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Development of ADHD: Etiology, Heterogeneity, and Early Life Course

Joel T. Nigg,[1] Margaret H. Sibley,[2] Anita Thapar,[3] and Sarah L. Karalunas[1]

[1]Department of Psychiatry, Oregon Health & Science University, Portland, Oregon 97239, USA; email: niggj@ohsu.edu, karaluna@ohsu.edu

[2]Center for Child Health, Behavior, and Development, University of Washington and Seattle Children's Research Institute, Seattle, Washington 98101, USA; email: Margaret.Sibley@seattlechildrens.org

[3]Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, Wales CF10 3AT, United Kingdom; email: thapar@cardiff.ac.uk

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) represents a powerful entry point for developmental approaches to psychopathology due to its substantial role in early emergence of major life problems. One key issue concerns the role of early environmental risks in etiology and maintenance in the context of genetic liability. Here, psychosocial aspects of development need more attention. A second key issue is that phenotypic heterogeneity requires better resolution if actionable causal mechanisms are to be effectively identified. Here, the interplay of cognition and emotion in the context of a temperament lens is one helpful way forward. A third key issue is the poorly understood yet somewhat striking bifurcation of developmental course in adolescence, when a subgroup seems to have largely benign outcomes, while a larger group continues on a problematic path. A final integrative question concerns the most effective conceptualization of the disorder in relation to broader dysregulation. Key scientific priorities are noted.

Contents

THE UNDERAPPRECIATED PROBLEM SPACE AROUND ADHD

Clinically significant mental health problems, encompassing psychiatric disorders (e.g., depression, anxiety, and schizophrenia), neurodevelopmental disorders [e.g., autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), and idiopathic intellectual disability], and substance use disorders, collectively constitute the single greatest source of health burden in the world when defined as years of life lost to disability, accounting for nearly a quarter of the total burden (Whiteford et al. 2013). Economic costs, though too-little remarked, are staggering (Bloom et al. 2011). Problems with inattention, disorganization, impulsivity, and hyperactivity, when severe, are usefully organized clinically as ADHD. ADHD at first can seem a minor player in the saga of mental health–related impairments alongside such crippling conditions as major depression, severe alcoholism, bipolar disorder, and schizophrenia. Many children under the ADHD umbrella attain a benign outcome with manageable remaining difficulties. When stimulant medications work, as they do in a majority of cases, the short-term benefit can be striking.

However, a closer look reveals ADHD to be a vastly underappreciated feature in the matrix of mental health–related burden and cost for three reasons. First, it is among the earliest emerging of behavioral conditions, with clear onset in the preschool period and peak age of identification in the early school years—earlier than most other serious psychopathology to which it can lead

(Kessler et al. 2014). Second, it is common, with best estimates of worldwide prevalence of 3% to 4%, representing millions of children (Erskine et al. 2013).[1] Third, despite the availability of ever more sophisticated treatments, long-term outcomes are largely unchanged and deeply concerning (Erskine et al. 2016, Hinshaw & Arnold 2015, Swanson et al. 2017). Treatment adherence and continuance is poor (Barner et al. 2011, Taylor 2019).

ADHD confers a 50% to 300% increased risk for serious secondary mental health problems including substance use disorders, depression, psychosis, and anxiety disorders (Groenman et al. 2017, Kessler et al. 2006, Lee et al. 2011). These problems appear causally explained by earlier ADHD (Riglin et al. 2020, Treur et al. 2019). Especially when complicated by secondary depression or substance use, ADHD magnifies the chances of costly to disastrous life outcomes: school and occupational failure, poor health, homelessness, unemployment, injuries, and suicide (Forte et al. 2020). Whereas mental disorders are among the most substantial direct or indirect drivers of premature death worldwide (Walker et al. 2015), ADHD is right in the mix (Sun et al. 2019).

In all, ADHD is of far more serious public health importance than often assumed (Fayyad et al. 2017; Kessler et al. 2006, 2014). It represents a critical early-risk phenotype for future severe outcome but with the possibility of resilience or recovery. Understanding it can transform a developmental understanding of psychopathology.

PLAN FOR THIS REVIEW

The review is necessarily selective. We bypass important but recently reviewed bodies of literature on ADHD's history, sex differences (Cortese & Coghill 2018, Hinshaw 2018), neuroimaging (Albajara Sáenz et al. 2019, Rubia 2018), genetics (Faraone & Larsson 2019, Thapar 2018), and peer and family relations (Hinshaw 2018) and ignore ADHD and aging, about which little is known. Instead, we update and address current issues concerning (*a*) risk factors, etiology, and role of modifiable environments and (*b*) heterogeneity and phenotype characterization, first in early life and childhood and then in the very different developmental context of adolescence and the early adult transition. Our lens is the intersection of cognitive and emotional development. We conclude with a discussion of key priorities for the field and how to conceptualize ADHD. We begin with a synopsis of clinical features.

CLINICAL FEATURES OF ADHD

ADHD is defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; APA 2013) by extreme problems in underspecified behavioral domains of inattention (better referred to as inattention-disorganization due to the association with executive functioning and arousal) and/or hyperactivity/impulsivity (symptoms relate to reward response and social problems). ADHD symptoms are a dimensional trait in the population (Willcutt et al. 2012). While the DSM-5 criteria do face some construct validity issues, a well-established factor-analytic literature on the universe of child problems, now extended to adults as well, has yielded a recognizable ADHD-like dimension for children and adults (Achenbach 2020, Achenbach & Edelbrock 1978). The ADHD syndrome is thus analogous to hypertension or obesity: defined by applying to a trait a clinical cut point with actuarial but not ontological meaning.

[1] Although population surveys in the United States identify more than 10% of youth as having ADHD, most reviews cite 5% to 7% as the prevalence based on formal studies (Polanczyk et al. 2007). However, use of Bayesian methods to correct for unmeasured regions yields a true prevalence estimate in the 2% to 4% range (Erskine et al. 2013).

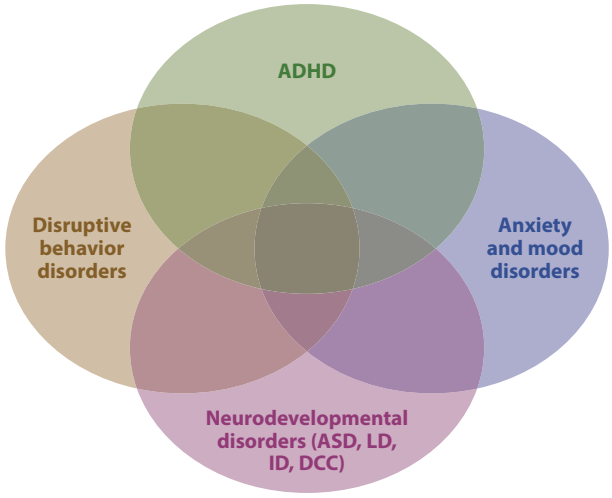

Figure 1

Overlapping problems, comorbidity, and correlations in the psychopathology and neurodevelopmental domains in childhood (*not to scale*). Disruptive behavior problems include oppositional defiant behavior, aggression, tantrums, irritability, conduct problems, and antisocial behavior. Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; DCC, developmental coordination disorder; ID, intellectual disability; LD, learning disorder.

However, this initial summary disregards the likely etiological and developmental subgroups within the syndrome profile. Heterogeneity is one overarching concern; phenotype boundaries are another concern. Besides the core symptoms, ADHD also involves problems in cognition, emotion regulation, and social skills. Thus, a full accounting of the clinical picture in a developmental context would require discussion of most aspects of the broader construct of self-regulation (Nigg 2017).

ADHD is believed to have roots in early life, perhaps during gestation (Hall et al. 2020). It cosegregates in families, shares polygenic genetic overlap, and co-occurs clinically beyond chance with autism spectrum disorder (Ghirardi et al. 2018, M. Miller et al. 2019, Musser et al. 2014), intellectual disability (Faraone et al. 2017), and communication and learning disorders (Thapar et al. 2017). Although some of these points also hold for ADHD's relation with disruptive behavioral disorders, the balance favored reclassifying ADHD from a behavioral to a neurodevelopmental disorder in DSM-5 (Frick & Nigg 2012, Thapar et al. 2017). **Figure 1** depicts ADHD's clinical neighborhood; **Figure 2** depicts its developmental position as a liability for other serious behavioral disorders.

RISK FACTORS AND ETIOLOGY FOR ADHD

Beyond dispute for ADHD are substantial heritability (polygenic liability) and several environmental risk factors. Less clear are the degrees to which (*a*) ADHD is influenced by very early life programming of development, (*b*) genotype by environment interactions (G×E) account for heritability,[2] and (*c*) genotype-environment correlations account for other risk factors. As a result, specific causal mechanisms remain poorly understood.

[2]Whereas all development requires biological gene-environment coaction, the specific kind of coaction seen in statistical moderation studies is usually called genotype by environment interaction.

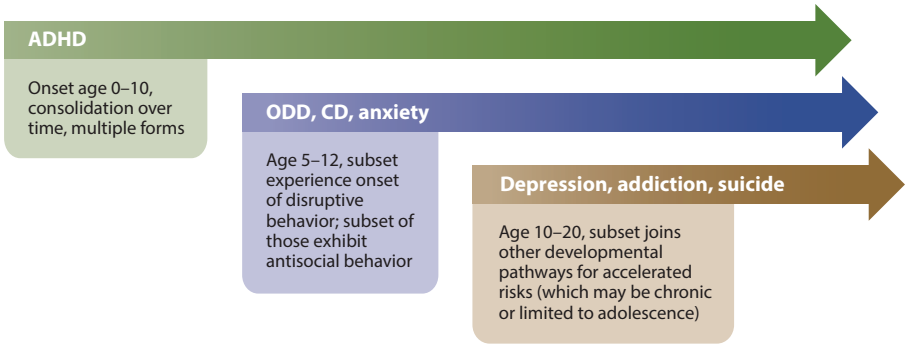

Figure 2

Expanding risk in ADHD development. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder.

Genetic Liability

ADHD's heritability of liability in twin studies is 0.7 to 0.8 (Faraone & Larsson 2019), which is higher than for personality, temperament, or depression and on par with schizophrenia, bipolar disorder, and autism spectrum disorder. Molecular genetic discoveries are emerging rapidly (Thapar 2018), although one primary conclusion is to underscore the genetic relatedness among ADHD and other later-emerging disorders (indirectly supporting the idea of ADHD as part of a liability pathway). Hypothesis-free whole-genome association studies have identified several genetic loci (chromosomal positions, not genes per se) for ADHD (Demontis et al. 2019); their number is sure to increase. However, effect sizes of individual loci are too small to be clinically relevant, nor do these probe findings yet tell us which gene(s) are causal. Other molecular studies suggest the involvement of rare genetic mutations (chromosomal deletions or mutations) with potentially larger effects (Satterstrom et al. 2019), but some of these involve multiple genes; in any event, these mutations pertain to only a small minority of ADHD cases (Thapar 2018).

Early Risk Factors

Several pre- and perinatal environmental risk factors are well established for ADHD, although none are unique to ADHD. Among the candidates deserving further causal and mechanistic investigation are prenatal maternal distress (Manzari et al. 2019), preterm birth and/or low birth weight (Momany et al. 2018, Serati et al. 2017), social disadvantage and adversity (Bjorkenstam et al. 2018), and average-level lead exposure (Goodlad et al. 2013, Nigg 2019, Nigg et al. 2016) as well as exposure to other environmental toxicants (Myhre et al. 2018, Rivollier et al. 2019). To date, these findings mostly rely on observational designs that might be explainable by unmeasured confounders including genetic liability (genotype-environment correlation) (Thapar & Rutter 2019).

Clarification of what effects are causal requires additional design considerations. Experimental designs are one option when ethically available, for example, to evaluate dietary effects on ADHD (Ramakrishnan et al. 2016). Alternatively, causal evidence can be sought in sibling comparisons, Mendelian randomization,[3] and other natural experiments. Initial studies, although preliminary, have called into question a causal role in ADHD for maternal smoking (D'Onofrio et al. 2013)

[3] In a Mendelian randomization study, researchers must assume that a functional mutation is randomly distributed, creating a presumed natural experiment in which biological handling of an exposure is manipulated

and prepregnancy maternal body mass index (BMI) (Musser et al. 2017) while supporting a causal role in ADHD for lead exposure (Nigg et al. 2016) and social disadvantage (Larsson et al. 2014).

Fetal Origins as an Important Hypothesis

Following on the interest in early exposures, researchers proposed prenatal origins and programming of risk for ADHD over a decade ago (Swanson & Wadhwa 2008); these now stand as major directions in developmental psychopathology generally (Monk et al. 2019). Whereas this effort faces unresolved interpretive challenges (Monk et al. 2019), the field has identified candidate mechanisms of interest for multiple conditions involving alterations in immunological (particularly cytokine), hypothalamic-pituitary-adrenal, and (more speculatively) microbiome functioning. All are undergoing initial investigation in ADHD. Particularly intriguing is the preliminary evidence that prenatal maternal inflammation may be a common pathway for early risk influences on offspring ADHD (Dunn et al. 2019; Gustafsson et al. 2019, 2020). However, subtle perinatal ischemia is another potential common pathway in some cases, belying the idea of a single heritable trait as the essence of ADHD (Whitaker et al. 2011).

Genotype-Environment Interplay as a Crucial Consideration

Most of the preceding exposures are rather common in the population and thus most likely shared between twins in a family—yet only a subset of exposed children develop ADHD. Whereas twin studies indicate that direct effects of shared environments are nil in ADHD, if shared environments interact with genetic liability, then twin heritability estimates are inflated. Thus, one hypothesis is that key exposures operate in a context of interaction with genetic liability. It is of particular interest for risk stratification and prevention. Most G×E studies of ADHD have relied on candidate genes, an approach that has been questioned. Thus, a key research opportunity is to discover the extent to which modifiable early environments can alter the trajectory of ADHD—but with careful consideration of G×E and genotype-environment correlation (Leppert et al. 2019).

Early Socialization: A Major Gap

By preschool, parenting style does not seem to cause ADHD; rather, children's difficult behaviors elicit negative interchanges from parents (Modesto-Lowe et al. 2008). In preschool, parenting intervention is effective mainly at managing disruptive, noncompliant, and aggressive behavior but not in reducing symptoms of ADHD (Daley et al. 2018). Yet from there, parenting behavior becomes a modifiable factor that can shape trajectory and influence recovery. The causality of the parenting role on trajectory is supported in both genetically informative (Harold et al. 2013) and randomized trial designs (Hinshaw & Arnold 2015).

The literature on ADHD and parenting, however, is largely confined to children aged 3 to 4 years or older. Parent-child processes preceding clinical ADHD in the first 12 to 24 months of life are hardly studied despite established literature on the role of early parenting in the consolidation of self-regulation (Morawska et al. 2019). Could ADHD be prevented in susceptible children by suitable parenting guidance in the first 24 months of life? The research gap is glaring, but ADHD is not definable in infancy. To know which children are relevant to study, relevant precursive phenotypes are needed for stratified designs. This last point intersects with a related problem

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by nature. While this assumption may be true, other aspects of randomization are not necessarily met, and pleiotropy (multiple effects of a given gene) is difficult to rule out. These are among the potential confounds.

in the childhood period: the need to refine the ADHD phenotype in relation to the overarching problem of heterogeneity. We consider these two issues together.

HETEROGENEITY AND PHENOTYPE REFINEMENT: EARLY LIFE AND CHILDHOOD

ADHD is heterogeneous both etiologically and phenotypically (Luo et al. 2019, Nigg et al. 2020a, Swanson et al. 2007). One issue is that the symptom-checklist method of diagnosis in DSM-5 and its precursors structurally ensures some degree of clinical heterogeneity in most disorders. The DSM-5 acknowledges this for ADHD by specifying three presentations: mostly inattentive, mostly hyperactive/impulsive, and combined. The challenge, however, extends well beyond symptom checklist artifact. Polygenic theory assures genetic heterogeneity for complex traits and disorders like ADHD (Wray et al. 2018). As noted, the relevant exposome for ADHD is likewise multifactorial and heterogeneous across individuals. The resultant obstacles to identifying generalizable mechanisms and etiology are substantial. For example, only a small minority of individuals with ADHD have brain structure changes similar to the group average (Wolfers et al. 2020).

Clarifying phenotypic heterogeneity and refining phenotypes is essential both to unravel etiology and mechanism and to guide new intervention discovery. Such phenotype refinement requires going beyond the symptom list and comorbid disorders to consider other domains (Nigg et al. 2020a). To illustrate, we consider ADHD in light of neuropsychology (especially executive functioning) and of emotion regulation via a temperament lens.

Neuropsychology

ADHD's neuropsychological correlates are extensive and, despite a complex literature and overall effect sizes too modest to be diagnostically informative, provide rich data to inform mechanism and heterogeneity. For example, ADHD samples show greater predominance of slow-wave activity in the electroencephalogram (EEG) power spectrum (Kiiski et al. 2020), smaller total brain volume (Klein et al. 2019, Mooney et al. 2020), slower rate of maturation of the cortical mantle (Shaw et al. 2007), and alterations in neural activity at rest and during challenge (Albajara Sáenz et al. 2019, Nigg et al. 2020a, Rubia 2018). Functionally, at the group level, ADHD is also associated with weaker performance in tests of executive functioning such as working memory, response inhibition, and planning and in tests of signal detection presumed to measure arousal or vigilance (Pievsky & McGrath 2018) as well as in reward motivation and response. Whether state regulation, arousal, or motivation problems degrade executive functioning, or vice versa, or represent alternative phenotypes remains an important debate (Karalunas & Huang-Pollock 2013, Lenartowicz et al. 2014, Metin et al. 2012, Unsworth & Robison 2017).

As a result, heterogeneity of these mechanisms has long been hypothesized to help account for variation in the ADHD population (Nigg et al. 2005, Sonuga-Barke 2005). A small number of studies have begun to model such heterogeneity in ADHD using statistical and mathematical clustering approaches. Those few studies, using various measures as features, do tend to find interesting subprofiles within the ADHD population that can be interpreted as variation in executive functioning (e.g., working memory) versus arousal (e.g., reaction time or signal detection) (Fair et al. 2012, Roberts et al. 2017, Vaidya et al. 2020). However, clinical value and long-term predictive validity are still emerging.

Emotion and Temperament

Many children with ADHD also have marked difficulties with emotional control (Shaw et al. 2014), particularly anger dysregulation (called irritability in the literature and henceforth). In part

because of its emotional features and in part because of features related to executive functioning, ADHD shares behavioral space with the development of temperament in reactivity-regulation models. For instance, rating-scale items for effortful control include many ADHD-symptom items; unsurprisingly, effortful control and ADHD share substantial genetic influence even when overlapping items are considered (Goldsmith et al. 2007). By adulthood, ADHD is also correlated with ratings of personality traits (particularly low conscientiousness or constraint and high negative emotion or neuroticism). Yet ADHD is not reducible to these constructs or their combinations; correlations simply are not large enough (Gagne & Goldsmith 2011, Martel et al. 2009, Nigg et al. 2002). The level of display of these traits therefore may inform liability (Goldsmith et al. 2004), capture early stages of ADHD emergence, or help clarify phenotypic heterogeneity.

Beginning with heterogeneity, Nigg et al. (2004) sketched a temperament-based, multiple-pathway perspective. They suggested that ADHD might emerge for some children primarily via negative emotion and display a phenotype characterized by impulsivity, anger reactivity, and perhaps reactive aggression. For other children, ADHD would emerge via excess approach (also termed exuberance or positive affectivity), likely due to its association with excessive risk-taking and impulsivity. Finally, cognitive control could be weakened later in preschool development for other reasons, with a phenotypic expression of inattention and executive dysfunction but not salient dysregulated emotion. Identifying such profiles seems plausible in light of clustering studies of unselected samples of young children that identify a subgroup with low regulation and high negative reactivity (Planalp & Goldsmith 2019, Scott et al. 2016).

A series of statistical clustering studies conducted on two ADHD case-control cohorts have consistently identified at least two distinct temperament profiles within the ADHD samples. These two profiles are respectively characterized by (*a*) high negative affect, irritability, or neuroticism and (*b*) normative temperament ratings (Karalunas et al. 2019, Martel et al. 2010, Smith & Martel 2019). Less consistently these studies identify a third profile with very high surgency, high activity level, and moderate anger proneness. Clinical relevance is promising. In one initial cohort, the emotionally dysregulated ADHD group of 7- to 12-year-olds was up to four times more likely to experience clinical deterioration 1 to 2 years later than the typical-temperament ADHD group. That result held even after accounting for ADHD symptom severity, comorbidity, or impairment; in fact, identification of the emotionally dysregulated group outperformed those other measures at identifying risk for clinical deterioration (Karalunas et al. 2014, 2019; Martel 2016; Smith & Martel 2019).

The subgroup of ADHD at highest risk has very high negative affect, in particular high irritability (here defined as high anger and poor recovery from tantrums). Its identification converges with growing evidence from other lines of work on the importance of irritability and emotional lability more generally in ADHD and other childhood disorders (Leibenluft et al. 2006, Stringaris 2011, Wakschlag et al. 2018).

With the profile characterized by high surgency appearing somewhat less stable over time yet tending to remain either positively or negatively dysregulated year to year, the most parsimonious first step toward a refined heterogeneity phenotype is distinguishing between emotionally dysregulated and emotionally typical ADHD. This simpler two-group distinction was more developmentally stable from middle to late childhood (Karalunas & Nigg 2020, Nigg et al. 2020a), fit with correlations to polygenic liability for ADHD (Nigg et al. 2020b), and mapped to EEG profiles (Alperin et al. 2019) better than a finer-grained valence distinction.

Dynamic Development in Early Life

The dynamic developmental progression of traits from infant to toddler to child to adolescent to adult (Gaertner et al. 2008, Kim & Kochanska 2019, Nozadi et al. 2018, Rothbart 2011) can

also be fruitful for understanding ADHD etiology. In early life, one proposal is that temperament develops sequentially in a cascade process (Rothbart 2011). Such sequential emergence may take a form that then may moderate or mediate emergence of ADHD (Auerbach et al. 2004, Rabinovitz et al. 2016, Sonuga-Barke et al. 2010, Sullivan et al. 2015).

A fundamental hypothesis (seen in these papers) is that extreme negative emotional reactivity in early life disrupts the consolidation of effortful or top-down control (Gagne & Goldsmith 2011), which in turn disrupts the consolidation of self-regulation and the maturation of executive functioning. However, a more accurate model for ADHD may be that extreme reactivity in positive or negative valence may set the stage for ADHD, as proposed by Nigg et al. (2004). With regard to negativity, infant (N.V. Miller et al. 2019a) and toddler (Goldsmith et al. 2004, Rabinovitz et al. 2016) anger reactivity predicted ADHD symptoms in middle childhood, mediated in one study by disrupted inhibitory control at age 5 years (N.V. Miller et al. 2019b). Yet on the positive reactivity side, infant positive reactivity or high approach (along with activity level) is a consistent predictor of childhood ADHD symptoms (Goldsmith et al. 2004, Jonas & Kochanska 2018, N.V. Miller et al. 2019a).

These results are broadly supportive of the general model being developed here in that future ADHD is related to early life extreme emotional reactivity (positive or negative) and breakdowns in cognitive control. As in the temperament profiles we described in the preceding section, in these infant prospective studies ADHD is associated with either infant/toddler negative affect or anger or infant/toddler positive approach or high activity level (sometimes also with anger reactivity).

Importantly, these effects when examined appear to also be dependent on early caregiving quality, underscoring our earlier concern with insufficient study of that domain in ADHD prediction. Developmental studies document the dynamic developmental relationships among emotional reactivity, consolidation of cognitive control, emergence of executive functioning, and subsequent adjustment; all are heavily contextualized by family characteristics (Clark et al. 2016, Gaertner et al. 2008, Kim & Kochanska 2012, N.V. Miller et al. 2019b, Planalp & Goldsmith 2019). At the same time, the effects of early temperament on childhood ADHD symptoms are also moderated by caregiving quality (N.V. Miller et al. 2019a).

After toddlerhood, the picture appears to slowly differentiate. By 36 months of age, the best predictor of future ADHD in the temperament realm is likely to be weakened effortful control rather than extreme reactivity (Einziger et al. 2018, Willoughby et al. 2017). Later still, in childhood and adolescence, more differentiation occurs. Concurrent relationships between dysregulated negative affect and weak executive functioning appear unreliable in children with ADHD in that period (Banaschewski et al. 2012, Sjöwall et al. 2013), perhaps due to the heterogeneity of profiles outlined in the preceding section.

Figure 3 illustrates a possible developmental sequence broadly consistent with the literature we reviewed so far. Incentive reactivity emerges in infancy prior to executive attention and effortful control, which then in turn play important regulatory roles; meanwhile, attentional orienting serves a regulatory function in infancy (Rothbart et al. 2011). Early extreme reactivity—either negative affect/irritability or, in the alternative path shown, positive approach reactivity—sets the stage for disruption of top-down control and subsequent weakened executive functioning. A recursive process then may canalize to instantiate a stable ADHD picture.

Solidification and refinement of this picture and integration with the proposed temperament profiles and cognitive profiles noted would provide an integrated account from early life. It could then be extended to integrate with **Figure 2**. The combination would suggest improved phenotype and heterogeneity description within ADHD. In turn, this would help guide revised models of early and perhaps subsequent intervention for at-risk youngsters.

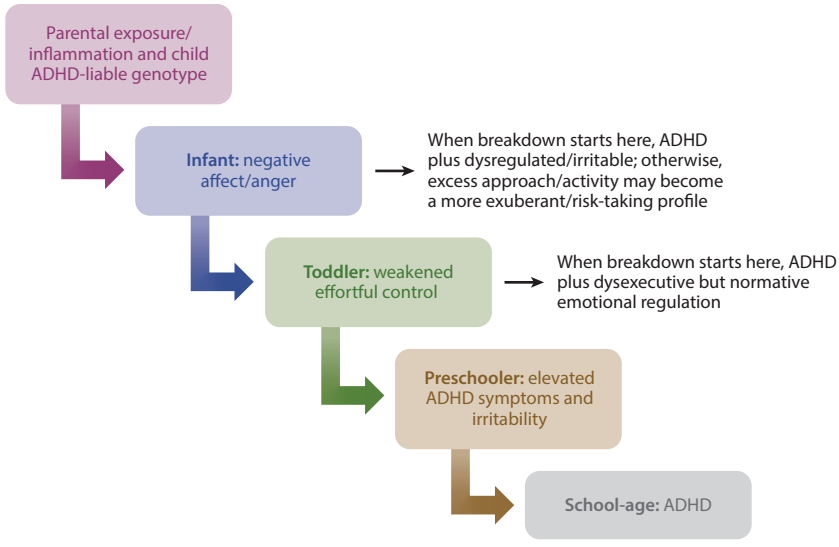

Figure 3

A hypothesized cascade of early temperament to attention-deficit/hyperactivity disorder (ADHD). Caregiver and family process are moderators (*not shown*). Nigg et al. (2004) proposed similar staged perturbations, leading to subsequent different temperament profiles within ADHD, perhaps emanating from different causal inputs.

HETEROGENEITY AND PHENOTYPE REFINEMENT: ADOLESCENCE TO YOUNG ADULTHOOD

Although our themes of emotion-cognition and relevance of context persist, we deliberately separate discussion of the adolescent and young adult periods from early life and childhood. Whereas the expression of ADHD changes somewhat qualitatively, ADHD-related trajectories also diverge more noticeably during this period. This poorly understood heterogeneity of clinical course remains the central scientific problem. We noted in the first section of this article that a subset of youth with ADHD appear to achieve benign outcomes, though sometimes after great struggle (Hechtman 1999),[4] while many face dire circumstances. Some aspects are known. Variation in outcome is partly due to normative reduction of hyperactivity in mildly affected cases (Hart et al. 1995). Outcomes are better for those with low aggression, above-average intellectual development, and reduced genetic risk. However, these associations remain too small to provide a satisfying or complete account. What else is pertinent?

Cognition and Emotion as Intrinsic Mechanisms

The emotion-cognition interplay or self-regulation theme remains a key dynamic. It evolves, however, in a very different neural and psychological developmental context in adolescence, where dynamic, asynchronous neural development influences the relative capacity for emotion regulation in the face of salient social-emotional stimuli (e.g., smartphones, peer challenges, alcohol,

[4]Their numbers are probably fewer than early studies reported. When developmental-norm-based criteria and variations in assessment methodology are taken into account, 50% to 70% of teens with childhood ADHD continue to meet criteria for ADHD in adulthood, and one-third have very severe negative outcomes (Sibley et al. 2012, 2016).

and drugs). These neural maturation processes include hierarchical development from childhood through adolescence: subcortical-to-cortical circuitry, then cortical-to-subcortical circuitry, and finally cortical-cortical circuitry (Casey et al. 2019). This layered, dynamic process may be delayed or disrupted in ADHD (Shaw et al. 2007). Likewise, the integrated consolidation of executive functioning and emotional reactivity may be key to ADHD's variable course during this period as well.

How cognitive development relates to changes in symptom expression with maturation has been a longstanding concern in ADHD. Weak executive functioning may be a liability trait for ADHD (Vaughn et al. 2011). At the same time, catching up in these functions seems to be associated with improvement of ADHD symptoms in this period (Murray et al. 2017). Extending the early life model outlined in the prior section, one hypothesis is that liability rests on excessive reactive processes in early life (e.g., emotional reactivity), but that sufficiently strong and timely consolidation of executive functioning (and the corresponding neural maturation), for some individuals, enables stable adjustment during and after adolescence (Halperin & Schulz 2006). Evaluating this, Karalunas et al. (2017) prospectively mapped trajectories of working memory and reward responding in a longitudinal study of 437 children with well-characterized ADHD receiving detailed annual assessments spanning 7 to 13 years of age. A child's trajectory of working memory development predicted degree of ADHD symptom change over time and persistence or decline in symptoms. That result was consistent with the Halperin & Schulz (2006) proposal.

Psychosocial Context

Psychosocial context remains underemphasized yet critical in this period. Its specifics, however, are also dramatically changed by late adolescence. During adolescence, academic, social, and environmental demands increase dramatically in practically all cultures. Worldwide, special pressures on adolescents range from moderate to extreme, often introducing multiple risks. Meanwhile, adolescence in many nations is extended by earlier puberty or extended time before acquiring adult responsibilities (Dahl et al. 2018, Worthman & Trang 2018). For adolescents with ADHD, longstanding difficulties with impulsivity, executive functioning, and emotion dysregulation can create a kind of double disorder when paired with typical challenges of adolescent development (Sibley et al. 2019), fueling secondary poor outcomes. The adolescent academic, family, and social environments seem to require precisely the self-regulatory skills in which adolescents with ADHD characteristically fall short.

Contextual moderators now appear as the elephant in the room. Just like in childhood, severity of adolescent ADHD is modulated by environmental demands, stressors and allostatic load, comorbid symptoms, compensatory skills, lifestyle behaviors, social supports and peer relations, and family chaos. Such contextual fluctuations may lead some individuals with ADHD to slip above and below the diagnostic threshold, temporarily or ongoing, even as impairing problems in fact persist—while pushing others onto a negative and troubled path (Roy et al. 2016). Yet specific mapping of these influences and identification of nodes for intervention has lagged other areas of research, mandating further examination.

Late Onset

Because the transition to and through adolescence is associated with new challenges that can exacerbate ADHD severity, it is no surprise that this period is associated with temporary ADHD-symptom spikes, even among youth without ADHD (Langberg et al. 2008). It also has been long known that a very small number of ADHD cases may have their onset in adolescence (Biederman et al. 1993). However, recent studies have provocatively suggested the appearance of

many spontaneous late-onset ADHD cases that first emerge in adolescence or young adulthood and persist (Agnew-Blais et al. 2016, Caye et al. 2016, Moffitt et al. 2015).

What is going on? It appears that many apparent late-onset cases had significant subclinical problems earlier in life, suggesting greater continuity than initially implied (Faraone & Biederman 2016), or had strong language, executive functioning, and intellectual development that helped delay symptom emergence (Cooper et al. 2018). Subsequent granular review of individual late-onset cases in fresh samples of participants tends to confirm and expand this picture (Sibley et al. 2018, 2020). These studies suggest that apparent late-onset cases of ADHD are largely accounted for by (*a*) subthreshold psychiatric or behavioral problems that take the form of ADHD in adolescence; (*b*) subthreshold ADHD liability sustained at that level in childhood due to strong intellectual or language development, which then emerges into the clinical range when demands increase and supports are withdrawn in adolescence; (*c*) ADHD symptoms that emerge in adolescence for only a limited time and then seem to resolve (Langberg et al. 2008); or (*d*) trauma or severe adversity that manifests as late-emerging, ADHD-like features. Clinical recognition of these cases and their particular needs should be enhanced by this aggregate recent literature.

Early Adulthood Transition and Niche Specialization

The person-context interplay remains a critical cutting-edge focus in adolescence just as in early life—only now the young adult has more say on choosing that context. Thus, in addition to the painful outcomes experienced by many, the transition into early adulthood provides new opportunities for youth with ADHD.

A major opportunity in this period is that youth with ADHD are now able to begin to select their own environments. They are able to niche-pick to maximize their own success. Niche specialization theory (Montiglio et al. 2013) purports that personality and other traits influence individual selection of social-ecological niches. In the human context, the familiar idea of person-environment fit is congruent here. Seen as an individual personality feature, niche specialists are thought to have relatively low trait flexibility, interfering with their capacity to adapt behavior to a contextual norm.

Low trait flexibility in the child development field is often defined as ego resiliency (not to be confused with psychological resilience, i.e., overcoming of adversity). Ego resiliency refers to the ability to adapt one's levels of self-control to the situation. It thus is involved in and evolves from self-regulation (Block & Block 1980, Eisenberg et al. 2003). Consistent with niche theory, low ego resiliency is associated with difficulty in the adolescent-to-young-adult transition (Alessandri et al. 2016). ADHD is also associated with low ego resiliency (Martel & Nigg 2006). This link to developmental literature adds a further perspective to difficulties in forced generalist niches (e.g., structured schools and sedentary jobs). Yet in addition to autonomous niche selection, adolescents and young adults with ADHD also benefit from environmental modifications made by others. Ego-resiliency (and consequently self-regulation and executive functioning) is strengthened by family and social supports in early life as well as in the adolescent-to-young-adult transition (Alessandri et al. 2016).

While these principles provide a general framework, not enough is known about specific ways for affected individuals or their supporters or clinicians to facilitate successful management or resolution of ADHD symptoms in young adulthood.

FUTURE DIRECTIONS AND SCIENTIFIC PRIORITIES

Several of the questions about ADHD are longstanding, but they have taken on a new twist with recently emerging data. In this section, we first recap key themes and then consider scientific priorities before offering conclusions.

Crosscutting Themes

Across the preceding sections, two themes emerge as important redirections of the field's foci: renewed examination of environmental exposures with a genetic and causally informed lens and more aggressive progress on mapping phenotypic heterogeneity for different utilities.

Heterogeneity. An overarching challenge for the field is the need for ever-improving and usable accounts of heterogeneity in the population. Phenotype refinement (for scientific discovery if not for formal diagnostics) is a critical element. Effective stratification by temperament profile, as exemplified in the section titled Heterogeneity and Phenotype Refinement: Early Life and Childhood, may provide one path forward for better clinical prediction as well as etiological and mechanistic discovery. Heterogeneity has two related facets that, if well addressed, will move the field to the next level: How early can ADHD development be detected (and by what precursive phenotypic or mechanistic features), and how can divergent outcomes be best explained (and better ones facilitated)? Meaningful progress on these core questions should be transformative for the field.

Genetics and the exposome. Whereas heritability is well established and molecular genetic research is moving into the big science realm, impact on clinical care depends on taking developmental, clinical, and environmental variables into account. Genetic findings will eventually inform clinical care in two areas. The first pertains to the small minority carrying rare deleterious gene variants. As that field progresses, genetic testing may be recommended for ADHD as it now is for autism spectrum disorders. The second is, like in other fields of medicine, the partial predictive utility of polygenic scores. Polygenic scores provide only weak prediction in isolation, but they can be useful as part of a next-generation multifactorial prediction algorithm to guide clinical decision-making. Caution will be necessary, however, to avoid misapplication in view of the current shortage of adequate data on underserved and ethnic and racial minority populations, at least in the United States.

That said, clearly lacking is an adequate emphasis on the exposome in relation to ADHD. We mean exposome to include the technical toxicant exposome (e.g., lead and other chemical pollutants that convey background risk almost universally, as cited in the section titled Early Risk Factors) and its interplay with genetic liability, but not only that. We also mean to include the broader contextual risk factors of stress, allostatic load, and poor nutrition that influence neural and behavioral development, particularly in early life and particularly, we hypothesize, for individuals with elevated genetic liability. More direct linkage from the robust developmental literature on the very early life exposome, as well as early life socialization and temperament, to the childhood clinical syndrome of ADHD should be productive and commends more investment.

Toward Better Lives: Scientific Priorities

In the vast array of competing priorities for ADHD, we highlight a handful that flow directly from the literature reviewed here. We first note promising directions and important gaps in early life research that can aid in primary prevention and then move on to adolescence and secondary prevention. We conclude this section with a note on key conceptual challenges the field must consider.

Early identification: moving toward primary prevention. ADHD research is poised to capitalize on growing interest in developmental origins. This perspective implies the need for more studies of maternal-offspring and maternal-paternal-offspring factors leading to ADHD and tracking of how those developmental pathways actually emanate in the clinical syndrome. Key questions

confront this effort, some shading into ethical questions, but they also focus the field: Is ADHD, or a recognizable dysregulation phenotype, sufficiently distinct to enable formalization of an early risk temperament profile? How can early risk be effectively characterized without returning to a new version of the underspecified "difficult temperament" label of the mid- to late-twentieth century? Can what has been learned from studies of normal-range problem variation about early parent-child relationships and the consolidation of self-regulation and prosocial behavior be effectively applied to help prevent or reduce the severe clinical problems of ADHD? Can this be done while maximizing, and without suppressing or trying to control, children's individual potential?

Interest in early intervention to improve executive functioning, cognition, and development is extensive and can potentially be applied to children with ADHD with more effect than so far identified. However, the range of interventions may be most effective for this population if paired earlier in life with family socialization supports. New early-life prospective data to address these central translational questions in relation to stratification and prediction will be most helpful. The forthcoming multisite, National Institutes of Health–sponsored HEALthy Brain and Cognitive Development Study should provide one opportunity for insights. However, for that benefit to be realized, measure selection must be attuned to the wider question of emergence of dysregulation across different measurement models and domains (see Nigg 2017). Meanwhile, other cohorts are underway that should provide new data even sooner. As well, continued work in developmental fields related to cognitive development and emergence of executive functioning (or related subdomains such as working memory) will be informative, particularly if it can be linked to the clinical syndrome and to individual variation.

Adolescent pathways: moving toward secondary prevention. The past decade has seen a revolution in understanding of the severity of secondary complications related to ADHD that enables framing the public health problem in stark terms. Research is increasingly able to identify and characterize divergent trajectories for ADHD in adolescence. Needed now is sufficient mapping of modifiable moderators of course, both intrinsic and contextual. To that end, whereas substantial bodies of literature on prevention of suicide and of substance use disorder provide encouragement, they also highlight a continued need for new insights (Calear et al. 2016, Gray & Squeglia 2018). Actionable mechanisms of persistence and desistance of ADHD, and thus reduction of secondary risks, are key targets. These look likely to emerge in at least two major domains.

The first is the consolidation of executive functioning in adolescence. However, interventions in this area remain underdeveloped. Substantial effort and cost have been expended to test increasingly sophisticated computerized interventions to train attention and working memory, but with unconvincing results with regard to real-world improvement. One possibility is that the mechanistic targets are incorrect. More likely is that the perennial generalizability problem of in-lab technology training for real-life functioning will be intractable for ADHD, absent a more applied, rehabilitative component. In that vein, interest remains strong in and results are more promising with therapies that either specifically train emotional coping skills or provide formalized organizational skills training for ADHD.

The second is in more focused consideration of environmental and contextual supports. Their role in ADHD course has been too-long minimized in the field's conceptualization of ADHD. We noted the potential value of increasing psychosocial support in adolescence for ADHD as a possible way of at least partially accounting for the sometimes desisting course of the syndrome. In young adulthood, more developmental transition support programs should be useful. For example, the ADHD Life Transition Model (Turgay et al. 2012) highlights how suboptimal environmental characteristics can exacerbate ADHD symptoms, particularly at developmental transition points. Interest level, fit between abilities and demands, and availability of support

resources are key considerations. In addition to niche selection, transition planning can help youth with ADHD identify and enact steps to actualize selected niches.

Indeed, growing appreciation of the importance of social supports in fostering resilience generally is quite relevant to transition-age youth entering adulthood with ADHD as well (Dvorsky & Langberg 2016, Luthar & Eisenberg 2017). In the meantime, social and personality development are likely to see strong opportunities to interface with developmental psychopathology at ever earlier ages (Taylor et al. 2014).

The question of intervention philosophy. To date, only short-term solutions to ADHD symptom management (i.e., medication and behavior modification) are extant. Longer-term, sustained resilience factors, such as social acceptance and positive parenting (Dvorsky & Langberg 2016), have been investigated only sparsely for ADHD (Morris et al. 2020). It would seem that an overreliance on short-term, randomized controlled trials for relatively brief intervention periods has been woefully inadequate for ADHD. Needed now is more investigation of recurrent or intermittent but sustained interventions that can promote ongoing resilience and slow but sustained maturation over time (i.e., extrinsic motivation for long-term goals, cultivation of personal strengths and interests, identification of best-fitting environments, emotion regulation, and planning skills) (Sibley & Yeguez 2018). More decisive shifts in intervention paradigms to realize long-term strategies that support the success of adolescents and emerging adults with ADHD over time need more emphasis.

Questions About ADHD's Definition and Conceptualization

This review highlights the value of conceptualizing ADHD more broadly than inattention or impulsivity alone. Practical questions do arise as a result. What range of phenotypes should be subsumed under the diagnostic label of ADHD (Caye et al. 2016)? Should ADHD be conceptualized (*a*) as it is now, framed by specific problems with inattention and hyperactivity, with typical onset before age 12, or (*b*) closer to how it was historically seen (before DSM-III), with broader features of dysregulation including emotion dysregulation and executive dysfunction that emerge developmentally? A third possibility is (*c*) to retain the current clinical definition but address etiology and intervention from a broader dysregulation perspective.

This third approach is prudent in the near term as scientific progress accelerates but may be insufficient in the long term. While a modified definition would find substantial scientific support, any substantive change in the official clinical formulation would need to proceed with due caution. It would risk disruption of clinical care and other unintended consequences. If based on a dysregulation model, it would risk a return to the overinclusiveness of the clinical diagnosis of minimal brain dysfunction in the mid-twentieth century. Indeed, dysregulation in some form characterizes practically every syndrome in the DSM, rendering the construct relevant but far from sufficient.

Meanwhile, better conceptualization can already assist in psychoeducation and be generative with regard to new therapeutic ideas. Growing recognition of the range of dysregulation problems characteristic of ADHD and inextricable from its origins and etiology, along with studies of adolescent pathways, shines a light on these definitional questions. For purposes of imagining etiological studies and novel therapeutics, it is preferable to recognize a broader conceptualization. In addition to inattention and dysexecutive features, integrating the role of emotion dysregulation fits the emerging scientific corpus. Moreover, the problems in the mid-twentieth century with the underspecified and overinclusive idea of minimal brain dysfunction might be readily overcome. The field's extensive subsequent work that is now available on heterogeneity as well as on specifying inattention, impulsivity, executive functioning, and emotional dysregulation is notable.

Together, these research directions can enable the field to characterize the population known now as ADHD in a more integrated and specifiable fashion.

Further considerations emerge as we widen this reflection. Overall, views of psychopathology are rapidly evolving away from an assumption of discrete disorders. They are converging instead on a consensus view of psychopathology as an extended family of overlapping syndromes linked by crosscutting traits. From this vantage, the dysregulatory logic may become even more compelling. ADHD may appear as a subgroup of forms of dysregulatory psychopathology characterized by executive dysfunction or inattention, often accompanied by significant affect dysregulation but without meeting criteria for a primary affective disorder at onset.

CONCLUSION

ADHD is an increasingly important clinical condition. It augers future mental and substance use disorders and identifies youth at high risk of substantial life hardship and shortened life span. Elucidating the emergence, persistence, and remission of ADHD has important implications for prevention of negative long-term outcomes and prevention of other psychopathologies. Developmental psychology has a major role to play in this quest. Opportunities for positive progress are exciting.

Despite the statistical validity of a behavioral dimension or dimensions for ADHD or ADHD-like problems in the population, a central obstacle is the etiological and phenotypic heterogeneity of the population that meets criteria for the syndrome of ADHD. Linkages to temperament theory are but one promising example of an approach that can help clarify phenotypic profiles and relate to diverse developmental pathways. Such rapidly growing approaches bode well for better clinical characterization. We noted growing hopes for transformative insights as to earlier detection and the potential to shift to primary or secondary preventative and mechanistic interventions for ADHD, with resultant longer-term stability, life quality, and autonomy at modest cost.

An integrated picture of ADHD is emerging due to work that crosscuts well-established cognitive features (breakdowns in executive functioning) with ADHD-related deficits in motivation and arousal as well as due to particular emerging emotional correlates that intersect with important bodies of work in developmental science. Understanding the interplay between these features will increase the versatility of intervention options and promote treatment individualization. Hope is likewise emerging for a more personalized approach that sees children as more than just a syndrome but as characterized by differentiated behavioral features and complexity, which can be more specifically supported. The crucial developmental periods of early life and the adolescent transition remain among the exciting areas of progress that offer hope of new treatments that will improve the prognosis of youth in this population.

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