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ORIGINAL PAPER

Etiologic Subtypes of Attention-Deficit/Hyperactivity Disorder: Brain Imaging, Molecular Genetic and Environmental Factors and the Dopamine Hypothesis

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Abstract Multiple theories of Attention-Deficit/Hyperactivity Disorder (ADHD) have been proposed, but one that has stood the test of time is the dopamine deficit theory. We review the narrow literature from recent brain imaging and molecular genetic studies that has improved our understanding of the role of dopamine in manifestation of symptoms of ADHD, performance deficits on neuropsychological tasks, and response to stimulant medication that constitutes the most common treatment of this disorder. First, we consider evidence of the *presence of dopamine deficits* based on the recent literature that (1) confirms abnormalities in dopamine-modulated frontal-striatal circuits, reflected by size (smaller-than-average components) and function (hypoactivation); (2) clarifies the agonist effects of stimulant medication on dopaminergic mechanisms at the synaptic and circuit level of analysis; and (3) challenges the most-widely accepted ADHD-related neural abnormality in the dopamine system (higher-than-normal dopamine transporter [DAT] density). Second, we discuss possible *genetic etiologies of dopamine deficits* based on recent molecular genetic literature, including (1) multiple replications that confirm the association of ADHD with candidate genes related to the dopamine receptor D4 (DRD4) and the DAT; (2) replication of differences in performance of neuropsychological tasks as a function of the DRD4 genotype; and (3) multiple genome-wide linkage scans that demonstrate the limitations of this method when applied to complex disorders but implicate additional genes that may contribute to the genetic basis of ADHD. Third, we review possible *environmental etiologies of dopamine deficits* based on recent studies of (1) toxic substances that may affect the dopamine system in early development and contribute substantially to the

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etiology of ADHD; (2) fetal adaptations in dopamine systems in response to stress that may alter early development with lasting effects, as proposed by the developmental origins of health and disease hypothesis; and (3) gene-environment interactions that may moderate selective damage or adaptation of dopamine neurons. Based on these reviews, we identify critical issues about etiologic subtypes of ADHD that may involve dopamine, discuss methods that could be used to address these issues, and review old and new theories that may direct research in this area in the future.

Keywords ADHD (or Attention-Deficit/Hyperactivity Disorder) · Dopamine · Molecular genetics · Brain imaging · Environmental risk · Minimal brain dysfunction

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is defined by a combination of symptoms of inattention and hyperactivity/impulsivity (DSM IV, 1994), which restricts diagnosis to individuals who manifest psychopathology (defined by impairment) in these two domains. Since ADHD is considered to be a syndrome without necessary and sufficient behavioral deficits, the diagnostic criteria are stated so that not all symptoms within a domain are required to be present, and the presence of sufficient symptoms (six of nine) in either one of both domains results in phenomenological subtypes: Combined type, Predominately Inattentive type, and Predominately Hyperactive/Impulsive type.

Neuropsychological deficits related to the diagnosis of ADHD are well documented, and a review of this area is presented in this Journal's special section on ADHD. A comprehensive review is provided by one of us elsewhere (Nigg, 2005), which will be summarized but not presented in detail here. In his review of meta analytic findings, Nigg (2005) identified the neuropsychological tasks that show the largest differences in performance by children with ADHD vs. children without ADHD. Based on effect sizes, the list includes Spatial Working Memory (0.75), Stop Task Response Suppression (0.61), CPT d-prime (0.72), Stroop Naming Speed (0.69), Full Scale IQ (0.61), Trails B Time (0.55), Mazes (a planning measure; 0.58). Other tasks with rather smaller effects include Tower of London (0.51), Verbal Working Memory (0.51), Stop Task Go Speed (0.49), WCST Perseverative errors (0.35), Stroop Interference (0.25), and Posner Covert Visual-Spatial Orienting (0.20). Nigg (2005) concluded that any one neuropsychologic deficit is not sufficient to account for ADHD, but the key domains in which deficits are manifested across cases are vigilance-attention, cognitive control (in particular, working memory and response suppression), and motivation (in particular, approach to reinforcement incentive).

These key domains (cognitive control and motivation) in which deficits are seen in ADHD highlight the importance of principles of dopamine reinforcement and its disruption in this disorder. Specifically, dopamine is involved in forming predictions about future outcomes and optimizing behavior as shown in dopamine neuronal firing being linked to detecting discrepancies between actual and expected outcomes (Schultz et al., 1997). Learning when, what, or in which contexts to expect an event is critical for adjusting behavior appropriately in different contexts (Casey & Durston, 2006; Nigg & Casey, 2005) and for signaling top-down cognitive control systems to adjust behavior when predicted outcomes are violated (Casey et al., 2006). Deficits in learning to detect regularities or irregularities in the environment could lead to impaired signaling to cognitive control systems that alter or adjust behavior accordingly (i.e., poor working memory and lack of response inhibition). Likewise, intact signaling but inefficient top-down control could result in poor regulation of behavior in a more general way. The variability in cognitive performance reported in the ADHD literature may be partly due to such differences.

Of course, other factors are important, too, such as the heterogeneity of the phenomenological or etiological subtypes of ADHD. The reliability of diagnosis (one of the primary goals of the DSM revisions starting in 1980) of ADHD is well established for the DSM-IV criteria, and this has facilitated the search for underlying bases of this syndrome. In DSM-V, an emphasis on etiology has been promised (Kruger et al., 2005). Here we will review some issues related to etiologic subtypes of ADHD.

Both genetic and environmental etiologies have been proposed to account for the behavioral and neuropsychological characteristic of ADHD. Over the past decade ADHD has typically been conceived as largely genetic, with only a small subgroup of children whose symptoms arise from some environmental factors (e.g., see Mick et al., 2002), but recent investigations have identified important environmental factors that increase the risk for ADHD. Indeed, it is becoming increasingly clear that complex conditions such as ADHD result from the interplay of genetic and environmental risk factors. We review some aspects of this literature, and to integrate the genetic and environmental findings on the assumption that dopamine dysfunction is one of the primary causes of ADHD.

The dopamine system is well defined, at both at the synaptic and the brain circuit level (see Volkow & Swanson, in press). At the synaptic level, a simplified model includes 3 distinct steps: (1) cell firing releases the neurotransmitter that has a specific receptor as a target, (2) a transporter recycles some of the released neurotransmitter, which regulates its temporal and spatial distribution in the extracellular space, and (3) enzymes operate to metabolize the neurotransmitter and inactivate it. Abnormalities in any of these steps

could produce a dopamine dysfunction. At the circuit level, a simplified model includes neurons with cell bodies in two locations in the midbrain (SN and VTA) with different projections to the striatum (SN) or directly to cortex (VTA). The circuitry of the cortical-striatal-thalamic-cortical loops is complex and involved multiple levels of feedback (Castellanos, 1997). The involvement of the cerebellum (see Nigg & Casey, 2005) and the dual pathways defined by ventral and dorsal component of the striatum (Sonuga-Barke, 2003) are probably necessary for a full account of modulation of activity by dopamine and other neurotransmitters.

A review of the literature on ADHD should be put into context in relation to dramatic changes in the recognition and treatment of this disorder. The current recognition rate in the US is astounding: the CDC Morbidity and Mortality Weekly Report (CDC, 2005) documented in a nationwide telephone survey that in 2003–2004 the rate of recognition was about 14% in 10-year-old boys and 6% in 10-year-old girls, and the rates of treatment with stimulant medication were about 9% and 4%, respectively.

The change over time shows how great the increase in recognition and treatment has been over the past decade. The increasing trend noticed a decade ago (Swanson et al., 1994) of medical visits for ADHD and prescriptions of stimulant medications has continued unabated (Fig. 1a). However major changes in prescription practices have occurred over the past five years (Fig. 1b). The use of immediate-release (IR) formulations of methylphenidate (MPH) and amphetamine (AMP) showed dramatic decreases when new controlled-release (CR) formulations were approved and, in turn, showed dramatic increases themselves.

This advance in drug delivery was spurred by the hypothesis of acute tolerance to clinical doses of methylphenidate (Swanson et al., 1999) and amphetamine (Greenhill et al., 2003). The development of commercial products based on this principle resulted in several second-generation controlled-release formulations of these drugs that rapidly replaced the IR formulations. The old drug delivery profile, which remained basically unchanged for a half century, was based on multiple daily doses of IR-MPH (most recently, TID) and IR-AMP (most recently, BID), with the initial dose set by individual titration due to great variation across individuals in dose (e.g., from 5 mg to 20 mg per administration of IR-MPH or 15 mg to 60 mg per day). A reverse-sculpted delivery with a lower dose in the afternoon than in the morning was considered optimal by a panel of experts in the early 1990s (see MTA Group, 1999). This dosing pattern approximates a constant (or zero-order) drug delivery. The first generation sustained-release formulations (Ritalin SR and Dexedrine Spansules), which had been available since the 1980s and were apparently developed with zero-order delivery as a target, were not widely used, due to the clinical impression of reduced efficacy.

Based on the implications of the theory of acute tolerance, a new drug delivery pattern was based an ascending or first-order drug delivery to counteract the presumed emerging negative effect at the neural site of action (see Swanson et al., 2003). The first product based on this concept was Concerta®, which was introduced in 1998 and rapidly replaced the IR formulations in clinical practice (see Fig. 1b). The second trend over the past decade was the revival of the use of racemic mixture of AMP that provides effective

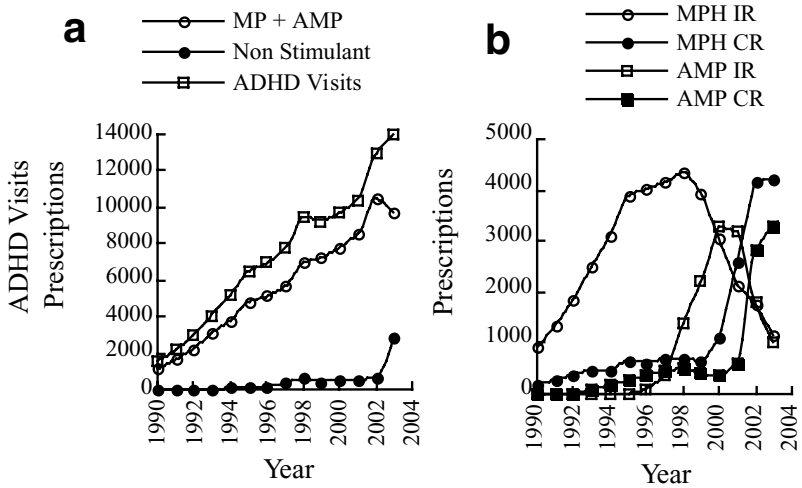

Fig. 1 (a) Medical Visits for ADHD (in thousands), Visits with stimulant medication prescribed, and Visits with prescriptions for non-stimulants, which increases in 2003 when Strattera®, gained approval for the treatment of ADHD; (b) Prescriptions for stimulant drugs (in thousands), including IR-MPH (e.g., Ritalin®), IR-AMP (e.g., Obitrol®, which increased in 1998 when this long-approved weight-reduction drug was renamed Adderall® and marketed for the treatment of ADHD), CR-MPH (e.g., Concerta®, which increased in 2000 when FDA approval was granted for the treatment of ADHD), and CR-AMP (e.g., Adderall® XR, which increased in 2002 when FDA approval was granted). Source: The Scott-Levin Reports from 1990 to 2003

clinical treatment of ADHD symptoms (see Bradley, 1937, 1950; Swanson et al., 1998; Pelham et al., 1999; Greenhill et al., 2003; McCracken et al., 2003). A controlled release formulation of AMP (Adderall XR®) was developed (see Greenhill et al., 2003) that used the ascending first order delivery (see Adderall XR® package insert). Over the past decade, the prescriptions of d,l-AMP showed a rapid rise, initially in 1998 for the IR formulation after the reintroduction with a new name (Adderall®) of a weight-reduction product Obetrol® that had been approved in the 1970s for the treatment of minimal brain dysfunction (MBD), and later for the CR formulation Adderall XR® (see McCracken et al., 2003).

The number of individuals treated with stimulants is difficult to estimate from these prescription records but can be estimated from production records. The World Health Organization (WHO) tracks yearly production and stock of stimulants in each country in terms of defined daily dose (DDD) per 1000 individuals, set as 30 mg/day for MPH and 15 mg/day for AMP. In a recent WHO report (WHO, 2003), the USA DDD was 5.21 for MPH and even higher (6.23) for AMP. For the USA population of approximately 290 million, the total (11.44) would be sufficient for the daily treatment of 3,326,866 individuals (about 1% of the population and 5% of children under 18 years of age). If the stimulant-treated individuals in the USA differ as documented by the National Ambulatory Medical care Survey by age (56% are school aged children from 7 to 12 years) and gender (76% are boys), then this drug supply is sufficient to treat about 1.4 million elementary school aged boys each day, or about 13% of the approximately 11 million children in this subgroup. This exceeds the estimate (9%) provided by the telephone survey conducted by the CDC noted above (MMWR, 2005).

It is interesting that estimates from epidemiological studies of ADHD (e.g., Bauermiester et al., 2003; Jensen et al., 1999) suggest that most (more than 85%) children with ADHD are not treated with stimulant medication, while estimates from survey studies or production records suggest the percentage of school-aged children treated matches or exceeds the estimated prevalence of the disorder. This mismatch of estimates from epidemiological and survey studies and from production records needs careful evaluation and could reflect discrepancies on the time when the data were collected, changes in demographics (e.g., increases in adults being treated for ADHD, which would affect the estimates from prescription records), how treatment is defined (e.g., any treatment during a period of treatment for most of the period), or many other factors. Even though it is possible that the current high numbers of medical visits and prescriptions may reflect a correction of prior under-recognition and under-treatment of ADHD, the possibility that this reflects an over diagnosis or a gradual increase in the true prevalence of ADHD cannot be discarded. Any of these possibilities might be cause for alarm.

The scientific rationale should be clear and indisputable to support this high level of diagnosis and treatment of ADHD treatment of the population of children in the US. The usual justification is that this specific pharmacological treatment corrects an underlying neurochemical deficit and normalizes the behavioral and cognitive deficits associated with the clinical manifestation of ADHD. Many neurochemical theories of ADHD have also been proposed, and here we will focus on Wender's (1971) catecholamine theory of MBD. In 1970, MBD was the predominate label used. It fell out of favor, in part due to its over-inclusiveness, and was replaced when DSM-III (1980) proposed the term Attention Deficit Disorder. Wender (1971) proposed that subtle abnormalities in the neurotransmitter systems related to dopamine and norepinephrine might accounted for the array of symptoms (including hyperactivity, inattention, and impulsivity), and that the stimulant medications used to treat these symptoms acted on these neurotransmitter to correct an underlying deficit.

The DA deficit theory is not the only viable biological theory of ADHD (Solanto et al., 2000; Gainetdinov et al., 1999), but it has directed important investigations of the mechanism of action of MPH (Volkow et al., 1995, 1998, 2001, 2002). We will not review the evidence for and against the DA deficit theory, but will confine ourselves to studies of etiologic factors that may produce a DA deficit, which may be an integration of factors that suggests one of many (and perhaps the most important) etiologies of ADHD or final common pathway for a range of alternative causal factors, and which leaves open the possibility that other neurochemical pathways may also result in symptoms of ADHD. We consider two classes of etiologic factors, genetic and environmental, either of which may account for the proposed differences in brain anatomy (smaller than normal size of specific DA regions) and genotype (presence of alleles of specific DA genes) between groups of ADHD and control individuals. Even though the dopamine deficit hypothesis can provide only a partial account of ADHD, we will present a focused update of previous reviews of the literature to provide some additional details about involvement of dopamine in the symptoms and the pharmacologic treatment of ADHD.

Evidence of dopamine deficits in ADHD

Brain imaging studies

Brain imaging studies over a decade ago (Hynd et al., 1990, 1991, 1993) suggested anatomical abnormalities in ADHD individuals, consisting in smaller than normal size for several brain regions. Two decades of intensive research have basically confirmed this seminal observation. We (Swanson et al., 2004) summarized this literature in a figure showing "effect size" (ADHD versus control differences in brain size) for different brain regions which suggested that

in addition to an overall reduction in size that was present in childhood and remains in adolescence (see Castellanos et al., 2002), three major findings about regional differences were notable: (1) the caudate nucleus and globus pallidus which both contain a high density of DA receptors are smaller in the ADHD than in the control groups; (2) ADHD groups have larger posterior regions (e.g., occipital lobes) and smaller anterior brain regions (e.g., right frontal white matter); and (3) areas involved in coordinating activities of multiple brain regions have specific subregions (e.g., the rostrum and splenium of the corpus callosum and the cerebellum vermis lobules VIII-X) that are smaller in ADHD than in control groups. A recent meta-analysis of structural imaging findings reported by Valera et al. (2006) provided quantitative estimates of reductions in size ($d = 0.408$) and implicated regional reductions in caudate (right), cerebellum (vermis), and corpus callosum (splenium).

An important finding is based on a study of the assessment over time (Castellanos et al., 2002; Shaw et al., 2006), which tracked changes in anatomical size with development in a large sample of ADHD cases ($n = 152$) and non-ADHD ($n = 139$) controls. The primary finding was that anatomical abnormalities (smaller size) were present in childhood and remained into adolescence, suggesting these differences were due to early environmental effect or to genetics (or perhaps to a combination of these factors). However, Castellanos et al. (2002) found that one of the initial anatomical abnormalities associated with ADHD (smaller caudate volume) resolved over time due to different downward trajectories for the ADHD and non-ADHD groups that may reflect general neural pruning that results in decreased volume with age. Shaw et al. (2006) extended the assessment of this group by obtaining more refined specification of size from measures of cortical thickness and also classified the ADHD cases on the basis of outcome (worse outcome in $n = 56$ with CGAS <64 vs. better outcome in $n = 51$ with CGAS $>/= 64$). This analysis show persistent global difference between the ADHD and non-ADHD groups, but also that the reductions in thickness of frontal and parietal brain regions in the ADHD subgroup with better outcome were smaller than in the subgroup with worse outcome, and that in the ADHD subgroup with better outcome normalization of the thickness of parietal regions was apparent due to differences in trajectory over time.

Recent functional MRI (fMRI) imaging studies have clarified prior reports of abnormalities related to hypoactivation of fronto-striatal-cerebellar networks that are revealed by task activation. The initial fMRI findings (see Viadya et al., 1998; Rubia et al., 1999; Durston et al., 2003) showed decreased activation of the DA pathway (the cortical-striatal-thalamic brain circuit). Recent studies have confirmed that the patterns of hypoactivation of ventral prefrontal and inferior parietal regions related to attentional networks appear to be present in unaffected siblings of children with ADHD as well as ADHD cases (Durston et al., 2006). Studies of acute effects of stimulant medication in treatment of ADHD cases showed that the pattern of frontal hypoactivation was partially corrected by DA-agonist effects of stimulant drugs (e.g., see Lee et al., 2005).

Extensions of prior findings include the assessment of medication naïve children with ADHD by Smith et al. (2006) and Plizska et al. (2006) during Go/no-go tasks, and the use of a novel task related to attention switching by Tamm et al. (2006). Casey and Durston (2006) reviewed these studies, which showed hypoactivation involving motor inhibition (frontal lobe) and task switching (prefrontal, temporal, and parietal regions).

In prior reviews (Swanson et al., 1998 and 2004) we used the three components of attention proposed by Posner and Raichle (1994) to suggest a "levels of analysis" approach for the assessment of ADHD. A recent up-date by Nigg and Casey (2005) extended this theoretical, neuroanatomical approach by accumulated knowledge from the cognitive and affective neurosciences, by providing an account of the involvement of fronto-striatal and fronto-cerebellar neural loops involved in predicting "what and when" information and detecting occurrence of events, and interactions with fronto-amygdala loops to assign emotional significance to the events predicted and detected.

In addition to fMRI studies, an early series of functional imaging studies of ADHD, which used Single Photon Emission Computed Tomography (SPECT) to measure blood flow in children with and without ADHD, showed that the children with ADHD manifested reduced blood flow to frontal lobes and basal ganglia but increased blood flow to occipital lobes (Lou et al., 1990). Another series of imaging studies, which used Positron Emission Tomography (PET) to measure glucose metabolism in adults with and without ADHD, showed lower metabolism in frontal lobes of the ADHD group when performing an auditory attention task (Zametkin et al., 1990).

Mechanism of action of stimulant medication

The mechanism of action of stimulants at the synaptic level has been controversial for decades. Certainly, a full account of symptoms and response to medications requires consideration of additional neurotransmitters systems, and research in the neurosciences has generated hypotheses about the involvement of norepinephrine (Plizska et al., 1996; Arnsten et al., 2006) and serotonin (Gainetdinov et al., 1999). For example, Arnsten (2006) reviewed the evidence that stimulant medications may have some of their therapeutic effects by increasing endogenous stimulation of alpha2A-adrenoceptors and dopamine D1-receptors in the prefrontal cortex, optimizing regulation of behavior and attention, and Gainetdinov

et al. (1999) showed that in hyperactive dopamine transporter (DAT) knockout mice with elevated dopaminergic tone, a decrease in locomotion in response to psychostimulants depended on serotonergic neurotransmission. Here, we will focus on dopamine, even though this only provides a partial account of the effects of stimulant medication.

Coyle and Snyder (1969) measured uptake in synaptosome preparations from the striatal region of a rat brain to evaluate the mechanism of action of the dextro (d) isomer of amphetamine (d-AMP, the isomer responsible for the primary clinical effects) and reported effects that were 10 times greater than levo (l) isomer (l-AMP) on uptake or norepinephrine (NE) and equal on uptake of dopamine (DA). From this pattern they concluded the underlying deficit in ADHD children was primarily related to NE. However, subsequent studies (Ferris et al., 1972; Harris et al., 1973; Heikkila et al., 1975) reported the opposite effect (i.e., a similar effect on NE uptake but a greater effect of d-AMP than l-AMP on DA uptake). Also, responses to the isomers in rats (North, 1974) revealed a greater increase in glucose metabolism in the caudate nucleus and globus pallidus after d-AMP than after l-AMP, which provided additional evidence that d-AMP preferentially affected DA neurocircuitry. These studies suggested that the underlying deficit in ADHD children might be primarily related to DA.

The direction of the effect of stimulant medication on DA levels in the brain has been controversial. For example, while Levy (1991) proposed the DA deficit hypothesis, with post-synaptic effects that amplified the DA neural response, Solanto (1998) proposed a DA excess hypothesis, with presynaptic effects of stimulant medication reducing release and reducing the DA neural response. The modern update of the presynaptic/antagonist and postsynaptic/agonist hypotheses was outlined by Seeman and Madras (1998), who proposed that tonic levels would suppress phasic release, so that stimulants would function as antagonists, thus correcting a dopamine excess rather than a dopamine deficit.

A series of PET imaging studies of methylphenidate (MPH) documented the site of action of MPH and the effect on synaptic dopamine. Volkow et al. (1998) evaluated the occupancy of DA transporters by pretreatment with therapeutic doses of MPH (or placebo) given 120 min prior to the administration of the DAT radioligand [^{11}C] cocaine. They showed dose-dependent blockade of DAT (for 20 mg MPH, about 50% and for higher doses of 40 mg and 60 mg 72% and 74%, respectively), suggesting that a standard clinical dose of 0.5 mg/kg would block about 60% or more of DAT. Dopamine transporter occupancies were significantly correlated with the plasma concentration of the active isomer (d-threo-methylphenidate) at 120 min, and the plasma concentration expected to block 50% of the DAT was estimated to be 6 ng/ml. Before this study, oral MPH had been traditionally considered a "weak" agent, much different than cocaine, assuming that not much of the drug would reach the brain, since it is rapidly metabolized into ritalinic acid, which has a weak affinity for the DAT and thus would have minimal pharmacological effects. The results from this study indicated that therapeutic oral doses of MPH do reach the brain, that MPH has a strong affinity for DAT, and defined the site of action of MPH in the living human brain. The synaptic (Volkow et al., 2002) and circuit (Volkow et al., 2003) effects of MPH were documented in subsequent PET studies with ^{11}C-raclopride. Oral doses of MPH displaced raclopride binding in the striatum, indicating increases in extrasynaptic DA, which supported the view that clinical MPH doses produce their therapeutic effects (symptom reduction) by increasing DA and correcting an underlying DA deficit. Neto et al. (2002) replicated this effect in an ^{11}C-raclopride PET study of adolescents with ADHD.

Drugs such as MPH and cocaine share the same mechanism of action (Volkow et al., 1995). While recognizing that MPH has some potential for drug abuse when administered intravenously or intranasally, Volkow and Swanson (2003) summarized literature that finds the abuse potential of oral MPH to be low (Volkow et al., 2000), due primarily to the relatively slow onset and offset of the effects of MPH at its site of action in the human brain (Volkow et al., 1995).

Spencer et al. (2006) recently used a different DAT radioligand ([^{11}C]altropane) and corroborated that oral doses of MPH in the therapeutic range for the treatment of adults produce about 60% blockade of DAT. This study also compared the brain pharmacokinetics and the reinforcing effects of MPH when delivered by an immediate release oral formulation (IR) to the effects when delivered by a slow release formulation (OROS), by measuring the levels of DAT blockade for a given dose of IR and of OROS MPH across time after administration for doses of IR-MPH (40 mg) and of OROS-MPH (90 mg) that result in equivalent maximum effects in the brain. The near-equal peak levels of DAT blockade (72% for IR-MP and 68% for OROS-MP) occurred at different time points, with peak DAT blockade occurring faster for the 40 mg IR-MPH (at 1.7 h) than for 90 mg OROS-MPH (at 5 h). The peak level of DAT blockade achieved by 40 mg of IR-MPH was associated with mild reinforcing effects, but the same peak effect for 90 mg OROS-MP was not.

Dopamine transporter density and attention deficit hyperactivity disorder

Imaging studies of DAT density present a confusing pattern of findings. The initial study (Dougherty et al., 1999) reported much higher (70%) than normal DAT density in striatum in a small sample ($n = 7$) of adult subjects with ADHD. This was followed by partial replications by Krause et al. (2000, 2002), who reported effects in the same

direction but smaller and dependent on subgroups. Spencer et al. (2005) reviewed the first eight studies and concluded there was fair agreement about the direction of differences (in six of the eight studies, higher DAT density in the ADHD group). However, the most recent studies with the largest sample sizes reported no differences in striatum (van Dyck et al., 2002; Jucaite et al., 2005) and lower DAT density in mesencephalon (Jucaite et al., 2005). Recent additional attempts to replicate have failed. Volkow et al. (2006) evaluated 20 adults with ADHD who had no history of treatment with stimulant medication or abuse of drugs, and in comparison to a non-ADHD group, no difference in putamen and lower than average DAT density in caudate. Hesse et al. (2006) also showed lower DAT density in treatment-naïve adults with ADHD than age and gender matched controls.

Volkow et al. (2006) reviewed the accumulated evidence of 10 studies and concluded that a dramatic higher than normal DAT density was not apparent in adults with ADHD, and in untreated cases the opposite may characterize ADHD (i.e., slightly lower than normal DAT density). Based on this, Volkow et al. (2006) suggested that DAT density might be plastic and vary over time, dependent on homeostatic mechanisms that operate to maintain tonic levels of synaptic or extra-synaptic DA. Thus, DAT density may decrease in the presence of low DA levels and increase in the presence of high DA levels. Treatment with stimulant medication increases DA levels dramatically, and this may result in homeostatic increase in DAT density. Thus, in untreated cases with ADHD without comorbidites involving DA-agonist drugs, the opposite pattern than that proposed by Dougherty et al. (1999) to account for a presumed deficit in synaptic DA levels—lower rather than higher than normal DAT density—may also be interpreted to provide support for the DA deficit hypothesis.

Despite this uncertainty, the US Patent Office awarded a patent in 2006 for the use of DAT density as a diagnostic test for ADHD (Madras, Fischman, & Meltzer, 2006). As part of the application, an analysis of a study of 20 ADHD adults and 20 age-matched controls was provided that claimed to show higher than normal DAT density in ADHD adults, and as a diagnostic test claims were made for high sensitivity (75%) and specificity (87.5%). However, in this study only 24 of the 40 subjects provided usable data and there was selective loss of subjects, with missing data from three times as many ADHD subjects ($n = 12$) as control subjects ($n = 4$). Even in this biased sub-sample, the size of the effect was less than half the effect initially reported (30% versus 70% elevation of DAT density in the ADHD group). This methodological flaw, along with several recent non-replications that suggest DAT density may be lower than normal rather than higher than normal, renders these claims unconvincing. The premature use of DAT imaging for diagnosis of ADHD should be challenged.

Molecular genetic factors and attention deficit hyperactivity disorder

Candidate genes and attention deficit hyperactivity disorder

Many genetic theories of ADHD have been proposed, based on family (Faraone et al., 1992), adoption (Deutsch et al., 1990), and twin (Stevenson et al., 1992) studies, which together suggest unspecified genetic factors may be the predominant etiology. Molecular genetic methods have been applied to identify specific factors by relating variations in DNA (genotype) to the diagnosis of ADHD (phenotype). Two approaches were used in the initial studies: the candidate gene approach and the genome scan approach. The candidate gene approach starts with a hypothesis about a specific gene at a known chromosomal location, perhaps suggested by theories of the biological basis of the cause or treatment of the disorder under investigation, and then tests if a specific genotype is statistically associated with the disorder. The genome scan makes no such assumption but instead starts with genetic "markers" (much like sign-posts along a highway) spread across the entire genome and attempts to locate chromosomal regions by statistical methods. One way is to find markers that are shared at a greater-than-chance rate in affected relatives and that are thus likely to be in chromosomal regions harboring genes associated with the disorder (linkage scans). Another way is to perform association tests at multiple points across the genome (association scans). Risch and Merikangas (1996) pointed out the strengths and weaknesses of these two approaches.

In the first published molecular genetic studies of ADHD, the candidate gene approach was used, and statistical association was documented for two candidate genes related to the neurotransmitter dopamine— the dopamine transporter gene (Cook et al., 1995) and the dopamine receptor type 4 (DRD4) gene (LaHoste et al., 1996). These candidates were chosen based on DA theories of ADHD (Wender, 1971; Levy, 1991) and the DA sites of action of drugs used to treat ADHD (see Volkow, 1995, 1998, 2001, 2002). The DAT and DRD4 genes have variation across individuals based on a variable number of tandem repeats (VNTRs) defined by a nucleotide or base-pair (bp) sequence (called a "motif") that is repeated (R) a different number of times in different alleles of the gene. For the DAT gene, a 40-bp VNTR in the 3′ untranslated (non-coding) region was investigated by Cook et al. (1995). In Caucasian populations the primary allelic variants are the 9R allele ($p \sim 0.25$) and 10R allele ($p \sim 0.75$). For the DRD4 gene, a 48-bp VNTR in exon 3 was investigated by LaHoste et al. (1996). The primarily variants defined by 2R, 4R and 7R alleles that produce structural differences across individuals in the 3rd intracellular loop of the receptor that couples it to pre- and post-synaptic G-protein effectors. Allele frequencies of the DRD4 gene vary across ethnic groups,

but in Caucasians the expected allele frequencies are about 0.10 for the 2R, 0.67 for the 4R, 0.12 for the 7R, and 0.11 for other alleles.

Cook et al. (1995) investigated parent-to-child transmission rates of the DAT alleles, and reported an increased prevalence (0.85) and transmission (0.60) of the most prevalent 10R-repeat allele in a sample of 119 ADHD children. LaHoste et al. (1996) observed a higher than expected frequency of the DRD4 7R allele (0.28) in a clinical group of ADHD cases, and Swanson et al. (1998) replicated this finding and extended it by showing linkage-disequilibrium in proband-parent triads.

Typically, initial positive findings of candidate gene studies are not replicated (Crowe, 1993). However, most studies of association of ADHD with the DRD4 gene replicated the initial findings (see Swanson et al., 2000; Faraone et al., 2001). This consistency was described by Collier et al. (2000) as ". . . a major achievement in psychiatric genetics: an association finding which has been observed in an overwhelming majority of attempts at replication." A recent meta-analysis (Li et al., 2006) confirms the association of ADHD with alleles of the DRD4 gene (with the 7-repeat allele as the "risk" allele). This meta-analysis did not support reliable association of ADHD with the proposed risk allele of the 40 bp VNTR of the DAT gene, suggesting that this allele may not be associated with ADHD or may be in linkage disequilibrium or interact with another polymorphism nearby, perhaps even in the DAT gene. In the Li et al. (2006) meta-analysis, association of ADHD with another dopamine gene (the DRD5 gene) was confirmed. Other meta-analyses have reviewed the limited evidence of association with some non-DA genes (see Faraone et al., 2005).

Recently, combinations of the polymorphisms of the DRD4 and DAT genes have been considered. For example, in an MRI study of brain anatomy of ADHD children and the siblings, Durston et al. (2004) used this approach by defining genotypes based on homozygosity of the most frequent alleles of the VNTR polymorphisms of the DRD4 gene (the 4R/4R genotype) and the DAT gene (the 10R/10R genotype) compared to the genotypes with at least one other allele (i.e., the 7R-present genotype of the DRD4 gene and the 9R-present genotype of the DAT gene). These genes were assumed to have effects on dopamine functions based on the hypothesis that the alleles of the DRD4 gene code for variants of the receptor with differential sensitivity to endogenous dopamine (with the 7R allele resulting in a subsensitive receptor) and the hypothesis that the alleles of the DAT gene in the promoter region modulate the expression of DAT to increase its activity (re-uptake). They reported that DAT genotype had a significant effect on size of one brain region and the DRD4 genotype on another. For the subgroup defined by the DAT 10R/10R genotype, the average caudate volume was smaller than the other genotypes, and for the subgroup defined by the DRD4 genotype, the average prefrontal gray matter volume was smaller than for the other genotypes. They proposed that the commonly assumed risk genotypes may have opposite effects, with the DAT 10R/10R genotype conferring risk for ADHD and the DRD4 7R-present genotype conferring protection. In a slightly different way, Mill et al. (2006) also used the combination of the same risk genotypes defined by the VNTR polymorphisms of the DRD4 and DAT genes to form subgroups of individuals. They evaluated the effect of the combination of risk genotypes on intellectual ability in genotype-defined subgroups of subjects in two cohort studies (one from the UK and one from New Zealand) and found that the average IQ was lower for the overall group of ADHD subjects than for the non-ADHD group, which had an average IQ of about 101. In the ADHD but not the non-ADHD subgroups based on genotypes, IQ was related to the number of risk genotypes present. The ADHD subgroup, defined by the absence of either risk factor, had an average IQ about 5 points lower than the non-ADHD group (about 96), while the ADHD subgroups with one risk genotype (DRD4 7R-present or DAT 10R/10R) showed a further reduction of about 5 points (with an average IQ of about 90) and the subgroup with both risk genotypes showed an additional reduction (with an average IQ of about 85). Based on the presumed effect of these polymorphisms of the DAT and DRD4 genes, they proposed that the combination of the risk genotypes of these genes might produce an extreme hypodopaminergic state that may be correlated with poor cognitive function.

Functional properties of the seven-present genotype

The functional significance of the DRD4 risk-related polymorphisms has been investigated by multiple groups. The initial surprising finding (Swanson et al., 2000) was in opposition to the prediction (i.e., the "risk" allele of the DRD4 apparently has protective effects instead of conferring risk). Swanson et al. (2000) used measures of reaction time (RT) and standard deviation (SD) from three neuropsychological tasks that required speeded response (Posner visual-spatial orienting, Stroop color-word conflict, and Logan go-stop), and compare subgroups based on DRD4 genotypes (i.e., those with vs. without a 7R allele). The 7-absent (those without a 7R allele; $n = 19$) manifested the characteristic pattern of performance deficit on RT tasks expected for children with ADHD (i.e., slow and variable responding). However, the 7-present (those with at least one 7R allele; $n = 13$) subgroup did not differ from the control group ($n = 21$) on performance on these tasks, as reflected by average RT and SD. Swanson et al. (2000) suggested that the 7-present subgroup of ADHD children may have a partial syndrome characterized by behavioral excesses (resulting in high symptom ratings by

parent and teachers) without cognitive deficits, while the 7-absent subgroup may have the full syndrome characterized by both behavioral excesses and cognitive deficits.

Several independent groups have reported similar results. Manor et al. (2001) used a commercially available sustained attention task, the Test of Variables of Attention (TOVA) that required choice RT. They separated ADHD subjects into those with short repeats of the DRD4 exon 3 VNTR (5R or less) and those with long repeats (6R or greater) alleles. The primary determinant of "short and long" was the presence of a 7R allele (classified as "long") or the absence of a 7R allele (classified as "short"). The subgroup defined by the long alleles ($n = 35$) showed significantly more commission errors (54 vs. 70, $p < 0.035$), lower variability in RT on the TOVA (70 vs. 54, $p < 0.03$) and non-significantly faster RT1s (57 vs. 68, $p < 0.125$) than the subgroup with the short allele ($n = 96$).

Langley et al. (2004) used multiple tests to assess performance, including the Matching Familiar Figures (MFF). On this task, response time depends on whether the participant used a strategy to search longer and acquire addition information from multiple "looks" (so it does not provide a discrete RT measure of choice RT). Another was the Stop task, which was the same as one of the tasks used by Swanson et al. (2000). This task assesses performance based on speeded responses (the "Go" RT response) as well as the inferred speed of withholding a response (which is estimated using complex analysis of performance related to the length of the interval between the "Go" and "Stop" signal). On the Stop task, the 7R-present subgroup ($n = 20$) had faster RTs than the 7R-absent subgroup ($n = 45$) on the Stop task response time measure (496 vs. 572 ms, $p < 0.05$). The 7R-present subgroup also showed evidence of cognitive style biased toward speed over accuracy, based on faster response and more errors on the MFF task.

Bellgrove et al. (2005) used a Go/NoGo task in which the digits 1 to 9 are presented and a response is required to all but the digit 3. RTs were recorded, but to minimize a speed-accuracy tradeoff, response time was "locked" to a separate response cue after presentation of the digit. The subgroups of ADHD subjects were formed based on presence (the 7R-present genotype) or absence (the 7R-absent genotype) of the 7R allele. They found that the subgroup defined by the 7R-absent genotype ($n = 31$) showed deficits relative to the control group (more errors and more variability in RT), whereas the subgroup defined by the 7R-present genotype ($n = 20$) did not differ from the normal control group.

Across four studies (Swanson et al., 2000; Manor et al., 2002; Langley et al., 2003; Bellgrove et al., 2005), the subgroup of children with ADHD defined the presence of at least one 7R allele (the 7R-present genotype) had faster and less variable responses on choice RT tasks than the subgroup defined by the absence of the 7R allele (the 7R-absent genotype). This provides some support for the speculation by Swanson et al. (2000) that the 7-present subgroup of ADHD children may have a partial syndrome characterized by behavioral excesses without cognitive deficits, while the 7-absent subgroup may have the full syndrome characterized by both behavioral excesses and cognitive deficits.

Genome scans and attention deficit hyperactivity disorder

In the first two genome scans reported, Fisher et al. (2002) evaluated 126 affected sib pairs and 404 markers, and Bakker et al. (2003) evaluated 164 affected sib pairs and 402 markers. Neither genome scan revealed a strong signal from a specific location on the human genome to direct the search for a specific gene, and the reported weak signals were different for these two genome scans (Fisher et al.: 5p, 10q, 12q, and 16p; Bakker et al.: 15q, 7p, and 9q). Thus, the directions for the next step in the search for genes associated with ADHD were not consistent across these two genome scans. The failure to detect a strong signal does not discount the existence of genes with high-probability risk alleles, multiple genes that combine to confer risk for ADHD, or genes with effects that depend on interactions with environmental factors. Ogdie et al. (2003) provided a report on an expansion of the sample reported by Fisher et al. (2002), and reported a signal for a gene in a region on 17p11 previously linked to autism. Also, in a family study of a population isolate, a linkage genome scan identified linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11, which identified chromosome regions that may contain genes associated with ADHD (Arcos-Burgos et al., 2004).

A recent report by Brookes et al. (2006) described a combination of the candidate gene and genome scan approaches, based on an assessment of 51 candidate genes in pathways related to dopamine, norepinephrine and serotonin. This study used a large sample of ADHD cases (674) and siblings (808, with 102 having diagnoses of ADHD) and dense anonymous markers (1038 SNPs) in the candidate genes as well as some polymorphism previous implicated genes (i.e., the 48*n* bp VNTR in the DRD4 gene and the 40 bp VNTR in the DAT gene). This study confirmed association of ADHD with the DRD4 and DAT genes, and also provided suggestive evidence of association of ADHD with 16 other genes.

Environmental factors and attention deficit hyperactivity disorder

Smoking and lead

In early statistical genetic studies of ADHD in biological (Faraone et al., 1992) and adoptive (Deutsch et al., 1990) relatives of probands, a high phenocopy rate was

incorporated into genetic models to account for sporadic, non-genetic forms of the disorder. Environmental exposures to toxic substances during pregnancy (such as nicotine) as well as early in childhood (e.g., lead) are possible sources of phenocopies or alternatively, of genotype by environment interactions toward an ADHD phenotype.

Linnett et al. (2005) reviewed the literature on maternal lifestyle factors that exposed the developing fetus to nicotine, alcohol, caffeine, and stress, and only nicotine conferred risk for ADHD. Two of the studies reviewed are notable. In a case-control study, Millberger et al. (1996) reported that prenatal maternal smoking was associated with a 4-fold increase in risk for ADHD. In a twin study, Thapar et al. (2003) showed that maternal smoking during pregnancy was associated with symptoms of ADHD in offspring, even when controlling for genetic effects, although the main effect of cigarette exposure was small. Recently, Knopik et al. (2006) used an interesting children-of-twins design to evaluate the genetic and maternal-fetal environmental effects of alcohol and smoking during pregnancy as well as genetic correlation with environmental exposure (see Taylor & Rogers, 2005). Offspring of monozygotic (Mz) and dyzygotic (Dz) mothers were subgrouped into those at high risk for genetic and environmental reasons (children born to Mz or Dz mothers with alcohol-use disorder), those with reduced environmental risk (children born to Mz mother without alcohol-use compared to children of co-Mz twin with alcohol use disorder), and those with reduced environmental and reduced-by-half genetic risk (children born to Dz mothers without alcohol use disorder compared to children born to co-Dz twin with alcohol-use disorder). The association of ADHD with alcohol was attributed to genetic factors (children born to Mz mothers who did not have alcohol-use disorder were at the same risk for ADHD as children born to the Mz co-twin who did). In addition, concurrent smoking was correlated with alcohol-use disorder and contributed additional to the risk for ADHD. Due to this genetic correlation, children at genetic risk for ADHD are also at increased environmental risk due to correlated parent behavior that increases the chance of environmental exposure to a toxic substance (nicotine).

Lanphear et al. (2006) reviewed the literature on the effects of low levels of lead on intellectual development, and performed a joint analysis of data from multiple groups that had assessed the effects of low levels of lead on IQ. The clear conclusion of these analyses was that levels under the established norms (<10 μg/dL) had negative effects on IQ. Because these low level lead exposures remain common in the population, Nigg (2006) suggested that they could represent a hidden major effect on ADHD incidence via genotype by environment interaction. In a population sample (the NHANES sample), Braun et al. (2006) reported that very low levels of lead (in the range of 10 μg/dL) were associated with ADHD, as defined by parent report of a diagnosis of ADHD and use of stimulant medication. Nigg et al. (2006) reviewed the literature on the effects of lead on ADHD-related behaviors and ADHD diagnosis and reported that both were increased even for low levels of lead exposure (<3 μg/dL).

Braun et al. (2006) analyzed data from the National Health and Nutrition Survey of about 3,800 children, which showed that 31.7% were exposed to prenatal tobacco exposure, 27.9% to blood lead >2.0 μg/dL, and 46.2% to at least one of these two factors. Association with ADHD diagnosis and treatment was documented for prenatal tobacco exposure (odds ratio $= 2.5$, with a population attributable fraction $= 18.4\%$) and blood lead concentration (odds ratio $= 4.1$, with a population attributable fraction $= 21.1\%$). The population attributable fraction for at least one of these two factors was 32.2%.

Braun et al. (2006) also reported that risk of ADHD was associated with lead exposures even below 5 μg/dL, which highlights the importance of evaluation of a possible gene-environment interaction model, because these levels of lead are common in the US population (CDC, 2005). However, a note of caution is necessary, since these associations between lead levels and ADHD-like behavior were not established for individuals formally diagnosed with ADHD. Also, other potentially correlated variables may account for these findings, which may be due to gene-environment correlation (see Taylor & Rogers, 2005; Rutter et al., 2006). Therefore, it is not yet clear whether lead can cause ADHD.

Fetal adaptations

Barker et al. (1989) proposed the hypothesis of developmental origins of health and disease (DOHaD), which was been elaborated by Gluckman et al. (2004) and Wadhwa et al. (2005). Barker et al. (1989) noted that birth weight was a predictor of adult cardiac disease, and proposed that physiologic stress (primarily maternal malnutrition) during pregnancy may result in low birth weight as well as fetal adaptations to the environment with long-term consequences on health and development. Gluckman et al. (2004) emphasized the predictive nature of adaptive responses to conditions during early development that may produce a thrifty phenotype that would maximize survival in the environment that prevailed during development, but may predispose the individual to disease in the context of a different environment in later life. Wadhwa et al. (2005) emphasized the effects of stress-related psychoneuroendocrine process in human pregnancy on fetal development. The DOHaD theory has been applied to explain the relationship of growth restriction to obesity and diabetes, as well as to cardiovascular disease and other physical disorders (see Gillman, 2005). This approach has expanded and been adopted as a focus of research by a number of investigators, and now an international organization

exists that focused on the developmental origins of health and disease (see www.DOHaD.org).

A similar hypothesis was proposed by Lou (1996) to account for MBD (Bax & McKeith, 1960; Wender, 1971). A prominent class of hypotheses was that a variety of types and degrees of stress during pregnancy produced a distribution of abnormalities in development, and that individuals with minor effects manifested in behavioral deficits (hyperactivity, attention deficit, specific learning disabilities, etc.) that may occur without clear evidence of underlying brain damage that, at least at the time, was judged too small to measure. Thus, physical signs (minor congenital dysmorphisms) and behavioral abnormalities were attributed to an underlying cause (MBD) that could not be verified, since methodologies at that time were not able to reveal direct evidence of the hypothetical effects on the brain.

Since the heyday of the MBD concept, animal models of MBD have been developed, based on known processes that produce subtle effects on the brain. For example, Altman (1986, 1987) and Amsel (1990) developed animal models with rats that could account for a type of fetal brain damage that would not be manifested post-natally as morphological abnormalities. Benveniste et al. (1991) documented that excess glutamate may produce brain damage in fetal development, and they developed the excitotoxicity hypothesis based on these observations. Mallard et al. (1995) showed that repeated bouts of anoxia and hypoxia in sheep selectively damage specific brain regions (due to known characteristics of the circulatory system in the brain).

The excitotoxicity hypothesis (Benveniste et al., 1991) was used by Volpe (1997) and Lou (1996) to explain how "minimal brain damage" may not be detected by brain imaging techniques: this damage affects late-developing granular cells (interneurons) by reducing the population of neurons that will later differentiate into specific brain structures. Thus, the morphology of the mature structure will be normal, and the abnormality will be expressed as smaller size of the structure. This is consistent with one of the primary findings from studies of brain anatomy of children with ADHD, which Castellanos et al. (2002) reported to be a 5% reduction in overall cerebral volume. This hypothesis fits with a curious pattern that has been observed in follow-up studies of premature infants: for those with documented brain damage by MRIs, few have later symptoms or diagnoses of ADHD, but for those without documented or mild abnormalities in MRIs, a high percentage do. For example, Krageloh-Mann et al. (1999) conducted a follow-up study of premature subjects without ultrasound abnormalities at birth, and found increases in ADHD were present in an assessment at 5 years of age when 37% manifested ADHD-like behaviors.

Other areas of research have addressed this issue, too. Studies of adults with brain damage (Pavese et al., 2004) implicated patterns of deficits manifested by children with ADHD, such as deficits on the CPT and the Stroop tasks. Studies of children who acquire persistent ADHD symptoms as a result of traumatic brain injury (Max et al., 1998, 2002) implicated damage to the striatal-frontal cortical circuitry as an etiology of ADHD symptoms. Similar patterns of neurochemical deficiencies were reported in groups of ADHD children (Wigal et al., 2004) and groups of children with traumatic brain injury (Konrad et al., 2003). In both of these studies, baseline differences in a resting state did not reveal difference between the clinical and control groups, but differences were detected in catecholamine levels after activation (e.g., by exercise or by a cognitive test battery). Some brain imaging studies suggest that early insults may affect dopamine function later in life. For example, in a PET study of six adolescents born premature, Neto et al. (2002) documented low levels of extracellular dopamine in striatal regions, consistent with the prediction of Lou (1996) based on MBD. Some brain signs of MBD can now be measured with Magnetic Resonance Spectroscopy (MRS). For example, in an MRS study of 12 children with ADHD, Jin et al. (2001) reported low levels of NAA (considered to be a sign of neuronal damage or loss) that suggested about 20–25% loss of or damage to striatal neurons.

Low birth weight and premature birth increase the risk for ADHD (Linnet et al., 2006; Bhutta et al., 2002; Lahiti et al., 2006). Interestingly, low birth weight and preterm birth can both result from prenatal tobacco exposure—in some cases passive exposure (see Jaakkola et al., 2001). Recent studies have evaluated the association of ADHD with low birth weight (<2500 g) or premature birth (<37 weeks gestation). Linnet et al. (2005) used a nested case-control design, and compare 834 cases to 20,100 controls from the Danish longitudinal registers. Attention-Deficit/Hyperactivity Disorder (hyperkinetic disorder) was associated with premature birth (rate ratio = 1.7 for 34 to 37 weeks gestation and 2.7 for less than 34 weeks) and with low birth weight for children born at term (rate ratio = 1.9 for birth weight 1500–2499 g and 1.5 for 2500–2999). Mick et al. (2002) evaluated the association of ADHD with low birth weight in a case-control design, and reported that ADHD cases were 3.1 times more likely than controls to have been born <2500 g. However, under the assumption of a population prevalence of low birth weight of 8.2%, they estimated that the population attributable risk percent was low (13.8%) and thus of limited practical significance, in part because the magnitude of the LBW effect was small. However, it may still serve as a model of mediation of effects via DA circuitry, and the population prevalence of low birth weight and premature birth has been increasing recently (from 11% in 1998 to about 12.5% in 2003), which resulted in a research program supported by the March of Dimes to find the cause and to reverse this unacceptable national trend (see www.marchofdimes.com). Martel, Nigg, and Breslau (in press) showed that the association of LBW

with age six ADHD symptoms was partially mediated by cognitive weaknesses in motor control and vigilance. Although these mediation effects were modest, they illustrate that environmental effects contribute to these neuropsychological profiles associated with ADHD.

Wiles et al. (2006) used data on 4,813 children from the ALSPAC cohort in Bristol UK to evaluate the association of behavioral problems at age seven year with fetal growth. They reported an association of birth length with ratings of hyperactivity on the SDQ questionnaire (a one SD increase in birth length was associated with a 10% decrease in odds of being in the top tercile of ratings of hyperactivity at 81 months of age).

Gene-environment interactions

Few molecular genetic studies of ADHD have addressed gene-environment interactions. Several publications about gene × environment interactions in the Dunedin birth cohort study have been reported (Caspi et al., 2002, 2003, 2004). These studies were recently reviewed by Caspi and Moffitt (2006), who discuss three areas of gene-environment interaction and behavior (or psychopathology): the moderating influence of enzyme monoamine oxidase A (MAO-A) genotype on the effects of child maltreatment and the cycle of violence (Caspi et al., 2002), the moderating influence of serotonin transporter (5-HTT) genotype on the effects of stress/life events and depression (Caspi et al., 2003), and the moderating influence of catechol-O-methyltransferase (COMT) genotype on the effects of adolescent cannabis use and psychosis (Caspi et al., 2004). These exposures (to child maltreatment, stress/life events, and cannabis use) accumulate over time. Thus, in these examples (as well as for hypotheses about ADHD), provisions should be made to track these exposures over time to test the a priori hypotheses about the moderating effects of environmental exposures on the established associations of genes with psychopathologies.

One gene-environment study that specifically addressed ADHD was by Kahn et al. (2003), which evaluated maternal smoking and the DAT gene. In the cases with maternal smoking during pregnancy, ADHD symptoms were more severe in individuals homozygous for the most frequent allele of the DAT gene (the 10R/10R genotype) but not if other alleles were present (e.g., the 9R/10 or the 9R/9R genotype). The presence of at least one minor allele of the DAT (the 9R) may protect against this environmental factor of maternal smoking. If confirmed, this effect may provide a clue as to how to mitigate this environmental factor and prevent ADHD in some cases. However, the number of cases with the 9/9 genotype is small, due to the relatively low frequency of the 9R allele of the DAT gene. To adequately evaluate this gene-environment interaction, a large number of cases as well as controls would be required with good information about the environmental exposure (in this case, due to maternal smoking).

Another gene-environment study that specifically addressed ADHD was by Brookes et al. (2006), who used the transmission disequilibrium test in parent-child trios to evaluate multiple DAT genotypes (an intron 8 VNTR as well as the DAT1 40 bp VNTR) and two environmental factors maternal alcohol consumptions (any vs. none) and heavy smoking (at least 20 cigarettes/day) during pregnancy. They reported an association with the common (77%) 3-repeat allele of the intron 8 VNTR, as well as with the common (73%) 40 bp VNTR and the combination of these two common variants which itself is common (59%). However, the linkage disequilibrium (non-random association of alleles) was present only in those cases where maternal alcohol consumption was reported, which suggests that DAT genotype moderates the environmental risk for ADHD. The interaction of DAT genotype with maternal smoking during pregnancy was not significant, and thus did not replicate the finding reported by Kahn et al. (2003), but this may be due to the limited assessment of maternal smoking during pregnancy in this study.

Jacobson et al. (2006) evaluated gene-environment interaction and correlation by evaluating ADHD ratings (one of many outcomes) in a study of maternal alcohol consumption and genetic polymorphism of the enzyme alcohol dehydrogenase (ADH1B) that catalyzes ethanol oxidation and thus is involved in the major pathway of alcohol elimination. In an assessment of 263 children at age 7.5 years, the maternal but not the child genotype interacted with prenatal exposure to alcohol to produce an effect on performance on cognition and behavior: the absence of the ADH1B*3 allele and prenatal exposure to alcohol was associated with higher ratings of ADHD symptoms and other problem behaviors as well as with poorer performance on neuropsychological tests. Interestingly, the child genotype appeared to be associated with the opposite pattern. This study concluded that in the presence of maternal alcohol consumption during pregnancy, the maternal ADH1B*3 allele provides some protection to the fetus, perhaps by more rapid metabolism of alcohol and reduction of the peak blood alcohol concentration that is an important determinant of fetal alcohol damage.

Summary

The literature on brain imaging clearly supports the presence of abnormalities in structure (smaller size) and function (hypoactivation) of critical brain regions related to dopamine. The literature on molecular genetics clearly supports the presence of associations with dopamine genes (DRD4 and DAT). The literature on environmental effects suggests an increased risk for ADHD is related to maternal smoking during

pregnancy, exposure to low levels of lead, premature birth or low birth weight, and other possibly factors that alter fetal development with lasting effects or permanent detrimental effects on attention and behavior. After decades of research and clinical experience, we have some promising hypotheses about specific factors related to brain development, genetics, and environmental exposures that may play a role in the multiple etiologies of ADHD, each with varying degrees of evidence to support them (see Nigg, 2006). However, the empirical data are based on small-scale studies, which cannot accommodate the interactive and confounding effects that are likely to occur in this field of research. To move forward in the ADHD area, large-scale studies are required which examine multiple potentially relevant factors within the same experimental design and on the same extensive population.

Some studies have used combinations of the DRD4 and DAT candidate dopamine genes to investigate gene-gene interactions that may define etiologic subtypes of ADHD based on the dopamine hypothesis of ADHD. One example of this is the study by Durston et al. (2005) that investigated whether brain anatomical differences are present in subgroups defined by the combination of DRD4 and DAT genotypes described above. They reported these candidate dopamine genes both had significant effects on brain anatomy but in different brain regions (DAT effects on caudate volume and DRD4 effects on prefrontal gray-matter volume), but suggested one presumed genetic factor (DAT 10R/10R genotype) may confer risk and another (DRD4 7R-present genotype) may confer protection. Another study by Mill et al. (2006) used the combination of the genotypes defined by the VNTR polymorphisms of the DRD4 and DAT gene to form subgroups of individuals from two cohort studies and to perform an innovative evaluation of the combination of risk genotypes for ADHD on intellectual ability. They reported that in the ADHD group the number of risk genotypes was related to a reduction in measured IQ. In both of these groundbreaking studies, the sample sizes for critical subgroup comparisons were small. For example, in the Durston et al. (2006) study, despite the relative large sample size overall for an MRI study ($n = 68$ to 70), the combination of factors based on diagnosis (normal, ADHD, and unaffected ADHD siblings, with 20 to 24 per group) and two genotypes, the subgroup size was small and hampered the evaluation of the potential gene-gene interactions of these candidate dopamine genes. The limitations of sample size are also apparent in the Mill et al. (2006) study, in which the combination of factors (subjects with ADHD vs. subjects without ADHD with subgroups defined by two genotypes) resulted in relatively small number of individuals in these critical subgroups. For example, in the combined subgroup across both cohorts with both risk genotypes on these candidate genes, the sample size was only $n = 43$. Thus, in addition to these studies pointing the way for future studies of genetic complexity, they both demonstrate that larger sample sizes will be required in these future studies to be able to address the interactions of multiple factors.

In addition to plausible gene-gene interactions (see above), the combination of multiple environmental factors is an obvious fertile direction for future investigation of the dopamine deficit hypothesis of ADHD. The study by Braun et al. (2006) provides direction in this area, based on its evaluation of information about smoking and lead. The study by Brookes et al. (2006) also considered multiple environmental factors, based on retrospective recall of environmental exposures related to alcohol consumption ("Did you give up alcohol during pregnancy?") and smoking ("Did you smoke at least 20 cigarettes a day for 3 months of the pregnancy?"). This study provided provocative information relevant to the dopamine hypothesis of ADHD, but the next step should address potential problems with retrospective accounts by the use of methods that have been described in detail for prospective assessments (Golding et al., 2001; Inskip et al., 2004) and direct measurements or biomarkers (Lanphear & Bearer, 2006). The use of these methods may be essential for the serious assessment of gene-environment interactions and correlations (see Rutter et al., 2006).

As outlined in Fig. 1, ADHD diagnoses have increased steeply in recent years in the United States. An even more striking increase has occurred with respect to diagnoses of autism (for review, see Stefanatos & Joe, 2007), as well as medical conditions such as asthma. Contributing factors to the rising incidence may be benign, such as less stringent diagnostic criteria and more effective ascertainment of cases. However, even if that is so, it does not exclude a true increasing incidence of the disorder in question, which would not be benign. Such an increase would be far too rapid to be due to genetic changes in nucleotide sequence, which is shaped by the environment over an evolutionary time scale. It more likely would reflect either the direct action of an environmental toxicant or an indirect environmental effect of factors such as maternal diet (see Waterland & Jirtle, 2004; Dolinoy et al., 2006) or mother-child interactions (see Meaney & Szyf, 2005; Weaver et al., 2005) that can produce profound epigenetic changes as shown in proof-of-principle studies in animals. The molecular mechanisms for environmental effects may involve epigenetic modifications to the genome, including chemical changes (methylation) and shape changes (histone modification), which may play a role in the etiology of disorders such as ADHD or autism (see Bjornsson et al., 2004; Callinan & Feinberg, 2006).

It is notable that the main effects of both individual genes and individual environmental risk factors related to ADHD are quite modest. It is also notable that some of the environmental risk factors that influence ADHD are quite common in the population (for example, low level lead exposure). This state of affairs suggests that it may be quite fruitful to examine gene-environment interactions further,

but the complexity of possible etiologies introduced by such combinations, surely present in nature, will require extraordinary sample sizes for adequate evaluation. The literature on gene-environment interaction shows the limitations imposed by sample size even in studies that start with what may be considered large sample sizes for studies of ADHD. For example, the study by Kahn et al. (2003) was based on a sample size of $n = 161$, but was divided to form subgroups based on maternal smoking status and DAT genotype of the child, resulting in the following subgroups sizes: Exposed + DAT − 10R/10R = 18, Exposed + DAT − Other = 16, Not Exposed + DAT − 10R/10R = 73, Not Exposed + DAT − Other = 54). These critical subgroups necessary for the evaluation of this interesting gene (DAT) by environment (nicotine exposure) interaction are small (i.e., in the exposed subgroups, less than 20 subjects). The reports of gene-environment interactions by Caspi et al. (2002, 2003, 2004) also show the need for a large sample. Despite the size of the Dunedin cohort ($n = 1045$), the critical subgroups generated to evaluate the hypotheses of gene-environment interactions were relatively small. For example, in the Caspi et al. (2003) study of the gene (5-HTT genotype) and environment (severe maltreated) interaction, the subgroup sizes for the extreme combination of severe maltreatment were $n = 16$ for the s/s genotype, $n = 33$ for the s/l genotype, and $n = 34$ for the l/l genotype.

Much larger sample sizes will be required to go beyond these important first steps to evaluate gene by environment interactions related to child psychopathology. Recent and planned large birth cohorts should provide the data to take the next steps to rigorously test these hypotheses. For example, the Danish National Birth Cohort identified 100,000 children (see Olsen, 2005) and efficiently obtained information from medical records and registries outcome, and the protocol also judiciously included the collection of biological samples from mothers and children, providing a rich resource for future investigations as well as for potential replication of interesting findings from studies with smaller samples. For example, as one of the initial outcomes about 6,000 preterm births were documented (see Olsen, 2005). This valuable sample should provide large subgroups to evaluate genetic and environmental effects (and gene-environmental interactions) that may explain the increased prevalence of ADHD associated with premature birth, which have been reported in many smaller studies in the literature as discussed here. Cross-national differences related to this factor may be one contributor to cross-national differences in prevalence, since the rate of premature birth is much higher in the US (12.5% in 2003; see www.marchofdimes.com) than in many European countries (about 6% in Norway in 2003; see Langhoff-Roos et al., 2006).

The National Children's Study (NCS) planned for the US proposes to match the size of Danish National Birth Cohort study and to collect much more detailed information directly from observation of mothers and children prospectively from before birth to adulthood (see www.nationalchildrensstudy.gov). If implemented as planned, the NCS will recruit a large birth cohort of 100,000 children representative of the contemporary birth population in the US centered around 2010, and will obtain broad measures of exposure and outcome taken in 16 visits scheduled across stages of development (before conception; three times during pregnancy; at birth; at 1, 6, 12, and 18 months of age in early childhood; at 3, 5, 7, 9, and 12 years of age in childhood; at 16 and 20 years of age in adolescence). This would provide a resource to address critical issues about the dopamine hypothesis of ADHD as well as critical issues about most childhood disorders. In the NCS, the real time evaluation of a broad range of exposures in a large and representative sample of 100,000 children, with specific diagnostic criteria for ADHD evaluated in a clinic visit at five years of age, should identify about 5,000 children diagnosed with ADHD, and also provide a matched control group that could be drawn (and re-drawn) from the large number without a diagnosis of ADHD.

This sample would provide an opportunity to replicate the few studies in the literature on gene-gene interactions and gene-environment interactions discussed here, which are critical for understanding etiologic subtypes of ADHD and other childhood disorders.

The size of the cohort and the intensity of measurement of exposures and outcomes of the children vary as expected (see Frank et al., 2006), with less detailed measures from birth records and questionnaires on the largest sample and detailed measures on subset of some of the smaller samples. Some established birth cohorts have used protocols to obtain detailed information to address some of the critical issues related to hypotheses about fetal adaptations and childhood outcomes. For example, the Avon Longitudinal Study of Parents and Children (ALSPAC) identified about 10,000 children by birth in 1992 (Golding et al., 2005). The hypothesis of gene-environment interactions and birth size has been addressed exquisitely by Dunger et al. (1998) and Ong et al. (1999). In these reports, a growth phenotype was established based on detailed measures of trajectory over time, so that the subgroups were defined based on a stable pattern of growth (non-changers) or a pattern reflecting catch-up or post-natal realignment by switching to a different growth curve. This definition of phenotype in terms of growth trajectory over time allowed for the resolution of a paradox about birth size and glucose tolerance: in the non-changers, a genetic factor was important (the III/III genotype of the insulin gene was associated with larger birth weight and impaired glucose tolerance), while in the changers, an environmental factor was important (smaller birth weight was associated with maternal nutritional restraint that produced fetal adaptations in

metabolic and endocrine function and was associated with impaired glucose tolerance). This demonstration of how to address the complexity likely to be present in genetic and environmental influences on development points the way for studies of effects on behavior in childhood (see Wiles et al., 2005). The Southampton Women's Survey (SWS) also provided a cohort of children with detailed prospective measures from before pregnancy and throughout critical phases of fetal, infant, and child development (see Inskip et al., 2005). In the SWS, 2,567 children were identified between 1998 and 2005 (Inskip et al., 2006), and initial evaluations focused on maternal diet and liver blood flow (Robinson et al., 2004), infant lung function and birth weight (Lucas et al., 2004), and maternal body composition, nutrition, and smoking on bone development during pregnancy (Javaid et al., 2005). As the children in this well-characterized cohort are followed, evaluation of contributions of these and other environmental factors on behavioral disorders such as ADHD will be possible. However, based on a standard assumption about the prevalence of ADHD, even these cohort studies would be expected to provide samples of only 500 ADHD cases in the ALSPAC cohort and 125 ADHD cases in the SWS cohort.

Recent trends in studies of and hypotheses about causes of ADHD have emphasized genetic factors, given that heritability is high (often estimated at >0.8 when parent ratings are relied upon). However, environmental effects, expressed as gene-environment interactions, have not been evaluated in twin studies. This will be possible in the National Children's Study. In the NCS, about 1.5% of the births should result in twins, and about half of these will be monozygotic and half dyzygotic. Thus, this study will produce a large number of twins for whom detailed measures of many environmental exposures will be available. This will provide opportunities to evaluate separately the pure genetic and the gene-environment interaction component of heritability. In prior twin studies of severity of ADHD, the high heritability estimates may be due to many gene-environment interaction effects, which can be evaluated using the data analysis methods proposed by Purcell et al. (2004).

An additional complicating factor in the analysis of gene by environment interactions is evaluation of the phenotype as it emerges over time. The monitoring of the course of fetal and infant growth to define phenotypes (e.g., subgroups of children who stay on expected growth trajectories or those who "change") provides an example of this strategy (see Golding et al., 2001; Dunger et al., 1998; Ong et al., 1999), and an example of the evaluation of cardiovascular disorder over time is provided by Sing et al. (2003). The developmental pattern of symptom presence defines different trajectories of outcome for subgroups of ADHD children in the follow-up phase of the Multimodal Treatment study of ADHD (see Swanson et al., in press) and different trajectories for brain neuroanatomical size for different brain regions related to dopamine and ADHD (Castellanos et al., 2002; Shaw et al., 2006). These studies suggest that the definition of phenotype as a trajectory over time may be essential to understand even the simple model that considered multiple gene and environmental factors in the evaluation of the dopamine deficit hypothesis of ADHD.

Real-time and repeated evaluation of fetal development during pregnancy and of the birth process will be provided by the National Children's Study. Detailed information about birth weight and gestation will be available to evaluate in a prospective fashion the hypotheses about effects of premature birth on the later presence and severity of symptoms of ADHD (e.g., see Lou, 1996). At age three years, when a clinic assessment of all cases in the study will occur, it should be possible to select cases with high and low risk for MBD, which could be compared to provide a test of the modern version of the MBD hypothesis.

An important advance in the evaluation of subtypes of ADHD would be to consider two types of etiologic factors – genetic and environmental. The review presented here suggests that at least two areas related to each type of factor should be considered. For example, the genetic factors should include at a minimum the DRD4 and DAT genotypes, and the environmental factors should include, at a minimum, some environmental toxicants (nicotine and lead) and some pregnancy factors (preterm birth and small size due to growth restriction). The literature reviewed here suggests some relatively simple hypotheses to test, such as a hypothesis about conditional genetic risk factors for ADHD (e.g., the 10R/10R genotype of the DAT gene but only in the presence of maternal smoking during pregnancy [as suggested by Kahn et al., 2004]), or a hypothesis about combinations environmental and genetic effects which may be independent, so that environmental exposures (e.g. to lead and smoking during pregnancy) increase the risk for the full syndrome of ADHD in all genotypes, but in addition the risk for a partial syndrome is increased in a specific genotype (e.g., for the 7R-present genotype of the DRD4 gene) even in the absence of environmental exposures (as suggested by Swanson et al., 2000).

The existing studies of genetic and environmental factors do not meet the standards for modern molecular genetic studies proposed by Sing and his colleagues (Sing et al., 2003; Clark et al., 2005), who emphasize that gene-gene and gene-environment interactions are likely to be present and require large sample size to detect and describe. They point out that most current studies fail to address the known and expected complexity of gene-gene and gene-environment interactions that has emerged in research of other complex disorders, such as hypertension. A review of the literature on gene and environmental effects related to ADHD should recognize these realities of complex disorders that have not yet, but must

be, addressed in the future to identify and refine meaningful etiologic subtypes of ADHD.

Over the next decade, the National Children's Study should provide extensive information about environmental factors related to ADHD and most other common disorders of childhood, such as autism and reading disabilities. If implemented as planned, this extraordinary study should provide a large sample size and detailed measures of exposures to multiple factors that will provide an opportunity to evaluate many of the intriguing speculation about gene-environment interactions that may account for a significant fraction of the children with ADHD.

Definition of technical terms

AMP: amphetamine, a stimulant drug with two optical isomers (d and l), that is considered to be a dopamine agonist that produces release and prevents reuptake of the neurotransmitter dopamine, and has been used for over a half century for the treatment of ADHD and related disorders.

BID: The Latin abbreviation for the drug administration schedule consisting of twice a day administration that has been used for regimes of immediate-release formulations for some stimulant medications to extend the duration of actions throughout the school day.

CDC: Center for Disease Control, a government agency that has as one of its charges to document and track the incidence and prevalence of disorders.

CR: Controlled-release, the programmed delivery of a drug by a system such as OROS.

DA: Dopamine, a neurotransmitter that is assumed to play an important role in the etiology of ADHD and other disorders.

DAT: Dopamine Transporter, a component of the system that regulates synaptic levels of the neurotransmitter dopamine.

DDD: Defined Daily Dose, the unit of a drug that is based on the typical daily dose used in the treatment of disorders for which it is prescribed.

DOHaD: Developmental Origins of Health and Disease, the hypothesis that the fetal maternal environment induces programming effects on the development of structures and processes before birth that have lasting effects throughout the life span, which is also the name of an international organization of investigators that focuses on the effects.

DRD4: Dopamine Receptor D4, a subtype of the class dopamine receptors thought to be dense of in the frontal brain regions (e.g., cingulated cortex).

DSM: Diagnostic and Statistical Manual, the manual of the American Psychiatric Association that contained the lists of symptoms and other criteria for making diagnosis of mental disorders.

Exon: A region of a gene that is expressed and codes for proteins, so that variations (polymorphism) create differences in structure.

IR: Immediate-release, the usual way a drug is absorbed when taken orally.

MBD: Minimal Brain Damage or Minimal Brain Dysfunction, the terms applied in the 1960s and 1970s as descriptions of an inferred but not observed underlying basis for ADHD and related disorders of activity, attention, and learning.

MPH: Methylphenidate, a stimulant drug with four optical isomers (d and l, threo and erythro) is considered to be an indirect dopamine agonist that acts by blocking the reuptake of the neurotransmitter dopamine, primarily in the striatal regions where the density of the dopamine transporter is high.

NE: Norepinephrine, a neurotransmitter that has been investigated as a contributor to the etiology of ADHD and other disorders.

OROS: Osmotic Release Oral System, a capsule that contains compartments for a short acting drug and a water-sensitive expanding polymer surrounded by a semi-permeable membrane, constructed so that expansion of the polymer after swallowing the systems produces pumping action to deliver the drug at a controlled rate across in the gastrointestinal tract.

PET: Positron Emission Tomography, methods of imaging the structures and function of the brain using a variety of radioactive tracers (ligands), which emit positrons that are detected to provide location in the brain.

Promoter: A region of the gene that is not expressed and for which variation (polymorphism) does not code for structural differences but may alter amount of protein or density.

SN: Substantia Nigra, a midbrain area that contains cell bodies of dopamine neurons that project into striatal brain regions.

SPECT: Single Photon Emission Computer Tomography, methods of imaging function and structures of the brain using radioactive tracers (ligands) with less precision than PET.

TID: The Latin abbreviation for the drug administration schedule consisting of three times a day administration that has been used as the regime for some immediate-release formulations of stimulant medications to extend the duration of actions across the day.

VTA; Ventral Tegmental Area, a midbrain area that contains cell bodies of dopamine neurons that project directly into the frontal cortex as well as to other brain regions.

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