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Future Directions in ADHD Etiology Research

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Abstract

Reviews salient emerging themes in the scientific literature related to identifying etiology and pathophysiology of ADHD. While bypassing the need for new treatment research, the review highlights three themes. First, recognition of the epigenetic effects is expected to revitalize the search for and mapping of early environmental influences on the development of ADHD. Second, neurobiological findings will have limited impact if not examined in the context of significant race and cultural variation in ADHD-related developmental processes, and in the context of rapidly changing social and technological contexts of children's development worldwide. Third, further examination of the phenotype and characterization of its dimensional and categorical structure remains a major need. Overall, the coming decades of etiology research on ADHD will be expected to capitalize on new scientific tools. The hope in the field is that new insights into fundamental prevention can emerge.

It is now exactly 200 years since Benjamin Rush (1812/1962) provided the first American medical description of extremely impulsive children 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 the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; American Psychological Association, 1980), officially revising and narrowing the older construct of minimal brain dysfunction. In a little noticed but conceptually profound change, *DSM-5* is proposing to categorize ADHD as a neurodevelopmental disorder—laying the groundwork for a conceptual bridge from its early conception as minimal brain damage to current and future recognition of the early developmental alterations in neurodevelopment that seem to characterize the syndrome. Apparent prevalence of ADHD has continued to climb in the past decade (Boyle et al., 2011), and the seemingly ever-more-frequent medical treatment of diagnosed children has spurred ongoing societal controversy for the past 40 years. The disorder is now recognized around the world.

Further, whereas ADHD is still sometimes dismissed by casual observers as a cultural construct or a symptom of weak parenting or unskilled teaching, the perniciousness of the disorder has become increasingly clear. Children (and adults) with ADHD are 50% (adults) to 80% (children) (nearly double) at risk of injuries requiring medical attention (Merrill,

Lyon, Baker, & Gren, 2009; Pastor & Reuben, 2006). When combined with mood or conduct problems, these individuals are at risk of suicide attempt and suicide (Agosti, Chen, & Levin, 2011; Impey & Heun, 2012). Mediated by their high probability of irritable aggression and conduct problems represent the main group of children who will go on to antisocial problems, substance use disorders, underemployment, divorce, and a range of interpersonal conflicts. ADHD also is beginning to show new associations with contemporary emerging health epidemics, particularly obesity (Cortese et al., 2008; Cortese & Vincenzi, 2012). However one explains ADHD, its developmental roots need to be understood. Its 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.

Encouragingly, in the past 20 years, we have witnessed dramatic discoveries related to etiology. For example, ADHD is associated with early emerging alterations in cortical development (Shaw et al., 2006). 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). On the genetic side, ADHD now has a half-dozen gene markers reliably identified with it (DAT1, DRD4, DRD5, 5HTT, HTR1B, SNAP25; Gizer, Ficks, & Waldman, 2009), and the first genome-wide significant linkage and association findings are emerging. Yet progress must also be accompanied by tempered enthusiasm. Neither neuroimaging nor genetics has yet benefitted clinical practice (although this may soon change; some clinicians have already begun routine genetic testing in cases of autism due to progress in that disorder's genetics). Furthermore, long-term treatment data indicate that, despite our ability to manage ADHD symptoms with a range of behavioral and pharmacological tools, in the long term treatment effects do not seem well sustained (Molina et al., 2009). Thus, whereas continued work on 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 remarks on etiology and related issues rather than on medium term directions in etiology-related research, and I bypass important directions related to treatment, psychosocial impacts, and course.

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. Advances in mathematics and informatics are changing the way research is done in all fields including developmental psychopathology. Exponential increases in computer power have rendered possible mathematical simulations, and as a result, advances in statistical methods, that were infeasible even a decade 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 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 and mathematics. 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 will have to make routine use of these newer mathematical modeling tools if it is to distinguish itself from work in the past, and this will cut across all of psychopathology and neuroscience.

Likewise, advances in neuroimaging and genetics continue to relativize prior findings decade by decade. Functional MRI studies of children were done for the first time in the 1990s; they are now normative in the research field. Yet 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 just in targeted brain regions but in circuitry throughout much of the brain (A. Konrad et al., 2010; K. Konrad & Eickhoff, 2010; Nagel et al., 2011; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012; Xavier Castellanos & Hyde, 2010), raising new questions about the type of developmental roots of ADHD that must be considered. 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). During that time, the massive background activity of the brain in between experimental task conditions was ignored. 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 (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.

Candidate gene studies of ADHD first began in the 1990s as well; they were soon supplanted by genome-wide association studies, and those in turn were 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 (see next).

Research in psychopathology thus now takes place against a backdrop of dramatic advances in physics, molecular biology, computer science, mathematics, as well as—bypassed here—the communications environment in which children live. These not only have changed how research is done but are probably 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 or not new technologies will revolutionize understanding—and thus quality of life for afflicted children—remains to be seen. But it will be necessary to make the attempt.

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 10 years, 25 years, or 75 years for understanding the roots of ADHD and other conditions like it? Three fundamental insights are likely to guide the next round of crucial discoveries.

EPIGENETICS AND DEVELOPMENTAL ORIGINS

Background

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; 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. First, that the heritability term contains an unknown amount of variance due to Gene $\times$ Environment interaction (Purcell & Sham, 2002). G $\times$ E interactions have now become a crucial focus of research in their 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.

G $\times$ E may be carried out 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 a recent text, Allis, Jenuwein, & Reinberg, 2007; for discussion of relevance to psychiatric disorder, see Kubota, Miyake, & Hirasawa, 2012). Although 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. 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”) that 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 large; 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 G $\times$ E 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 crucially, 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, on the potential to explain *how* environmental effects work, and open 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.

Thus, interest is very 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). Although, as noted, much of the work relevant to brain development necessarily has been conducted with nonhuman model species, that 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.

Prospect

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, 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. Because such validation would open the prospect of preventing ADHD before it ever begins, restoring full health to susceptible children, the field cannot afford to ignore this possibility.

Question of Environmental Causality

Whereas early developmental risks for ADHD have been documented for some time, those findings were often dismissed as a potential artifact of gene–environment correlation (rGE). Indeed, at times it may be: 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 that assumption. 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. 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 (less than 5 ug/dL; Braun, Kahn, Froehlich, Auinger, & Lanphear, 2006; Nigg, Nikolas, Knottnerus, Cavanagh, & Friderici, 2010; Nigg et al., 2008). 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 PON1 (paraoxynase 1) gene regulates metabolic processing of organophosphates (Engel et al., 2011). 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 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, Lewis, Edinger, & Falk, 2012).

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) 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). Once again, there are initial hints that $G \times E$ 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). It will be of interest to determine not only whether these associations are causal, and have epigenetic mediators, but whether they 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, 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, 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? On one hand, 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 as Reid et al. (1998) reported. Moreover, 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.

On the other hand, important race and culture effects seem to exist. There is a tendency, for example, for African American children to be rated as having more behavior problems than Caucasian American children (Epstein, March, Conners, & Jackson, 1998; Miller, Nigg, & Miller, 2009) but to less often have ADHD (Kessler et al., 2006). Further, it appears that race of child and of examiner interact to influence ratings of ADHD severity (Mann et al., 1992). 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 and neurobiological findings will be crucial in order to support fundamental insights into the etiology of ADHD.

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. Concurrently, obesity, 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, who now spend amounts of time in front of electronic screens that were unheard of a 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, 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

Most fundamental to future directions is the question that geneticists and neuroscientists will most want to know: What is the phenotype? Clinical psychology, 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. Both are needed for different purposes, and currently these two traditional approaches have each become more sophisticated. The dimensional approach, presently in vogue at the National Institute of Mental Health via its RDOC 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 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 dimension. An affiliation dimension also appears robust. Each of these is now related to particular biomarkers, and may become targets for alternative formulations of psychopathology. In the case of ADHD, a small body of literature maps its relation to these fundamental personality dimensions, setting the stage for considering this type of dimensional approach.

Further, it is now clear that ADHD is at least a two-domain condition. A recent meta-analysis (Willcutt et al., in press) documents the reliably 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 distinct genetic inputs. These two analyses cement perhaps the most fundamental advance in ADHD phenotype definition in the last 30 years: 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 and trifactor models, 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 behavioral regulation 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; Bauermeister, Barkley, Bauermeister, Martinez, & McBurnett, 2011). Impulsivity, itself 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).

However, for all its currency, the dimensional approach has significant limitations. In particular, despite its versatility in mixing multiple dimensions to create profiles and in helping 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. For that, one requires categorical decisions. Children with ADHD (or an associated configuration of traits) are not all alike. From a trait perspective, in fact, they can be grouped into two or three types (Martel, Nigg, & von Eye, 2009). 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 cluster analysis or latent class 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).

The near-term future direction here will probably entail utilization of newer tools, such as mathematical techniques derived from graph theory (i.e., modularity analysis using community detection algorithms) and machine learning (e.g., support vector machine), and then integrating these with the statistical methods to determine where convergent and divergent results pertain. 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 signal.

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.

First, 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. Second, 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. Third, correctly characterizing the ADHD phenotype remains the enduring problem that has preoccupied ADHD research for the past several decades and will continue to do so. Although more hard work on characterizing the phenotype is needed, recognition of its bi- or multidimensional structure is an important step forward in the last generation. Improved characterization of its mechanistic or etiological heterogeneity may prove as important in the next.

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