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

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Abstract

ADHD represents a powerful entry point for developmental approaches to psychopathology due to its major 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 seem to have largely benign outcomes, while a larger group continue 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.

Keywords

Attention Deficit Disorder with Hyperactivity; ADHD; temperament; adolescent development; development; executive functions

The Underappreciated Problem Space around ADHD

Clinically significant mental health problems, encompassing psychiatric disorders (e.g., depression, anxiety, schizophrenia), neurodevelopmental disorders (e.g., Autism spectrum disorder, ADHD, idiopathic intellectual disability), and substance use disorders, collectively

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comprise 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 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 a syndrome called Attention-deficit/hyperactivity disorder (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 is among the most dramatic in psychiatry.

However, a closer look reveals ADHD as in fact a vastly under-appreciated 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%−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, Khoza, & Oladapo, 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, Janssen, & Oosterlaan, 2017; Kessler et al., 2006; Lee, Humphreys, Flory, Liu, & Glass, 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, too--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, McGee, & Druss, 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; Kessler et al., 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 Paper

The review is necessarily selective. We bypass important, but recently reviewed literatures on ADHD's history, sex differences (Cortese & Coghill, 2018; Hinshaw, 2018), neuroimaging (Albajara Saenz, Villemonteix, & Massat, 2019; Rubia, 2018), genetics

[1]Although in the United States over 10% of youth are identified as having ADHD in population surveys of parents, most reviews cite 5–7% as the prevalence based on formal studies (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). However, use of Bayesian methods to correct for unmeasured regions yields a true prevalence estimate in the 2–4% range (Erskine et al., 2013).

(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

ADHD is defined in DSM-5 (APA, 2013) by extreme problems in under-specified behavioral domains of either: inattention (better referred to as inattention-disorganization due to the association to 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-criteria do face some construct validity issues, a well-established factor-analytic literature on the universe of child problems yields a very recognizable ADHD-like dimension for children and adults (Achenbach, 2020; Achenbach & Edelbrock, 1978). The ADHD syndrome thus is analogous to hypertension, or obesity: defined by applying, to a trait, a clinical cut-point with actuarial but not ontological meaning.

However, this initial summary disregards the likely etiological and developmental subgroups within the syndrome profile. Heterogeneity is one overarching concern; phenotype boundaries are another. Besides the core symptoms, ADHD also involves problems in cognition, emotion regulation, and social skills. Thus, a full accounting of the clinical picture in 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 co-segregates in families, shares polygenic genetic overlap, or co-occurs beyond chance clinically with: autism spectrum disorder (Ghirardi et al., 2018; Miller, Musser, et al., 2019; Musser et al., 2014), intellectual disability (Faraone, Ghirardi, Kuja-Halkola, Lichtenstein, & Larsson, 2017), and communication and learning disorders (Thapar, Cooper, & Rutter, 2017). Although some of these points hold for ADHD's relation with disruptive behavioral disorders too, 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

Beyond dispute for ADHD are substantial heritability (polygenic liability) and several environmental risk factors. Less clear are the degree to which (a) ADHD is influenced by very early life programming of development, (b) genotype by environment interactions

account for heritability, and (c) genotype-environment correlations account for other risk factors. As a result, actual causal mechanisms still remain poorly understood.

Genetic liability.

ADHD's heritability of liability in twin studies is .7 to .8 (Faraone & Larsson, 2019)--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 (GWAS) 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 what 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 and in any event, these will apply to only a small minority of ADHD cases (Thapar, 2018).

Early risk factors.

Several pre- and peri-natal 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, Matvienko-Sikar, Baldoni, O'Keeffe, & Khashan, 2019), pre-term birth and/or low birth weight (Momany, Kamradt, & Nikolas, 2018; Serati, Barkin, Orsenigo, Altamura, & Buoli, 2017), social disadvantage and adversity (Bjorkenstam, Bjorkenstam, Jablonska, & Kosidou, 2018), and average level lead exposure (Goodlad, Marcus, & Fulton, 2013; Nigg, 2019; Nigg, Elmore, Natarajan, Friderici, & Nikolas, 2016) as well as other environmental toxicants (Myhre et al., 2018; Rivollier, Krebs, & Kebir, 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).

To address this gap, experimental designs are used when possible; for example, to evaluate dietary effects on ADHD (Ramakrishnan et al., 2016). Alternatively, causal evidence can be sought in sibling comparisons, Mendelian randomization,[2] and other natural experiments. While still early days, initial studies have called into question a causal role for maternal smoking (D'Onofrio et al., 2013) and pre-pregnancy maternal BMI (Musser et al., 2017) while supporting a causal role for lead exposure (Nigg et al., 2016) and social disadvantage (Larsson, Sariaslan, Långström, D'Onofrio, & Lichtenstein, 2014) in ADHD.

[2]In Mendelian randomization study, it has to be assumed that a functional mutation is randomly distributed, creating a presumed natural experiment in which biological handling of an exposure is manipulated 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 among potential confounds.

Fetal origins?

Following on the interest in early exposures, prenatal origins and programming of risk was proposed for ADHD over a decade ago (Swanson & Wadhwa, 2008) and now stands as a major direction in developmental psychopathology generally (Monk, Lugo-Candelas, & Trumpff, 2019). Whereas this effort faces unresolved interpretive challenges (Monk et al., 2019), the field has identified as candidate mechanisms of interest to multiple conditions: immunological (particularly cytokine), hypothalamic-pituitary-adrenal (HPA) axis, and (more speculatively) microbiome alterations. All are undergoing initial investigation in ADHD. Particularly intriguing may be the preliminary evidence that prenatal maternal inflammation may be a common pathway for early risk influences on offspring ADHD (Dunn, Nigg, & Sullivan, 2019; Gustafsson et al., 2019; Gustafsson et al., 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.

Most of the preceding exposure 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. Whereas all development requires biological gene-environment co-action, the specific kind of co-action seen in statistical moderation studies are usually called “genotype environment interaction” or GxE. It is of particular interest for risk stratification and prevention. Most GxE studies of have relied on candidate genes, an approach that has been questioned. Thus, a major unknown and a key opportunity is to discover the extent to which modifiable early environments can alter the trajectory of ADHD—but with careful consideration of genotype-environment interaction and correlation (Leppert et al., 2019).

Early socialization: as major gap.

By preschool, parenting style does not seem to cause ADHD; rather, child difficult behaviors elicit negative interchanges from parents (Modesto-Lowe, Danforth, & Brooks, 2008). In preschool, parenting intervention is effective mainly at managing disruptive, non-compliant, 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 3–4 years or older. Parent-child processes preceding clinical ADHD in the first 12 to 24 months of life are hardly studied--despite an established literature on the role of early parenting in the consolidation of self-regulation (Morawska, Dittman, & Rusby, 2019). Could ADHD be prevented in susceptible children by suitable parenting guidance in the first 24 months of life? The 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 in the childhood period: the need to refine the ADHD phenotype in relation to the over-arching problem of heterogeneity. We consider these together.

Heterogeneity and Phenotype refinement: Early Life and Childhood

ADHD is heterogeneous both etiologically and phenotypically (Luo, Weibman, Halperin, & Li, 2019; Nigg, Karalunas, Feczko, & Fair, 2020; Swanson et al., 2007). One issue is that the symptom-checklist method of diagnosis in DSM structurally ensures some degree of clinical heterogeneity in most disorders. The DSM-5 acknowledge this for ADHD by specifying three presentations (mostly inattentive, mostly hyperactive/ impulsive, combined). The challenge, however, extends well beyond symptom checklist artifact. Polygenic theory assures genetic heterogeneity for complex traits and disorders like ADHD (Wray, Wijmenga, Sullivan, Yang, & Visscher, 2018). As noted, the relevant exposome for ADHD is likewise multi-factorial 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 will be 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, Karalunas, Feczko, et al., 2020). To illustrate, we consider ADHD in light of neuropsychology (especially executive functioning), and of emotional regulation via a temperament lens.

Neuropsychology

ADHD's neuropsychological correlates are extensive and, despite a rather noisy literature and effect sizes too modest to be diagnostically informative, can inform mechanism and heterogeneity. For example, ADHD samples show greater predominance of slow wave activity in the 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 Saenz et al., 2019; Nigg, Karalunas, Feczko, et al., 2020; Rubia, 2018). Functionally, ADHD is also associated with weaker performance in tests of top-down control (also often termed executive function, including working memory, response inhibition, planning) and in tests of signal detection presumed to measure arousal or vigilance (Pievsky & McGrath, 2018), as well as related functions such as reward motivation. Whether state regulation/arousal/ motivation problems degrade executive functions or vice versa, or represent alternative phenotypes, remain important debates (Karalunas & Huang-Pollock, 2013; Lenartowicz et al., 2014; Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Unsworth & Robison, 2017).

As a result, heterogeneity of these mechanisms has been long hypothesized to help account for variation in the ADHD population (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2005). A small literature has 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 sub-profiles within the ADHD population that can be interpreted as variation in top down functions (working memory) versus arousal (reaction time, signal detection) (Fair, Bathula, Nikolas, & Nigg, 2012; Roberts, Martel, & Nigg, 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, Stringaris, Nigg, & Leibenluft, 2014), particularly anger dysregulation (called “irritability”). In part because of its emotional features and in part features related to top-down control, 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, Lemery-Chalfant, Schmidt, Arneson, & Schmidt, 2007). By adulthood, ADHD is also correlated with ratings of personality traits (particularly low conscientiousness/constraint and high negative emotion/ neuroticism). Yet ADHD is not reducible to these constructs or their combinations —correlations simply are not large enough (Gagne & Goldsmith, 2011; Martel, Nigg, & von Eye, 2009; Nigg et al., 2002). Standing on these traits therefore may inform liability (Goldsmith, Lemery, & Essex, 2004), capture early stages of ADHD emergence or, help clarify phenotypic heterogeneity.

Beginning with heterogeneity, Nigg, Goldsmith, and Sachek (2004) sketched a temperament-based multiple-pathway perspective. They suggested that ADHD might emerge for some children primarily via the negative emotion and display a phenotype characterized by impulsivity, anger reactivity, and perhaps reactive aggression. For other children, ADHD would emerge via excess approach (“exuberance” or positive affectivity), leading to 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. That such profiles might be able to be identified 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).

Within an ADHD population distinct temperament profiles have been seen in a series of statistical clustering studies from two large case-control samples that consistently identify profiles of children with ADHD characterized by (a) high negative affect/irritability/ neuroticism and (b) normative temperament ratings (Karalunas, Gustafsson, Fair, Musser, & Nigg, 2019; Martel, Goth-Owens, Martinez-Torteya, & Nigg, 2010; Smith & Martel, 2019). Less consistently they identify a profile (c) 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 7–12 year olds was up to 4x more likely to experience clinical deterioration one to two years later than was the typical-temperament ADHD group. That result held even after accounting for, and outperformed, baseline ADHD

symptom severity, comorbidity, or impairment (Karalunas et al., 2014; Karalunas et al., 2019; Martel, 2016; Smith & Martel, 2019).

The sub-group of ADHD with very high negative affect, anger, and poor recovery from anger was at highest risk. 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, Cohen, Gorrindo, Brook, & Pine, 2006; Stringaris, 2011; Wakschlag et al., 2018).

With the Surgent-active profile 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 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, Karalunas, Feczko, et al., 2020), fit with correlations to polygenic liability for ADHD (Nigg, Karalunas, Gustafsson, et al., 2020), and mapped to EEG profiles (Alperin, Smith, Gustafsson, Figuracion, & Karalunas, 2019) better than a finer-grained valence distinction.

Dynamic development: Early Life

The dynamic developmental progression of traits from infant-to-toddler-to-child- to-adolescent-to-adult (Gaertner, Spinrad, & Eisenberg, 2008; Kim & Kochanska, 2019; Nozadi, Spinrad, Johnson, & Eisenberg, 2018; Rothbart, 2011) can also be fruitful for understanding ADHD. In early life, one proposal is a temperament cascade perspective (Rothbart, 2011) which may then moderate or mediate emergence of ADHD (Auerbach, Atzaba-Poria, Berger, & Landau, 2004; Rabinovitz, O'Neill, Rajendran, & Halperin, 2016; Sonuga-Barke, Bitsakou, & Thompson, 2010; Sullivan et al., 2015).

A fundamental hypothesis (seen in these papers) is that early life extreme negative emotional reactivity disrupts the consolidation of top-down control (Gagne & Goldsmith, 2011), which in turn supports self-regulation and the maturation of executive functions. 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 (Miller, Hane, Degnan, Fox, & Chronis-Tuscano, 2019) 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 (Miller, Hane, et al., 2019). Yet on the positive reactivity side, infant positive reactivity or high approach (along with activity level) are consistent predictors of childhood ADHD symptoms (Goldsmith et al., 2004; Jonas & Kochanska, 2018; Miller, Degnan, Hane, Fox, & Chronis-Tuscano, 2019).

These results are broadly supportive of the general model being developed here, in that future ADHD is related to early extreme emotional reactivity (positive or negative) and breakdowns in cognitive control. As in the earlier profiles described, in the infant prospective studies see prediction by either negative affect/anger, or positive approach/activity level (sometimes also with anger reactivity).

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

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, Gottfredson, & Stifter, 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, Roth, Lindqvist, & Thorell, 2013) perhaps due to the heterogeneity of profiles that we have outlined above.

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 or effortful control, which then in turn plays an important regulatory role; meantime, attentional orienting serves a regulatory function in infancy (Rothbart, Sheese, Rueda, & Posner, 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 function. A recursive process then may canalize to instantiate a stable ADHD picture.

Solidification and refinement of this type of 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, earlier. 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.

Heterogeneity and Phenotype refinement: Adolescence to Young Adult

Although our themes of emotion-cognition and relevance of context persist, we have separated the adolescent-young-adult period from early life and childhood deliberately. First, while 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 early on that a subset of youth with ADHD appear to achieve benign outcomes, though sometimes only after great struggle (Hechtman, 1999)[3] 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, Lahey, Loeber, Applegate, & Frick, 1995). Outcomes are better for those with

low aggression and above average intellectual development, and with reduced genetic risk. However, these associations remain too small to provide a satisfying or complete account. What else pertains?

Intrinsic mechanisms: Emotion/cognition.

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, dynamic, asynchronous neural development influences the relative capacity for emotional regulation in the face of salient social-emotional stimuli (smartphones, peer challenges, alcohol or drugs). These neural maturation processes include hierarchical development, from childhood through adolescence of sub-cortical-to-cortical, then cortical-to-sub-cortical, and finally cortical-cortical circuitry (Casey, Heller, Gee, & Cohen, 2019). This layered, dynamic process may be delayed or disrupted in ADHD (Shaw et al., 2007). Likewise, the integrated consolidation of executive functions 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 functions may be a liability trait for ADHD (Vaughn et al., 2011). At the same time, "catch up" in these functions seems to be associated with improvement of ADHD symptoms in this period (Murray, Robinson, & Tripp, 2017). One recent hypothesis is that liability rests on excessive reactive processes in early life (e.g., emotional reactivity, or disrupted reward-motivational responding), which sufficiently strong and timely consolidation of top down control (and the corresponding neural maturation), for some individuals, enables stable adjustment during and after adolescence (Halperin & Schulz, 2006). Karalunas et al. (2017) mapped trajectories of working memory and reward responding prospectively in 437 children with well-characterized ADHD receiving detailed annual assessments in a lag panel design from 7–13 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 and Schulz (2006) proposal.

Psychosocial context.

Psychosocial context remains under-emphasized 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. Meantime, adolescence in many nations is extended by earlier puberty or extended time before acquiring adult responsibilities (Dahl, Allen, Wilbrecht, & Suleiman, 2018; Worthman & Trang, 2018). For adolescents with ADHD, longstanding difficulties with impulsivity, executive control, and emotion dysregulation can create a kind of "double disorder" when paired with typical challenges of adolescent development (Sibley, Graziano, Ortiz, Rodriguez, & Coxe, 2019)--fueling secondary poor outcomes. The

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

adolescent academic, family, and social environments seems 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 a 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 onset in adolescence (Biederman et al., 1993). Provocatively, however, recent studies have provocatively suggested the appearance of a large number of spontaneous late-onset ADHD that first emerges in adolescence or young adulthood and persists (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015).

What is going on? It appears that many apparent onset cases had significant sub-clinical problems earlier in life, suggesting greater continuity than initially implied (Faraone & Biederman, 2016) or else who 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 tend to confirm and expand this picture (Sibley, Ortiz, Graziano, Dick, & Estrada, 2020; Sibley et al., 2018) . These studies in suggest that apparent late onset cases of ADHD are largely accounted for by either (a) subthreshold psychiatric or behavioral problems that take the form of ADHD in adolescence; (b) individuals with ADHD liability but who can manage in childhood due to strong intellectual or language development, until demands increase and supports are withdrawn in adolescence; (c) adolescent limited ADHD symptoms (Langberg et al., 2008), or (d) trauma or severe adversity that manifest 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.

In adolescence, the person-context interplay thus remains a critical cutting edge focus here 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, Ferrari, & Réale, 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 adapting 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, 1982; Eisenberg et al., 2003). Consistent with niche theory, low ego-resiliency is associated with difficulty in the adolescent to adult transition (Alessandri, Eisenberg, Vecchione, Caprara, & Milioni, 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 (structured schools, colleges, 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 also strengthened by family and social supports in early life, and also now in the adolescent-to-young adult transition (Alessandri et al., 2016).

While these principles provide a general framework, too little remains known about specific ways for affected individuals or their supporters or clinicians to help facilitate successful management or resolution of ADHD symptoms in young adulthood.

Future Directions, Scientific Priorities, and Conclusions

Whereas several of the questions about ADHD are longstanding, they have taken on a new twist with recently emerging data. Here we note key points and questions for the field. Across the preceding, 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.

Cross cutting themes

Heterogeneity.—An overarching challenge for the field is the need for ever-improving and useable 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 we illustrated, 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)?

Genetics and the exposome.—Whereas heritability is well established and molecular genetic research is moving into the "big science" realm, impact on clinical care will depend on taking developmental, environmental and clinical variables into account. On the one hand, 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. These will, however, provide only weak prediction in isolation; instead, they can be useful as part of a next-generation multifactorial prediction algorithm to guide clinical decision making.

That said, clearly lacking is an adequate emphasis on the *exposome* in relation to ADHD. By exposome, here do include the technical toxicant exposome (e.g., lead and other chemical pollutants that convey background risk almost universally as cited earlier) and their interplay with genetic liability. But not only that. We also mean 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, into the childhood clinical syndrome of ADHD should be productive and demands more investment.

Toward Better Lives: Scientific priorities

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 into 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 an early temperament-risk profile to be formalized? How can early risk be effectively characterized without returning to the under-specified “difficult temperament” of an earlier era? Can what has been learned about early parent-child relationships and the consolidation of self-regulation and pro-social behavior be effectively bridged from studies of normal range problem variation to help prevent or reduce the severe clinical problems of ADHD? Can this be done while maximizing, and 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 likely will be most effective for this population if paired earlier in life with family socialization supports (Diamond & Lee, 2011). However, new, early-life, prospective data to address these central translational questions in relation to stratification and prediction will be most helpful. The forthcoming multi-site NIH-sponsored HEALthy Brains 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). Meantime, 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 sub-domains such as working memory) will be informative, particularly if it can be linked to the clinical syndrome and to individual variation.

Adolescent pathways: 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 literatures 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). Thus, actionable mechanisms of persistence and desistance of ADHD, and thus reduction of secondary risks, is a key target. These look likely to emerging in at least two major domains.

The first is the consolidation of executive functions in adolescence. However, interventions in this area remain underdeveloped. Substantial effort and cost has been expended to test increasingly sophisticated computerized interventions to train attention, and working memory, but with unconvincing results in 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 and results more promising with in therapies that specifically train emotional coping skills as well as in 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 accounting for desisting course of the syndrome. In young adulthood, more development transitional 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 will be relevant to transition-age youth with ADHD (Dvorsky & Langberg, 2016; Luthar & Eisenberg, 2017). Social and personality development are likely to see strong opportunity to interface with developmental psychopathology at ever earlier ages (Taylor, Eisenberg, VanSchyndel, Eggum-Wilkens, & Spinrad, 2014).

New 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), are only sparsely investigated for ADHD (Morris, Sheen, Ling, Foley, & Sciberras,

2020). It would seem that an over-reliance on short-term randomized controlled trials for relatively brief intervention periods has been woefully inadequate for ADHD. Needed now will be 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.

Conceptual Implications: Redefining ADHD?—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 should be conceptualized (a) as it is now, framed by specific problems with inattention and hyperactivity, that typically onset before age 12, or (b) closer to how it was historically seen (before DSM-III), with broader features of dysregulation including emotional 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 longer 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 over-inclusiveness of *minimal brain dysfunction* in an earlier era. Indeed, dysregulation in some form characterizes practically every syndrome in the DSM, rendering the construct relevant but far from sufficient.

Meantime, 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 in its origins and etiology, along with studies of adolescent pathways, shine a light on these definitional questions. For purposes of imagining etiological studies and novel therapeutics, it will be 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 an earlier era with the under-specified and over-inclusive idea of minimal brain dysfunction might be readily overcome with the more extensive subsequent work now available on heterogeneity and on specifying inattention, impulsivity, executive function, and emotional dysregulation more effectively to characterize the population known now as ADHD in more integrated 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 cross-cutting 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(s) 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 in a useful manner and relate to diverse developmental pathways. Such rapidly growing approaches lend hope of better clinical characterization. We have 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 and 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, and in 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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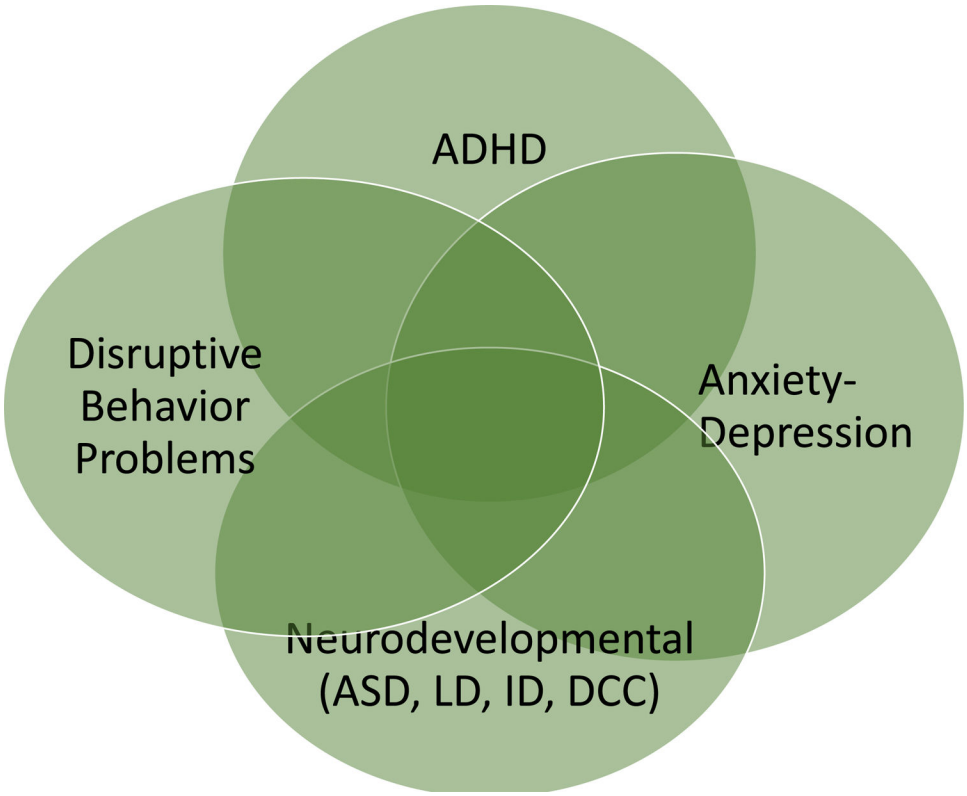

Figure 1:

Overlapping problems, “comorbidity”, and correlations in the psychopathology and neurodevelopmental domain in childhood (not to scale)

Disruptive behavior problems: oppositional defiant, aggressive, tantrums/irritable, conduct, antisocial. ADHD: Attention deficit/hyperactivity disorder; ASD: autism spectrum disorders; LD: learning disorders: ID: Intellectual disability; DCC: Developmental coordination disorder

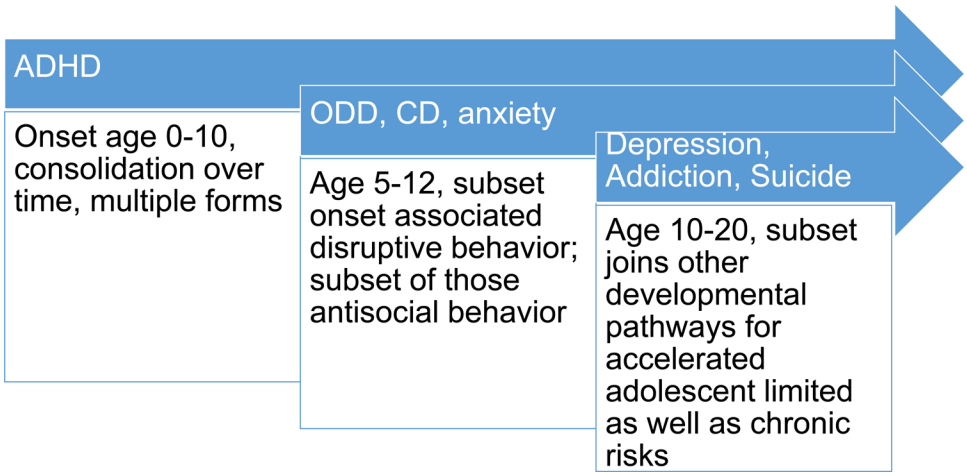

Figure 2:
Expanding risk in ADHD development

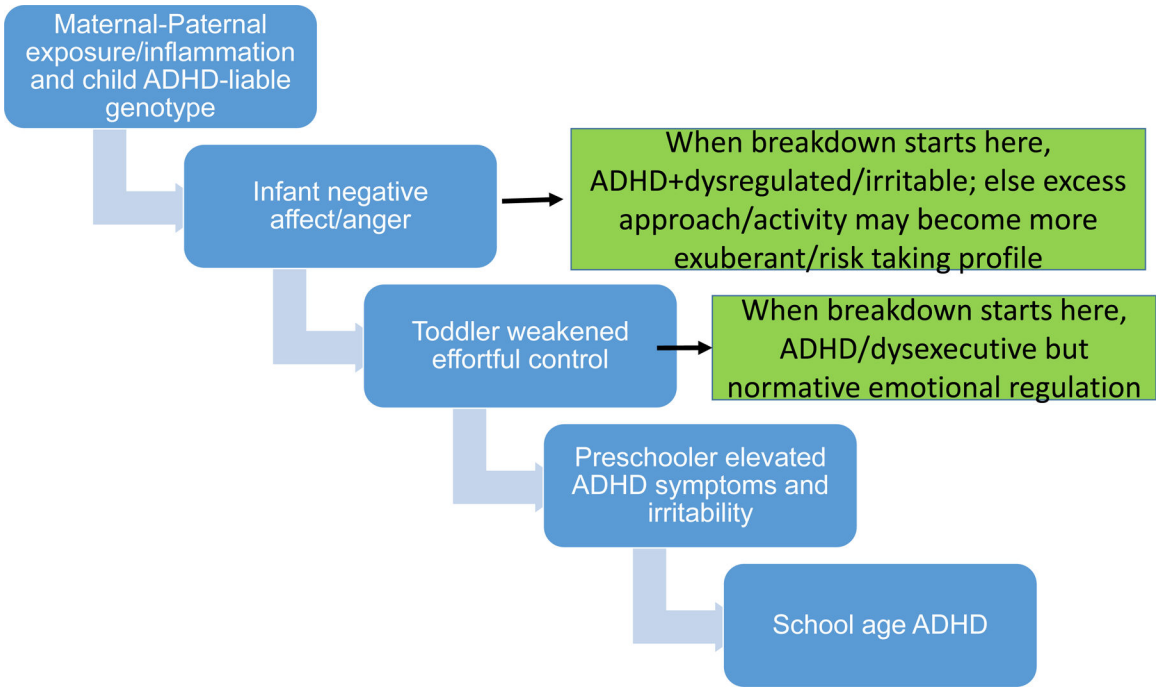

Figure 3: An hypothesized cascade of early temperament and ADHD.

Rothbart (2011) adds moderation by infant orienting response and approach, fear tendencies in early life. 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.