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## Attention deficits and hyperactivity–impulsivity: What have we learned, what next?

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### Abstract

The domains of self-regulation, self-control, executive function, inattention, and impulsivity cut across broad swathes of normal and abnormal development. Attention-deficit/hyperactivity disorder is a common syndrome that encompasses a portion of these domains. In the past 25 years research on attention-deficit/hyperactivity disorder has been characterized by dramatic advances in genetic, neural, and neuropsychological description of the syndrome as well as clarification of its multidimensional phenotypic structure. The limited clinical applicability of these research findings poses the primary challenge for the next generation. It is likely that clinical breakthroughs will require further refinement in describing heterogeneity or clinical/biological subgroups, renewed focus on the environment in the form of etiological events as well as psychosocial contexts of development, and integration of both with biological understanding.

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Attention deficits, hyperactivity, and impulsivity have risen to sustained prominence in the last 25 years as a central concern for parents, teachers, educators, mental health practitioners, and researchers. It is fitting for the timing of this review that it is precisely 200 years since Benjamin Rush (1812/1962) provided the first American medical description of extremely inattentive individuals similar to today's attention-deficit/hyperactivity disorder (ADHD); 75 years since the discovery that amphetamine-like drugs could help them (Bradley, 1937); and nearly 25 years since the first formal diagnostic criteria for attention-deficit disorder were promulgated in DSM-III, officially revising and narrowing the older construct of minimal brain dysfunction (Taylor, 2011). It is also fitting that this article appears around the same time as the publication of DSM-5 in 2013, marking the latest update in diagnostic criteria and accompanying advisory and descriptive text for mental disorders in psychiatry. The ICD-10 will follow. Thus, the 25-year anniversary of *Development and Psychopathology* coincides well with other milestones that suggest an excellent point for looking back and even more for looking forward with regard to the vexing issues of what we currently call ADHD.

Before proceeding, a handful of contextual remarks are in order. First, it is important to recall that the topics of impulsivity and inattention are hardly confined to the DSM syndrome of ADHD. Substance use disorders, gambling problems, “impulse control

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disorders not otherwise specified,” several personality disorders, mania, and other psychopathological syndromes are characterized by impulse control problems. Second, inattention is a surface symptom of numerous underlying problems including mood problems, physical health problems, neurological disease, and idiopathic ADHD. Moreover, severe impulsivity or inattention is a comorbid or secondary problem in still other conditions, such as autism spectrum disorders, learning disorders, closed head injuries, and others. Third, across the population as a whole, impulsivity, inattention, and ADHD-like problems are conceptually and empirically related to concepts like self-control and self-regulation. A substantial literature now shows that self-control, defined in various ways, is a meaningful predictor of life outcomes in almost every domain, including not only psychopathology but also health, learning, economic well-being, and longevity, as well as negative outcomes like antisocial behavior and substance use disorders (Blair & Razza, 2007; Calkins & Keane, 2009; Clausen, 1993; Kern & Friedman, 2008; Moffitt et al., 2011; Nigg, 2006). Thus, the entire matrix of adaptive–maladaptive development in the broadly defined domains of impulsivity, self-control, self-regulation, and attention not only cut across several domains of psychopathology but also are extremely important to many fields of human development. It is overly simplistic to think of self-control only as a single dimension running from adaptive to maladaptive, both because excessive control may also be maladaptive and because it is not yet clear that the structure and determinants of control subdomains is the same across normal and extreme behaviors. Nonetheless, it is clear that inattention, impulsivity, and self-regulation also are related to normally developing temperament and personality traits that are correlated with, but not identical to, ADHD at their maladaptive end (Nigg, 2006). When we focus on ADHD, we focus on a maladaptive extreme that likely captures only a subset of the forms of adjustment/maladjustment in this broader domain.

Second, ADHD is also an excellent example of a syndrome for which the developmental psychopathology perspective (Cicchetti & Posner, 2005; Cicchetti & Richters, 1997; Cicchetti & Toth, 2009) is extremely relevant. ADHD exemplifies the complexity of distinguishing normative and maladaptive behaviors, the importance of a lifespan perspective, the importance of multilevel understanding of mechanism and process, and the dynamic pathways that exemplify multifinality. These can be illustrated in turn.

To take the question of development and the cross talk between normal and abnormal development in the direction of psychopathology, in the past generation a great deal has been learned about normative cognitive, emotional, and neural development in typically developing and psychopathological youth (Cicchetti & Cannon, 1999). It is now more well appreciated that neural, and thus cognitive and emotional, development is (a) nonlinear, (b) nonuniform, and, underscoring the importance of life span perspective, (c) continues well past our usual conceptual boundaries of adolescence. For example, the cortical mantle develops and modifies in nonlinear fashion all the way into the 20s, with ongoing myelination, pruning, differentiation, and shaping, governed by both genetic and learning inputs. The health of cortical–cortical and cortical–subcortical neural circuits is integral to the maturation of the control of impulse, attention, and motoric activity. As another example, some cognitive abilities mature early (e.g., by middle childhood some forms of

attentional selection are at adult levels), whereas others (such as cognitive control) develop much later (Huang-Pollock, Carr, & Nigg, 2002).

However, despite the late final maturation of effortful control of attention and impulse systems in reaching their full adult capabilities, the early precursors of these abilities begin to form in the toddler years when they presumably are quite sensitive to genetic and experiential perturbations. Thus, there is a growing emphasis and appreciation not only for the adolescent-to-adult transition to maturation of attentional and impulse control but also for the early origins and early developmental roots of these abilities that may set a life trajectory from very early on.

Thus, one of the areas of marked progress in the field in the last 25 years has been a greater appreciation and formal description of the multiple component processes that underlie the behaviors of inattention, being disorganized, and being impulsive (and in children, overactive). The field as a whole has come to appreciate that these overarching dimensions of behavior (cognitive control and impulse control) cut across normal adjustment and psychopathology, while perhaps having somewhat different meaning and context when concentrated in a singular impairing syndrome.

With regard to multifinality (Bergman, Andershed, & Andershed, 2009), it is now much more well appreciated than 25 years ago that ADHD itself occurs on a series of developmental progressions that are not static, but dynamic and nonlinear. In one pathway, children who are hyperactive, impulsive, irritable, defiant, and aggressive as preschoolers go on to meet criteria for ADHD and oppositional defiant disorder in grade school. A subset of these children develop conduct disorder and persistent delinquent behaviors, and many of those in turn fall into substance use disorders and other chronic, seriously negative outcomes. The moderators and determinants of this developmental pathway and the important differences for boys versus girls are increasingly well described conceptually (Beauchaine & Gatzke-Kopp, 2012). Some of these children are sufficiently angry, explosive, and irritable that they would fall into the group more recently described as “irritable” or as falling into the group DSM-5 now designates as disruptive mood dysregulation disorder (Leibenluft, 2011). Some of these children will also go on to mood disorders and the potentially disastrous combination of impulsivity and severe depression, with a 10-fold increase in suicide risk compared to typically developing individuals (Agosti, Chen, & Levin, 2011).

However, children who are extremely inattentive, hyperactive, and impulsive in preschool or early elementary school also proceed to several other possible outcomes, again exemplifying multifinality. An above-chance minority go on to mood or anxiety disorders even though they were not classified as oppositional defiant disorder or severely irritable early in life. Others exhibit primarily learning and achievement problems and may be relatively socially withdrawn, and still others exhibit strengths in social confidence, or athleticism, or intelligence and have sufficient charm or resilience to have quite good outcomes. Even though a substantial minority of children with ADHD seem to have successful adult outcomes, the specific resiliency mechanisms associated specifically with ADHD’s positive outcomes are scarcely described (but see Nigg, Nikolas, Friderici, Park, & Zucker, 2007). A

formal mapping of these various developmental pathways and routes is lacking, with the exception that there are beginning to be longitudinal maps of inattention versus ADHD + aggression (Barker et al., 2011; Jester et al., 2005).

Third, and exemplifying further the normal–abnormal continuum, over the past generation, despite varying emphases nationally on bipolar disorder, autism spectrum disorder, and other conditions in children, ADHD has remained controversial. This is not least because problems staying organized, handling information overload, coping with stress, and focusing seem to pervade modern society with its perceived “hectic pace of life.” When is the typical or normative response to a busy culture actually a disorder? Fundamental questions like this have no simple answer but vex the lay public and push clinical scientists to search for better characterization of developmental and biopsychosocial integration of behavioral syndromes such as ADHD.

It also motivates research and provokes periodic controversy that in the United States and several other nations the apparent prevalence of ADHD has continued to climb in the past decade (Boyle et al., 2011); thus, the seeming increasingly frequent medical treatment of diagnosed children has spurred ongoing societal controversy. The disorder is now recognized around the world, but treatment rates vary widely despite fairly consistent estimates of population prevalence (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

Fourth, as noted in the introductory section and following on the last issue, another major theme in the literature of the past two decades has been that whereas ADHD is still sometimes dismissed by casual observers as a mere construct or a symptom of weak parenting or unskilled teaching, the perniciousness of the syndrome has become increasingly clear. Large-scale population surveys have replaced anecdotal or small sample observations to reveal increased risk of injuries requiring medical attention in both children (odds ratio = 1.8, or 80% increase in risk) and adults (odds ratio = 1.5, or 50% increased risk; Merrill, Lyon, Baker, & Gren, 2009; Pastor & Reuben, 2006). When combined with mood or conduct problems, these children are at elevated risk for suicide attempt and suicide (Agosti et al., 2011; Impey & Heun, 2012); mediated by their high probability of irritable aggression and conduct problems, these children represent the main group of children who will go on to antisocial problems, substance use disorders, underemployment, divorce, and a range of interpersonal conflicts. Moreover, the field’s grasp of the broad interrelationship of self-control and health has linked population variation in ADHD-related behaviors to numerous health outcomes such as smoking, accidental injury, obesity, and sleep problems (for a review, see Nigg, 2012).

Thus, the combination of growing evidence for (a) ADHD as an important early gateway to a wide range of poor life outcomes, (b) widely varying and in places like the United States rapidly increasing rates of medical treatment, and (c) solidifying yet still not clinically applied evidence for neurobiological changes associated with ADHD will ensure that an ongoing focus on genetic, neural, physiological, and neuropsychological biomarkers for ADHD will remain extremely important for the field and for society going forward. In short, however one explains ADHD, its developmental roots need to be understood. A

developmental psychopathology perspective is extremely helpful here because it commends the necessary multilevel, dynamic conception that is needed. ADHD's all too real financial, social, and quality of life costs remain substantial. Thus, understanding what drives this syndrome will remain a major yet formidable priority in health-related research into the foreseeable future.

## Progress and Status Report on the Past 25 Years

Perhaps the most important insight of a developmental psychopathology perspective for ADHD is a multilevel understanding. As recently illustrated, this approach is quite productive with regard to a range of behavioral and developmental problems (Burnette & Cicchetti, 2012). I here consider progress on ADHD at multiple levels of analysis. Later, I consider potential integrations across levels.

### Genetics

Scientific progress on understanding the neurobiological correlates of ADHD in the past 25 years has been dramatic. On the genetic side, 25 years ago there were no candidate gene studies of ADHD. Candidate gene studies of ADHD first began in the 1990s; they were soon supplanted by genomewide association studies. The candidate gene studies have been summarized in meta-analyses, which have concluded that several gene markers are correlated with ADHD (dopamine transporter 1, dopamine receptors D4 and D5, serotonin transporter, 5-hydroxytryptamine [serotonin] receptor 1B, synaptosomal-associated protein 25 (*SNAP25*; Gizer, Ficks, & Waldman, 2009). Another meta-analysis looking at a subset of genes related to neural plasticity confirmed this association for only one gene, *SNAP25* (Forero, Arboleda, Vasquez, & Arboleda, 2009). Significant heterogeneity of effects was notable in the meta-analysis and needs to be explored, and conclusions could still be overturned by a sufficient number of future negative findings. This does not mean, however, that any of these genes are necessary or sufficient to cause ADHD; these genes likely confer a slight change in liability. The effect sizes suggested in the meta-analyses are in the range of odds ratio of 1.1 to 1.3, which is large enough to have some population effect but not large enough to be clinically meaningful in individual cases.

The first genomewide significant linkage and association findings were largely negative, resulting in the discovery that there were no common markers of major effect among the single nucleotide repeats available. Subsequent, more powerful studies suggest additional candidate genes, such as cadherin 13 (Lasky-Su et al., 2008; Poelmans, Pauls, Buitelaar, & Franke, 2011), but these will also not be of major effect. What is emerging is a picture in which ADHD, like many other complex traits, is not related to major effects of common gene variants but rather to aggregated small effects of numerous common variants, in relation to other types of genetic effect (see next paragraph).

The limited explanatory reach of the single marker studies has led to a problem noted as "missing heritability." That is, while the heritability of ADHD is estimated in the range of 0.7 or so, the individual SNP markers identified to date appeared to only account for a very small fraction (<5%) of that heritability. How was this to be understood? There are now

several possibilities emerging. I provide here my sense of how these are likely to play out, although new data could change the picture rapidly.

The first is that the effects of common variants have been underestimated by failure to consider their joint effects. Newer analyses that consider genes acting in concert (rather than individually) find a very different picture: a meaningful portion of the genetic variance is explained by common variants. Data from the ADHD collaborative group in the Psychiatric Genetics Consortium (5,621 cases, 13,589 controls) reveal a SNP heritability indicating that about 23% of genetic liability for ADHD is accounted for by *polygenic effects* (van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). That is, many common DNA variants partially underlie the etiology of ADHD (the same may prove true of many complex traits).

A second possibility is that the common variants included in studies to date are not the main genetic factor in ADHD; instead, rare variants (e.g., copy number variants), some of which may be new (*de novo*) mutations in particular families, may be more important (Grayton, Fernandes, Rujescu, & Collier, 2012). Rare variants can have large effects in individual cases, but because they are rare in the population, each individual variant provides only a small explanation of the overall incidence of a disorder. It is unclear what proportion of developmental disorders could ultimately be explained by numerous distinct rare mutations, but it will probably remain a minority of cases. Thus, both common and rare variants in combination will likely account for structural aspects of genetic liability to ADHD.

At the molecular level, genomewide studies looking at single genetic markers are being supplanted by focused sequencing studies and metabolic pathway analyses. The latter in turn are likely to be heavily contextualized by molecular epigenetics and other gene-expression studies in the next few years (Grigorenko & Cicchetti, 2012). However, the key issue for accounting for remaining aspects of heritability will likely hinge on a fresh understanding of environmental effects in relation to Gene  $\times$  Environment ( $G \times E$ ) interactions and epigenetic mechanisms. I therefore consider those in more detail later when I discuss future directions.

## Neuroimaging

Almost all of the genes of interest, and most genetic theory in general for ADHD, are related to genes expressed in the brain. Thus there is considerable interest in neural markers that might assist with understanding pathophysiology and, eventually, be connected up with specific gene or environment etiologies. Neuroimaging findings represent a dramatic development in the study of developmental psychopathology in the past 25 years. The brain develops rapidly and dynamically in the first weeks, months, and years of life, and is therefore likely uniquely susceptible to perturbations early in development. Thus, understanding how the brain is altered during development may provide important clues to mechanisms of developmental psychopathology. This is certainly the case for ADHD, which has been thought for over a century to involve some subtle brain alterations.

Twenty-five years ago, structural magnetic resonance imaging (MRI) studies of ADHD were rare, and functional MRI studies of child psychopathology did not yet exist. The literature today has matured to the point where major reviews and meta-analyses can draw on dozens of studies involving thousands of participants to show numerous structural and

functional neural correlates of ADHD across age (Cortese et al., 2012; Dickstein, Bannon, Castellanos, & Milham, 2006; van Ewijk et al., 2012). Castellanos et al. (2002) attempted a lag-longitudinal analysis spanning ages 4–18 looking at brain structural volumes. Simple volumetric differences between ADHD and non-ADHD children were present by age 4 years, and the group difference was stable in magnitude during that period of time. Thus, ADHD is associated with early emerging and enduring alterations in structure and function of particular neural circuits. Subsequent studies of the same cohort suggest that additional nonlinear differences in aspects of brain growth are also occurring in ADHD (Shaw et al., 2006), but they do not change the fundamental conclusion that ADHD is associated at a group level with early changes in the brain.

Dramatic changes have marked this literature and have changed the way research and conception of ADHD is approached. Twenty-five years ago, functional MRI studies of child psychopathology did not exist (they began in the 1990s). They are now commonplace if not normative in the research field. New imaging technologies continue to take hold, highlighting the complex interconnectivity in the brain as a new focus. Diffusion tensor imaging studies of white matter tracts in ADHD have exploded in just the past 5 years. They illuminate a startling realization: alterations are apparent not only in targeted brain regions but also in circuitry throughout much of the brain (Castellanos & Hyde, 2010; Konrad et al., 2010; Konrad & Eickhoff, 2010; Nagel et al., 2011; van Ewijk et al., 2012), raising new questions about the developmental roots of ADHD.

On the brain function side, researchers have focused on task-related brain activations for most of the past two decades, helping clarify alterations in task-related brain function (Bush, 2011). For example, the neuroimaging literature has grown large enough to allow powerful meta-analyses, which confirm that ADHD is associated with alterations in functioning of neural regions in the prefrontal cortex, as well as the posterior cortex and subcortical structures consistent with alterations in the maturity of frontal control neural networks as well as cortical–cortical neural networks associated with distinct forms of attention (Cortese et al., 2012). Further, functional data support the idea that ADHD involves alterations in functioning of ascending dopaminergic systems, although this is neither specific nor sufficient to explain ADHD (Gatzke-Kopp, 2011; Kollins et al., 2008; Volkow et al., 2011). Other neuroimaging data have demonstrated well-replicated alterations in how the brain responds to task demands in samples with ADHD, with particular alterations in frontal–striatal–thalamic circuitry (Bush, 2011). New methods, like single-proton emission computerized tomography, optical imaging, and others, are sure to continue to advance the frontiers of brain description in ADHD and other developmental conditions.

However, a further comment on brain function is of interest. Until recently, the massive background activity of the brain in between experimental task conditions was ignored in functional imaging studies. In the past decade, neuroscientists realized that the spontaneous activation patterns of brain regions that were not in any obvious way “in use” had recognizable patterns. Mapping of these synchronized neural oscillations across the brain at rest via functional MRI then began in earnest for many behavioral traits and conditions, including ADHD (Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008). Such

studies in relation to ADHD or other mental disorders were exotic only 5 years ago; now they are a common strategy of research.

In summary, the past generation has seen dramatic technological developments and thus a rich and exciting descriptive database of neural correlates of ADHD. These data have brought much greater specificity and nuance to conceptual understanding of how ADHD may develop and how alterations in brain development may relate to the syndrome. At the same time, this new field is still growing. It is important to note that brain imaging effects, like genetic findings, are visible in group data but are still too small to be clinically applicable: they cannot pick out individuals with ADHD or with reliable biological subtypes of ADHD. I return to this issue of individual clinical application when considering the future, below.

### Neuropsychology

The cognitive and neuropsychological characterization of ADHD has been heavily enriched in the last 25 years by increasingly sophisticated use of experimental paradigms imported from experimental psychology. Twenty-five years ago, the field was engaged in pursuing the critical idea that attention, rather than hyperkinesis, might form the core of the ADHD syndrome. A wealth of experimental studies in the 1980s and 1990s applied sophisticated attentional measures. The upshot of this literature was a sharp clarification of the kinds of attention that are affected and apparently not affected in relation to ADHD.

**Arousal and alertness**—Contrary to what is sometimes believed, several kinds of attention are normal or, at best, debatable as deficits in ADHD, including perceptual selection and interference control (Huang-Pollock & Nigg, 2003; Huang-Pollock, Nigg, & Carr, 2005).<sup>1</sup> However, one kind of attention with which ADHD is associated is *alertness*. Alertness pertains to one's ability to be vigilant, to sustain focus, and to notice changes around himself. It is sometimes seen as related to tonic cortical arousal and changes in slow wave electroencephalographic signaling from scalp electrodes (Loo & Makeig, 2012). At the extremes, alertness is defined by sleep or coma versus panic or rage. When defined this way, contrary to how they may at first appear, children with ADHD are more often under- than overalert (Barry, Johnstone, & Clarke, 2003). This effect was actually relatively well recognized in the 1970s, but it has continued to be refined by evolving understandings of the related concepts of energy, effort, arousal, alertness, and motivation. Neurobiology of right-lateralized brain attention alerting systems are better understood and seem to conform to the pattern of effects seen in ADHD at the group level.

**Executive functioning**—During the past 25 years, a major theme in ADHD neuropsychology has been the improved specification of the role of executive functioning. Classically, executive functioning was equated in a somewhat circular manner with the operations of the frontal lobes of the brain. Over the past 25 years, the specification of operations within this domain has advanced dramatically. The field now benefits from carefully designed paradigms to assess verbal and spatial working memory, response

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<sup>1</sup>A few studies have suggested this statement may be overturned, but they tend to rely on extremely high cognitive loads, leaving some question as to whether the problem is perception/attention or cognitive control.



interference, task switching, response suppression or response inhibition, and planning. While these components cannot be fully isolated, experimental paradigms can isolate them partially with an eye toward finding differential profiles in ADHD. The upshot of this literature in the past 25 years has been an overwhelming documentation of the association of ADHD with problems in executive functioning (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008), so much so that some observers have considered the disorder or, at least, the inattentive symptom domain as primarily an issue of disturbed executive functioning.

However, despite the consistent findings at the group level, these effects are modest in size (amounting to  $<1 SD$  between groups). Clinical applicability thus remains uncertain, at least with regard to diagnostics. Nigg, Willcutt, Doyle, and Sonuga-Barke (2005) illustrated this with a reminder that, at this effect size, less than half of individuals with ADHD would have an abnormal score on a given neuropsychological or executive function test. Thus, either neuropsychological data will remain useful only as an ancillary clinical descriptor or they will eventually help to describe neuropsychologically distinct subtypes of ADHD. They will not, however, reliably diagnose the currently defined behavioral syndrome.

A key remaining question concerns whether isolating component operations is the right strategy. This is because in real life executive function problems are seen in the inability to assemble complex behavior over time, something that is not captured well in a single experimental task. For example, in a planning context (carrying out a recipe, organizing a party, or doing long division), individuals with ADHD may have difficulty carrying out the steps in the correct sequence, resulting in inaccurate and inefficient performance. However, this could be due to breakdowns in any of the component operations or to problems in coordinating the component operations.

**Temporal discounting, reward delay, and time estimation**—Another idea that has pervaded the ADHD literature for more than 40 years concerns the interplay of judgments of time and evaluations of rewards. This idea, as well, has been refined and now more well articulated in relation to distinct neurobiology over the past 25 years. What is interesting is that this focus in the past decade has tended to shift the field away from attention and toward impulsivity as the “core element” of the ADHD triumvirate of inattention, hyperactivity, and impulsivity. Impulsivity is classically seen as being related both to overvaluing of immediate rewards and to inaccurate evaluations of time. Advances in cognitive neuroscience that seemed to locate some types of internal clock in the cerebellum sparked renewed interest in the relation of time processing to impulsivity, so that reward valuation and time estimation are quite interrelated.

The evaluation of potential rewards and the matching of consequences to behavior entail both an affective response to (spontaneous activation to a cue) and cognitive computations (magnitude and temporal properties) of the potential reward or consequence of an action. Learning and maximization of behavioral pay-off both require accurate evaluation of temporal and magnitude linkages. These evaluations happen continuously during learning and behavior. In ADHD, in the presence of cues for reward or incentive, immediate rewards are given disproportionate weight over larger but later rewards (Luman, Oosterlaan, & Sergeant, 2005).

Consistent with older literature on impulsivity, work in the past two decades on ADHD has confirmed that in contexts in which time judgment is relevant to learning or decision making, temporal information processing is altered, with a tendency to overestimate time intervals (Toplak, Rucklidge, Hetherington, John, & Tannock, 2003). It probably represents a distinct cognitive finding from that involved in the evaluation of reward salience. The reason for this is that reward salience is increasingly understood as involving dopaminergically enervated limbic–frontal circuitry in the brain. In contrast, the evaluation of time intervals likely involves complex interplay of cerebellar–frontal circuitry. These two circuits may be involved in some yet to be defined combination in ADHD-type impulsivity.

**Emotion**—Finally, an interesting dynamic in the field of ADHD-related neuropsychology currently concerns the interplay of cognitive control with emotion regulation. Over the past 25 years, the study of emotion has become tractable for the first time, and this has opened the door for new investigations that can integrate emotion processing and cognitive processing in psychopathology. This opportunity is extremely important. Clinical observation makes clear that individuals with ADHD have problems not only in planning or memory but also in managing anger, sadness, frustration, or excitement. Neuroscience likewise makes clear that the neural systems that subserve cognitive control are also very closely related to the neural systems that subserve emotion regulation (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Shackman et al., 2011). Integrating these operations in our conceptual formulations is critical to modeling actual behavior in the case of individuals with ADHD (Nigg & Casey, 2005).

### **Caveat: Treatment**

Unfortunately, all this progress must be accompanied by tempering of enthusiasm. Neuropsychological assessment has become better, but in the case of ADHD, it is only secondarily helpful in treatment planning, not in diagnosis. Neither neuroimaging nor genetics has yet much benefitted clinical practice (although this may soon change; some clinicians have already begun routine genetic testing in cases of autism owing to progress in that disorder's genetics). Changes in clinical practice in the past generation reflect efforts to incorporate findings from neurobiology, yet their impact on clinical practice remains quite limited.

First, medication treatments were altered by the introduction around the turn of the 21st century of new molecular delivery methods for stimulant medication, with a handful of incrementally different medication compounds. These treatments have numerous practical advantages, including once daily dosing, fewer side effects, and reduced drug rebound effects.

Second, there has been increasing formalization of behavioral treatments of various kinds. Behavioral management is better systematized in relation to anger, defiant behavior, and the like. In addition, behavioral strategies borrowed from rehabilitation psychology have begun to infiltrate educational and occupational planning for individuals with ADHD. These improvements, while lacking in much formal outcome study, seem likely to be incremental but meaningful.

Third, there has been an explosion of interest in the potential for new treatment modalities. Biofeedback techniques (with names such as neurofeedback) have come back into vogue. These have been commercialized widely despite limited evidence of their efficacy (Moriyama et al., 2012). However, the literature remains promising, and further study of these techniques with appropriately controlled experiments may yet bring them into the treatment mainstream. The same holds for computerized cognitive training methods, which have previously been helpful with focused skills like reading and memory. These may help working memory, but the hope that this would lead to reliable change in ADHD symptoms has yet to be realized (Melby-Lervag & Hulme, 2012; Rutledge, van den Bos, McClure, & Schweitzer, 2012). The picture is only a little more promising for restriction diets and nutritional interventions. Work in this area essentially stopped in the United States over the past generation, but it continued in other nations. The development of meta-analyses has allowed a fresh look and, combined with new and larger trials, suggests there may be real promise for a meaningful proportion of children with ADHD (Hurt, Arnold, & Lofthouse, 2011; Nigg, Lewis, Edinger, & Falk, 2012; Stevens, Kuczek, Burgess, Hurt, & Arnold, 2011).

Fourth, perhaps most sobering has been the completion over the past 20 years of a major multisite, multimodal treatment study of ADHD that compared state-of-the-art medication and behavioral interventions. Although both kinds of intervention and their combination were quite effective when done properly (and much more effective than “treatment as usual” in the community), long-term follow-up indicates that none of the changes caused by treatment are enduring (Molina et al., 2009). The alternatives in turn have some distance to go before they can change mainstream practice. Thus, whereas continued work on experimental treatments is a priority, the need remains acute for a more fundamental understanding of this syndrome in order to inform entirely new ideas of treatment or prevention of ADHD. For that reason, I focus my future-oriented remarks on etiology and related issues rather than on the aforementioned and interesting treatment research that is going on and that remains very important in the near term.

## Looking Ahead

In this rapidly evolving context, few “big” etiological issues are specific to any one mental disorder; instead, the same issues tend to cut across all mental disorders. With that in mind, what are the core issues for the next 25 years or more, for understanding the roots of ADHD and other conditions like it? I selectively emphasize three themes, which may apply to research on psychopathology generally: informatics and statistics; epigenetics and developmental origins, which intersects with changing contexts of development and research, and thus underscores the value of a developmental psychopathology perspective; and last but not least, phenotype parcellation.

## Informatics

When we consider the future of work on the etiology of ADHD (and perhaps eventually its treatment or prevention), it is difficult to ignore changes in science itself. Research in psychopathology takes place against a backdrop of dramatic advances in physics, molecular biology, computer science, mathematics, and (not discussed here) the communications and

technology environment in which children live. These have not only changed how research is done but are probably also changing the phenomenon being studied through alterations in how society is organized and how it socializes its members through the technologies embedded in it. Whether new technologies will revolutionize understanding, and thus the quality of life for afflicted children, remains to be seen. However, it will be necessary to make the attempt.

Advances in mathematics, statistics, computational science, and informatics are changing the way research is done in all fields, including developmental psychopathology. Exponential increases in computer power have rendered possible mathematical and statistical simulations, and as a result, we have advances in statistical methods that were infeasible even a decade or two ago. These advances have made it possible to model neural networks, to simulate human decision making and map it mathematically, and to begin to contemplate the daunting challenge of analyzing the billions of data points embedded in the human DNA sequence. Tools such as advanced mixture modeling, machine learning algorithms (e.g., the support vector machine), Bayesian prediction, graph theory modeling of community metrics in brain organization or in social organization, permutation and simulation testing of true Type I error probability (replacing the crude and now outdated simple  $p < .05$  rule), item response theory analysis, and real-time worldwide data sharing are all rapidly becoming the norm in cutting-edge psychopathology and neuroscience research, all moved from exotic to accessible by advances in computing. Looking ahead a decade or two, it is now possible to imagine a diagnostic algorithm guided by a trained machine (informed by all known diagnostic instruments and all known data on those instruments) that can have hundreds of steps yet reach an accurate and valid psychiatric diagnosis in only a few minutes, asking only a few questions. Future research that is distinguished from the past will likely make routine use of these newer mathematical and statistical modeling tools.

In the past 25 years, and with the advent of DSM-5, one of the biggest disappointments has been that dramatic technical and scientific advances have been so difficult to apply in transformative ways to clinical practice in relation to psychopathology. However, the growing concentration of technical advances in multiple fields, the permeability of disciplinary boundaries, and the sheer recognition of the need and opportunity all conspire to suggest that the next 25 years have reason to maintain the hope of the last 25 for fundamental advances.

### **Epigenetics, developmental origins, and renewed interest in environments**

Here, I first consider genes and environments. Twin and adoption studies over the past 60 years have steadily established that mental disorders (and most behavioral traits) are heritable; the past 25 years have shown that ADHD is among the most heritable phenotypes. Until recently, the general assumption was that these genetic effects reflected the structure of DNA and thus were “inborn” or “hardwired.” Often forgotten were two crucial facts. The heritability term contains an unknown amount of variance owing to  $G \times E$  interaction (Purcell & Sham, 2002).  $G \times E$  has now become a crucial focus of research in its own right (Rutter, Moffitt, & Caspi, 2006) and established in psychopathology, even in the absence of gene main effects (Karg, Burmeister, Shedden, & Sen, 2011). The limited evidence to date

suggests  $G \times E$  operating in ADHD as well (Nigg, Nikolas, & Burt, 2010). Those studies used candidate genes and measured key environmental variables. More studies of that nature will be of interest, and the concept of  $G \times E$  itself needs to be enriched further by development of the idea of Gene  $\times$  Phenotype interactions (Deyoung & Clark, 2012).

$G \times E$  interactions may be implemented by stable changes in gene expression. Thus, crucial to recognize is that there is more to the genome than the structural DNA, the part of the genome that is fixed at conception and (for purposes of this discussion) does not change thereafter. In the past few years, it has been more well recognized that the genome contains vast information beyond what is in the structural DNA. This additional information is regulatory: it determines whether genes are turned “on” or “off,” that is, whether they are expressed (for summaries and reviews of principals of epigenetics, see Allis, Jenuwein, & Reinberg, 2007; for discussion of relevance to psychiatric disorder, see Kubota, Miyake, & Hirasawa, 2012). While all behavior and learning requires, by definition, temporary change in gene expression (e.g., more or less protein production), some gene regulation changes persist over time. They are “inherited” from one generation of cells to the next during cell division. Such changes are termed epigenetic.

Much of the regulatory information is carried in the nucleosome embedded in the chromatin, in which the DNA exists. For example, the nucleosome contains regions, amino-(N)-terminal “tails,” which in turn carry extensive markings, including methylation, acetylation, and many others (Riccio, 2010; Van den Bergh, 2011). Five fundamental discoveries about epigenetic processes may revolutionize how medicine thinks about therapeutics and how psychopathologists think about prevention in coming decades.

First, epigenetic effects are potentially powerful; they can markedly change a phenotype (behavioral or physical outcome). Second, epigenetic changes can be stimulated by experiences, such as exposure to environmental toxicants, changes in dietary health, or major stressful events (a direct mechanism of Gene  $\times$  Environment interaction). Those experiences, in other words, can make permanent changes in what genes are turned off or turned on, creating permanent changes in how the body (and thus the brain, and thus behavior) operate. Third, epigenetic changes can be inherited across mammalian generations, meaning that what the mother experiences during pregnancy can influence the behavior of her granddaughter via changes in the genome. Fourth, when combined with work using adult stem cells (e.g., taken from an individual’s skin), scientists can, in principal, determine how neurons are regulated in individuals with particular disorders (a line of work very active in cancer and still nascent in neuroscience). Fifth, and most crucial, in some instances epigenetic effects can be completely reversed either via new experiences or, recently, via synthetic means (Haynes & Silver, 2011).

These discoveries necessarily place a new focus on early (prenatal) development, on environmental sources of brain and endocrine development and thus psychopathology, and on the potential to explain *how* environmental effects work, while opening previously unimagined possibilities for explaining mechanisms and designing preventions. Despite its emergence in basic science decades ago, to date, the harnessing of epigenetics in human health research is still very new: nearly all epigenetic work has been on model organisms

and/or on target tissues (e.g., liver, kidney, or a particular and small brain region). However, work in humans, using peripheral tissues that are correlated with expression in other tissues including the brain, is now beginning. In all, it is now possible to imagine (perhaps decades or even centuries from now) a drug, perhaps containing a nanobot, that would change an epigenetic mark and, in so doing, change a medical condition or even cure a psychiatric disorder with a single dose. Scientific as well as legal, ethical, and moral questions arising from such possibilities are potentially profound and will come upon the psychopathology field sooner than we may expect.

**Prospects**—Thus, forward-looking interest is quite strong in health-related epigenetics, defined as the study of which methyl marks and other regulatory indicators are altered by particular experiences and early environmental exposures in relation to human development (Gluckman, Hanson, & Low, 2011). While much of the work relevant to brain development necessarily has been conducted with nonhuman model species, that situation will change if relevant markers in peripheral tissue can be related to markers in the brain. This potential has already begun to revive and accelerate the hope for discovering powerful environmental influences in the onset of ADHD, which may operate via epigenetic mechanisms. This line of thought represents the outgrowth of the past decade's extensive discussions of gene by environment interactions in psychopathology.

Thus, the first fundamental future direction is the recognition that ADHD *is not necessarily a genetic condition* in the simplistic sense previously believed. This overturns some assumptions of the past 20 years. Rather, although ADHD certainly does arise in part from genetic influences, it may very well be heavily influenced by early experiences, perhaps and even probably prenatal experiences, which alter gene expression and do so to varying degrees in susceptible individuals (Belsky & Pluess, 2009; Dominguez-Salas, Cox, Prentice, Hennig, & Moore, 2011; Mill & Petronis, 2008). Further, growing appreciation of the early developmental origins of disease (via programming effects prenatally, effects which can occur via multiple mechanisms including epigenetic change) are increasing the emphasis on understanding prenatal developmental influences on brain and behavior (Sandman, Davis, Buss, & Glynn, 2011; Swanson, Entringer, Buss, & Wadhwa, 2009). The exploration of early environmental effects and their interplay with the genome, and the use of genetic tools to validate those environmental effects, will be a crucial direction in the coming decade in ADHD research.

**Issue of environmental causality**—A *risk factor* is correlated with future onset of disease, but it may not be causal. An *etiological factor* is causally related to future disease. Whereas early developmental risk factors for ADHD have been documented for some time, those findings were often dismissed as a potential artifact of gene–environment correlation. At times, it may be that too few studies have used causally informative designs. An object lesson comes from studies of maternal smoking and ADHD in offspring. Prospective data long suggested that maternal smoking predicted offspring ADHD (Linnet et al., 2003). Recently, two studies used clever designs to test a causal interpretation of those data. One study looked at surrogate mothers who were related and unrelated to their offspring (Thapar et al., 2009). Another looked at sibling pairs discordant for maternal smoking (D'Onofrio et

al., 2008). Both called into question whether maternal smoking plays an important causal role in ADHD.

However, that object lesson notwithstanding, smoking is an unusual risk factor because it is strongly associated with maternal behavior and thus maternal psychopathology, so it becomes at least partially a behavioral marker of family genetic risk. Other exposures, particularly those that are nearly universal in a population, are less likely to be artifactual markers of genetic risk. Several correlational studies in the past decade have confirmed a correlation of ADHD with elevated levels of blood lead, even when those blood levels are well within the currently accepted safe range (<5 µg/dl; Braun, Kahn, Froehlich, Auinger, & Lanphear, 2006; Nigg et al., 2008; Smeester et al., 2011). Prospective population studies in the past 5 years now identify prenatal or early life exposure to classes of household pesticides as nearly universal in the population, and as risk factors for ADHD and for subtle delays in cognitive development (Sagiv et al., 2010; Xu et al., 2011). Further, these effects are modulated by genotype, because the paraoxynase 1 gene regulates metabolic processing of organophosphates (Engel et al., 2011), supporting a causal role. Toxicological exposures have demonstrated epigenetic effects (Smeester et al., 2011). Further causally informative studies of these exposures, of the sort done for maternal smoking, will be crucially informative to worldwide concepts of how to prevent developmental disorders.

Another provocative possibility is that the food we eat is related to ADHD. This is not a new idea, but it has not heretofore been taken seriously as a major explanation for ADHD. This may yet change. Dietary additives were occasionally suggested as the culprit in children's adjustment for nearly 100 years, and in the 1970s, Feingold (1975) made a specific proposal that reactions to food, and particularly to additives like artificial food coloring, might cause ADHD in some youngsters. This general idea appeared disproven at first (Kavale & Forness, 1983), then as studies accumulated it began to seem the idea might have some basis (Schab & Trinh, 2004). A recent meta-analysis indicates that experimental studies of causal effects support a small effect of either food colors or other additives. More striking in that review was that double-blind placebo-controlled studies do suggest that changes in diet can alter ADHD symptoms markedly in a substantial minority of affected children (Nigg et al., 2012). Nonetheless, controlled studies are few and badly outdated; renewal of research in this area will be needed to assure conclusions.

More important than food intake during childhood, however, may be the growing appreciation of the importance of prenatal nutrition and placental health, and before it, maternal health, in shaping neural development of children. Primate studies have demonstrated that maternal diet causes changes in offspring temperament (Sullivan et al., 2010; Sullivan, Nousen, & Chamlou, 2012) independent of offspring diet. This lends weight to human prospective and experimental data that maternal diet may predict offspring ADHD (Colombo et al., 2004; Gale et al., 2008). There are again initial hints that gene by environment interaction is involved (Stevenson et al., 2010).

In the prenatal period, there is already intriguing evidence that maternal emotional stress may influence offspring temperament and behavior, perhaps even influencing onset of ADHD (Harris & Seckl, 2011). All of the studies to date are too small to shed light on

population-wide effect magnitudes or to be sure they are not isolated findings. The potential in this direction of work is obvious. It will be of interest to determine whether these associations are causal, have epigenetic mediators, or share common downstream mechanisms (e.g., immunological or inflammatory response). Of interest will be studies that properly integrate prenatal risk factors, epigenetic mechanism, and brain development.

**Summary**—Overall, a key future direction will be to harness growing appreciation of the mechanisms of prenatal health and very early neural formation, and to replace simplistic gene main-effect models with dynamic models of genome adaptation in response to experience, including potential sensitive periods early in life when epigenetic marks may be more plastic than later. At a broader level, this future direction will entail a deeper appreciation of how human development involves adaptation to expected and actual environments, in the context of genetic susceptibility. Fine-grained understanding of environmental inputs will in turn open the door in the longer term for more ambitious attempts at prevention.

### Cultural and historical contexts of development

Fine work on epigenetics, neuroscience, or probability modeling all may fail, however, if done without appreciation of developmental context, both historical and cultural. First, cultural variation in how ADHD is expressed, in its biological correlates and in its behavioral structure, has hardly been studied. To the extent that ADHD is an entity that can yield to a search for biomarkers, this absence of true cross-cultural comparative work presents a crucial obstacle. Second, the sociocultural context itself is dynamic: it is itself changing as populations, technology, beliefs, and family life changes. The few studies on these topics to date provide a complex initial picture.

**Race, ethnicity, and culture**—In the United States as well as worldwide, the racial and ethnic composition of societies is rapidly changing, rendering prior era research potentially of limited value if it did not examine these populations. How does this affect ADHD? The factorial structure of ADHD, like the general structure of common psychopathology (or at least, of common childhood problems) appears to be to a large extent universal across a wide range of cultural and racial groups (Bauermeister, Canino, Planczyk, & Rohde, 2010). Likewise, measurement and structural invariance were supported when comparing Malaysian parent ratings to those of Australian (Gomez, 2009) and American parents (Burns, Walsh, Gomez, & Hafetz, 2006), although not when comparing African American and Euro-American youth (Reid et al., 1998).

However, important race and cultural effects seem to occur when it comes to assessment. For example, there is a tendency for African American children to be rated as having more behavior problems than do Caucasian American children (Epstein, March, Conners, & Jackson, 1998; Miller, Nigg, & Miller, 2009) but to less often have ADHD (Kessler et al., 2006). However, recent data (Frazier et al., 2011) suggest that African American youth are now about as likely as Caucasian American youth to be diagnosed and treated for ADHD, unlike data just a few years earlier.



Further, it appears that race of child and of examiner interact to influence ratings of ADHD severity (Mann et al., 1992). That striking experimental study has yet to be followed up, despite its potentially profound importance to practice and theory. Virtually nothing is known about patterns of comorbidity, risk, protection, and treatment outcome across cultures (Canino & Alegria, 2008). A critical limitation in all of these studies is their small samples, lack of replication, and uncertain generalizability. More work on the cultural generalizability of clinical description (the structure of the behavioral profiles) and of neurobiological findings will be crucial in order to support fundamental insights into the etiology of ADHD and to ensure culturally appropriate treatment approaches.

**Historical-cultural effects on environment health and development**—Moreover, as cultures converge throughout the world through globalization, historical context may become especially important in coming decades. As elegantly summarized by Taylor (2011), it is only in the last 200 years or less that Western societies have compelled nearly all children to attend school. As noted by Keverne (2011), in the last 50 years, the Western diet has diverged especially dramatically from what the human organism might have expected based on the evolutionary past. Obesity, which was rare in the United States 40 years ago, is now very common. Individuals with ADHD may be particularly prone to it (Cortese & Morcillo Penalver, 2010), suggesting the possibility of a new outcome risk related to changing societal context that did not exist a few years earlier. In the past 10 years, social media have again transformed the experiences of children at least in the developed West, who now routinely spend amounts of time in front of electronic screens that were unthinkable just one generation ago. The effects on attention, cognition, language, and social relations are surely complex and as surely are scarcely understood. Once again, it may be that particular individuals are less able than others to successfully adapt to these rapid contextual changes during development.

Overall, the study of the changing developmental context of children, including consideration of technology, culture, and race, will be an essential complement to neurobiological studies. Understanding of these contexts will also be essential to successful translation of insights about etiology and prevention into clinical care.

### **The phenotype, heterogeneity, and clinical diagnostics**

Most fundamental to future directions is the question that geneticists and neuroscientists must ask: what is the phenotype? Clinical psychology, cognitive and affective neuroscience, statistics, and mathematics will all be crucial. Here, I bypass incremental improvements that are nonetheless important in the immediate future for ADHD, such as appropriate symptom sets for adults and preschoolers, refinement in the dimensional structure, and age and impairment criterion. Instead, I focus on the fundamental conceptualization of the phenotype.

Two complementary schools of thought have characterized clinical phenotype analysis for decades: focus on category or focus on dimension. Like the wave and particle theories of light, both perspectives are useful and informative for addressing different aspects of the phenomenon. These two traditional approaches have each become more sophisticated. The

dimensional approach, presently coming into vogue at the National Institute of Mental Health via its Research Domain Criteria initiative (Sanislow et al., 2010), in its current form seeks to identify dimensional, transdiagnostic phenotypes that can be correlated with neural or genetic activity and thus provide clues to structure of psychopathology (for an accessible overview of this logic, see Nolen-Hoeksema & Watkins, 2011). Although consensus on these fundamental dimensions has not been achieved, several dimensions appear to have strong support. Will ADHD prove to be better understood as an extreme on a core dimension of incentive approach? Will these dimensions reach consensus and replace research on the much-maligned (and apparently excessively numerous) DSM disorders?

Such fundamental questions fuel a need for further integration of psychopathology, and personality and temperament (for extended discussion and definitions, see Nigg, 2006). The field of personality psychology has begun to converge on consensus behavioral dimensions that appear to have neurobiological validity, although the precise neurobiology related to these basic dimensions is still in dispute. These dimensions include an anxiety/fear dimension, an appetitive/approach dimension, and a regulatory or effortful control dimension. The first two dimensions are readily modeled and studied in nonhuman animals, whereas the control dimension can only be partially modeled in nonhuman animals. An affiliation dimension also appears robust on humans, although animal analogues are fraught with the challenge of translating to the human sociocultural milieu. Each of these is now related to particular biomarkers and may become a target for alternative formulations of psychopathology. In the case of ADHD, a small body of literature maps its relation to these fundamental trait dimensions (Martel, Nigg, & Lucas, 2008; Martel, Nigg, & von Eye, 2009; Nigg et al., 2002), setting the stage for considering this type of dimensional approach.

Further, a major achievement in the past 25 years is the clarification that ADHD is at least a two-domain condition. A recent meta-analysis (Willcutt et al., 2012) documents the reliability of different effect sizes associated with a wide range of correlates that differentiate the behavioral domain of inattention–disorganization and that of hyperactivity–impulsivity. Another recent meta-analysis (Nikolas & Burt, 2010) clarifies that these two symptom dimensions have partially distinct genetic inputs. These two analyses cement perhaps the most fundamental advance in ADHD phenotype definition in the last generation: the confirmation that it has at least a two-dimensional structure. That two-dimensional structure may reflect a shared underlying liability of some type, and new modeling techniques continue to explore factor models such as the bifactor models (Martel et al., 2009), to clarify how and why these two distinct dimensions so stubbornly co-occur.

These two dimensions have been extensively theorized about, in regard to particular neural systems and in regard to a variety of dual-process models. The increasingly dominant dual-process models all have in common the fundamental distinction (outlined for a nonspecialist audience very well by Kahneman, 2011) between relatively automatic processes and relatively intentional (requiring mental resources) regulatory processes. Correctly characterizing these two dimensions in regard to neuroscience, factor structure, personality, and optimal assessment will remain important in identifying phenotypes for ADHD research. In addition, it may yet be possible to identify additional or refined dimensions. For example, debate continues about a domain of sluggish or low-energy behavior that is

positively correlated with inattention and hyperactivity (Barkley, 2011, 2012; Bauermeister, Barkley, Bauermeister, Martinez, & McBurnett, 2011). Impulsivity, which is a multidimensional construct (Nigg, 2000; Whiteside & Lynam, 2003), is still surprisingly poorly characterized in relation to ADHD. Irritable and negative emotion related behaviors remain in need of investigation (Leibenluft, 2011).

Further, as noted earlier, the past 25 years have seen extensive work on the neuropsychology of ADHD. To recapitulate, this work has accomplished several things. We now know that at a group level, ADHD is associated with reliable and robust alterations in working memory, response inhibition, response variability, temporal information processing, and executive functioning (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). However, these effects are too small to be of diagnostic use, despite providing some characterization of learning style that may assist with treatment and educational planning in individual cases. Further, they have not yielded the hoped for breakthrough with regard to endophenotype signal (much stronger genetic signal), even though several of these measures are familial and do appear in unaffected relatives. Further work on refining the cognitive measures in the laboratory will remain important. For example, response variability and response time are central measures but are multiple determined (Karalunas, Huang-Pollock, & Nigg, 2012). Can alternative ways of modeling response parameters yield a cleaner measure for either clinical assessment of attention or even perhaps larger effect sizes in predicting back to etiology or forward to outcome? At the same time, more work on motivational and emotional components of ADHD will be central (Castellanos et al., 2005).

However, for all its many advantages, the dimensional approach has limitations. In particular, despite its versatility in mixing multiple dimensions to create profiles and in helping to quantify risk, it does not directly lend itself to identifying distinct etiologies, unique genotypes, or unique developmental histories that may result in different forms of a condition. It does not provide the distinctions needed to design differential prevention or intervention trials or to make treatment decisions. For that, one requires categorical decisions. Children with ADHD (or an associated configuration of traits) are not all alike. Methods of identifying homogenous groups remain extremely important. These can draw upon trait methods, of course, but also upon neuropsychological, cognitive, neuroimaging, and genetic measures.

The crucial element in finding appropriate types will be to determine the appropriate validation strategy. Investigators in the past have relied on statistical approaches like hierarchical cluster analysis or mixture models (also called latent class or latent profile analysis) to analyze ADHD. These approaches suggest types, but the types in turn appear to be encompassed by a simple severity classification (Frazier, Youngstrom, Naugle, Haggerty, & Busch, 2007).

Nevertheless, because of the aforementioned advances in computing, corresponding rapid progress in mathematical analysis of community structure, networks, and classification continues. When considered from the perspective of the many modeling techniques available, the appropriate parcellation of behavioral and cognitive measures of the ADHD or other psychopathology phenotypes has only scratched the surface. New studies of this

problem, using combinations of new methods including machine learning algorithms combined with genetic and neuroimaging validation, will be of considerable interest. The results will clarify what, if any, kinds or types are (a) robust to the selection of inputs and (b) valid in relation to genetic or other etiological signals.

## Conclusions

Dramatic advances in the technical and methodological tools available to psychopathological science raise striking possibilities for the next several decades of progress in understanding and preventing ADHD. However, to date, advances in genetics, neuroimaging, and other basic tools have not been translated into breakthroughs in clinical assessment or practice. In the medium term future, work on ADHD, as in many other mental disorders, is likely to see breakthroughs when several conceptual considerations are taken in hand together.

A developmental psychopathology perspective will become even more crucial, as the field attempts to integrate levels of analysis (genetics, neuroimaging, and environmental inputs), consider nonlinear developmental trajectories, and wrestle with the nature of adaptation versus mal-adaptation in domains of self-control and ADHD.

Several summary points thus commend themselves.

1. Description of the specific role of early environments on brain development and behavior, operating through epigenetic and other mechanisms, will replace an assumption of simplistic gene main effects.
2. The developmental context for children's development is changing rapidly within and across societies; failure to consider those contexts will limit the impact of biological discoveries in psychopathology.
3. Optimally characterizing the ADHD phenotype remains the enduring problem that has preoccupied ADHD research for the past several decades and will continue to do so, even as neurobiological and genetic findings accumulate.

Recognition of its bi- or multidimensional structure marks an important advance in the past generation. Further differentiation of the phenotype may be possible. Improved characterization of its mechanistic or etiological heterogeneity may prove as important in the next.

In conclusion, ADHD research has witnessed an explosion of information in the past generation that fits well with a multilevel, developmental psychopathology perspective. Because of the close relation of ADHD symptoms to normal-range self-control, the cross talk between normal and abnormal development may be particularly illuminating. A key disappointment in the past generation has been the limited extent of clinical application of new advances in genetic and neuroscience research. However, those fields are still very new and rapidly changing. Their utility will depend on appropriate integration with understanding of the clinical phenotype, and the environmental and social context of the behavioral syndrome, an integration for which a developmental psychopathology

perspective is most helpful. The next 25 years hold out the hope that exciting new information about the biological and social correlates of ADHD will be translated into new initiatives for prevention of ADHD and reduction of its costs to individuals and society.

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