to have decreased serum orexin A levels (Baykal et al., 2019). Also, suvorexant – a dual orexin/hypocretin receptor antagonist – produced a decrease in cocaine-induced premature responding in an animal model of impulsivity (Gentile et al., 2018). Modafinil, a DAT blocker and partial orexin agonist, has shown positive effects in ADHD clinical trials, although there have been concerns about adverse side effects (Wang et al., 2017). Recent research has also focused on the serotonergic effects of viloxazine ER, a newly approved (in the US) nonstimulant (Yu, GarciaOlivares, Candler, Schwabe, & Maletic, 2020). While the currently accepted mechanism of action is attributed solely to NET blockade – viloxazine is a moderate inhibitor of NET and elicited moderate activity at noradrenergic and dopaminergic systems – it also acts on the serotonin system. In vitro binding studies with viloxazine demonstrated antagonist activity at 5-HT2B and agonistic activity at 5HT2C receptors. In vivo administration of viloxazine to rats yielded increased extracellular serotonin levels in the prefrontal cortex (PFC). It remains to be seen whether these insights can lead to new treatment approaches, which target selected difficulties in people with ADHD. For example, might subgroups of individuals (perhaps those with impulsive

aggression) respond preferentially to ADHD medications, which include prominent serotonergic effects? Might novel drugs targeting the orexin system be useful in treating individuals with ADHD and low motivation and/or under-aroused clinical presentations (e.g., sluggish cognitive tempo)?

Outstanding questions

How will smaller investigator-initiated neuroimaging studies contribute? Improvements in phenotypic dimensionalization and improved reliability of brain imaging methods will provide the basis for the next generation of smaller-scale individual investigator-initiated studies. These will complement

Big Data efforts, such as ENIGMA and ABCD, by examining causal interventions, such as treatment effects, while benchmarking to the datasets that will define the study of brain development and its behavioral and clinical manifestations over the next decade. They could also provide analysis of ADHD components and secondary features, in ways that the large consortia to date lack the data to do, and so set the stage of hypotheses for the next generation of large consortia efforts in a kind of feed-in, positive cycle.

Which dimensions will be the most powerful predictors of brain structure and function? Dimensional analyses outperform categorical perspectives; but which dimensions are most relevant? In the ABCD sample, Michelini and colleagues factor analyzed the CBCL and the adult version (Adult Self Report) and derived five dimensions for both sets of data (Michelini et al., 2019). Although the CBCL is proprietary, it is ubiquitous, with validated versions in more than 100 languages. While the essential validation will occur in prospective longitudinal efforts such as ABCD, quantifying the advantages of this approach could be straightforward in many existing datasets and in ENIGMA. As this dimensionalization putatively extends across the lifespan (Michelini et al., 2019), it may

inform the puzzling absence of significant brain findings in adult ADHD.

How can brain imaging be made more reliable? Advancing science depends on improving instrumentation. MRI technology is both astonishingly advanced in some ways, and, at the same time, rudimentary in others. The field has been sufficiently humbled by lack of replicability to coalesce on a range of best practices (Nichols et al., 2017), which include implementing proven methods to enhance reliability (e.g., ME-ICA; Raimondo et al., 2021) and using movies as stimuli for functional imaging (Vanderwal, Eilbott, & Castellanos, 2019).

Can drug discoveries enhance personalized care by targeting brain processes implicated in different sub-groups of people with ADHD? Increased awareness of clinical and neurobiological heterogeneity in ADHD has given rise to calls for a more a personalized approach to intervention. In this context, a nuanced understanding of neurochemistry and its clinical application could be highly relevant. Unfortunately, several novel drugs recently examined for use in ADHD either failed in Phase 3 or need additional study to establish their therapeutic benefit – including: vortioxetine (SNRI; 5-HT1A/1B partial agonist); metadoxine (ion pair salt of pyridoxine; 5-HT2B agonist/GABA modulator), dasotraline (DA + NE reuptake inhibitor), fasoracetam (metabotropic glutamate agonist); molindone (D2 and 5HT2B antagonist) (Nageye & Cortese, 2019; Pozzi et al., 2020). Previous research using nicotinic agonists (Potter, Schaubhut, & Shipman, 2014), H3 antagonists (Weisler, Pandina, Daly, Cooper, & Gassmann-Mayer, 2012), and ampakines (Danysz, 2002) – all known modulators of catecholamine neurotransmission – also failed to show efficacy. While there is no doubt a multiplicity of possible reasons for these failed trials, a key question yet to be adequately considered is whether medications, which indirectly impact catecholamine function, might be more suitable for a subpopulation of individuals with ADHD – in which case studying them

in the larger ADHD population might yield an overall inadequate response. It is hoped that future research will use a more targeted approach with refined ADHD phenotypes.

The future of the ADHD construct in the light of scientific progress – Some cross-cutting themes

The historical introduction of the ADHD diagnosis, like those relating to other psychiatric/neurodevelopmental conditions in DSM, provided a bridge between science and practice that, for the first time, allowed a truly evidence-based system of care (Coghill & Sonuga-Barke, 2012). It did this, most obviously, by providing clinicians and researchers with a systematic conceptual framework allowing the rigorous characterization and reliable measurement of the condition. Just as importantly, it provided a catalyst for decades of scientific progress by making explicit the transitional status of the ADHD concept as a working hypothesis open to updating in the light of new scientific discoveries during periodic review – most recently through the publication of DSM-5 (Posner et al., 2020). Essential to its scientific value are the stable set of assumptions about what disorder generally, and ADHD specifically, at its core, is – something that philosophers of science call a paradigm (Sonuga-Barke, 2020). The assumptions within a paradigm are essential for incremental progress during periods of normal science. At the same time, they provide a meta-theory of ADHD that constrains enquiry by defining the research questions considered relevant, the methods used to address those questions, and interpretations of findings made. Kuhn believed that these periods of normal science are punctuated by periods of radical change when it becomes clear that paradigmatic assumptions are no longer reconcilable with scientific 'reality'. The current review and accompanying perspectives highlight the way in which research data increasingly challenges some core assumptions of the current DSM paradigm. Here, a number of the most significant of these are reviewed.

ADHD – A category?

A core assumption in DSM is that ADHD is a category with nonarbitrary boundaries that distinguish cases from noncases. The most direct test of this assumption comes from large-scale, populationbased taxometric studies, which statistically test for discontinuities in underlying causes around diagnostic boundaries (Haslam, McGrath, Viechtbauer, & Kuppens, 2022). To date, evidence from these and other studies do not support the categorical assumption – rather, ADHD is best understood as an extreme expression of a continuous trait.

ADHD – A singular entity?

A second DSM assumption is that, despite its obvious surface level heterogeneity (i.e., symptom profiles, co-occurring conditions, and impairment), ADHD represents a causally distinctive condition at a deeper level, marked by a common etiology and pathophysiology. As extensively described here, this is not the case. On the one hand, cases that manifest clinically in a similar way (e.g., combined type) show great heterogeneity in genetic and environmental risk, underlying pathophysiology and associated neuropsychological deficits and differences. No particular factor or combination of factors represent a necessary and sufficient basis for the condition. Such heterogeneity almost certainly contributes to the very small ADHD-related effects reported in recent large-scale neuroimaging and genetic studies. At the same time, there also appears to be considerable genetic, environmental, and neuropsychological/biological overlap between ADHD and conditions that DSM conceptualizes as distinct from it. This encourages a fundamental remapping of ADHD symptoms to their underlying causes as proposed, for instance, within the RDoC initiative (Pacheco et al., 2022).

ADHD – A neurodevelopmental condition?

DSM also assumes that ADHD is a neurodevelopmental condition unfolding across development from its roots in early childhood. The evidence from longitudinal studies testing this assumption is somewhat

mixed. On the one hand, there appears strong continuity in childhood cases and little indication of permanent remission. On the other hand, some individuals are first identified with ADHD in adulthood with apparently unclear evidence of the condition in childhood. Many of these late-onset cases appear distinctive in terms of genetic risk, cognitive profile, environmental exposures, and cooccurring mental health problems. This has led some to suggest that, at least from a research perspective, late- and early-onset cases could be considered different conditions – although this point of view remains controversial. However, given the heterogeneity in ADHD mentioned above, it may be more accurate to consider late-onset ADHD as a non-neurodevelopmental presentation. In addressing this issue, it will be important to explore whether early- and late-onset cases require different clinical management approaches.

ADHD – A unisex condition?

ADHD was first characterized largely based on clinical observations made about male children.

However, like other neurodevelopmental conditions, it is conceptualized as a disorder of equivalent meaning and significance for males and females – despite substantial sex-related differences in presentation and prevalence. Most sections of this review have described important new leads and raised key questions for future research that highlight ways in which ADHD may be different for males and females – in terms of clinical manifestation, developmental pathways, the experience of stigma, as well causal factors. These questions in turn beg the broader question of whether ADHD needs to be reformulated to some degree to ensure that females with the condition receive the care that they require sufficiently early in their development.

ADHD – Neurodivergence not disorder?

Perhaps the most radical challenge to the ADHD paradigm comes not from the empirically-based arguments outlined above, but rather from a new socio-cultural rights-based concept that has emerged outside the clinical and scientific sphere – neurodiversity (Pellicano & den Houting, 2022). This both casts ADHD as part of a wider spectrum of naturally occurring variation and challenges the DSM assumption that ADHD is a disorder caused by dysfunction within the individual – replacing it with the assumption of ADHD as neuro-divergence (Sonuga-Barke & Thapar, 2021). It emphasizes acceptance of, and accommodation to, ADHD by family, peers, schools/employers, and the wider community and looks to build the best ways to create environments that promote personal agency and build resilience to foster developmental growth. Impairment shifts from being something intrinsic to ADHD per se, to being something that is socially constructed, situated, and context-contingent. Crucially it privileges the personal perspectives of the individual with ADHD as being as important as those of clinicians or scientists and, therefore, promotes participatory approaches to research. The implications of this approach for science are still being worked through, but they have the potential to reframe its purpose in fundamental ways (SonugaBarke & Thapar, 2021). The neurodivergence perspective highlights how vital is that people with ADHD are involved in shaping research priorities in a way that ensures that their expertise by experience can inform the research questions asked, the methods employed and the interpretations of results made.

Concluding remarks

As we have illustrated here, scientific progress is challenging some of the core assumptions of the current DSM model of ADHD and the way it is conceptualized with regard to related disorders.

Given this, it is worth reflecting on whether the time is ripe for a paradigm shift in the field to ensure that diagnostic constructs accurately reflect the underlying multiform and dimensional structure of ADHDrelated psychopathology, acknowledging also its situated nature and the role of normative environmental constraints in determining associated impairment. However, in

considering this, caution is required. First, because we do not want to risk losing the advances that the current model has afforded, unnecessarily. Second, far more research is needed to identify the core underlying crosscutting dimensions that could replace current categories. Third, because even after we have identified these, they need to be operationalized as clinically workable constructs in ways that avoid abruptly breaking the bridge of meaning that links research to clinical practice.

Acknowledgements

Correspondence

Key points
Remarkable scientific progress has been made in understanding ADHD – with many discoveries challenging the assumptions on which current models rest.
 Recent science demonstrates that ADHD is the extreme expression of complex and dimensional traits that are mostly persistent with diverse developmental trajectories.
 It commonly overlaps with other mental health and neuro-development conditions, phenotypically and in terms of risk processes.

Similar to many other neuro-developmental and psychiatric conditions, its causes are complex and heterogeneous with an accumulation of multiple and interacting contributing genetic and environmental risks associated with subtle alterations in brain structure and function.

Key foci for the future relate to clinical and causal heterogeneity and overlap, risk prediction, gene– environment interplay, the female presentation, the social environment's role in impairment and stigma, resilience and personal growth.

Going forward, participatory research approaches involving people with ADHD will be vital.

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