Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3: 617-628

ARTICLE *in* NATURE REVIEWS NEUROSCIENCE · SEPTEMBER 2002

Impact Factor: 31.38 · DOI: 10.1038/nrn896 · Source: PubMed

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NEUROSCIENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE SEARCH FOR ENDOPHENOTYPES

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Research on attention-deficit/hyperactivity disorder (ADHD), a highly prevalent and controversial condition, has, for the most part, been descriptive and atheoretical. The imperative to discover the genetic and environmental risk factors for ADHD is motivating the search for quantifiable intermediate constructs, termed endophenotypes. In this selective review, we conclude that such endophenotypes should be solidly grounded in the neurosciences. We propose that three such endophenotypes — a specific abnormality in reward-related circuitry that leads to shortened delay gradients, deficits in temporal processing that result in high intrasubject intertrial variability, and deficits in working memory — are most amenable to integrative collaborative approaches that aim to uncover the causes of ADHD.

Attention-deficit/hyperactivity disorder (ADHD) is one of many labels for one of the most prevalent conditions in child psychiatry, and, undoubtedly, the most controversial. ADHD is conservatively estimated to occur in 3.0–7.5% of school-age children[1], but more permissive criteria yield estimates of up to 17% (REF. 2), and up to 20% of boys in some school systems receive psychostimulants for the treatment of ADHD[3]. Despite the absence of controlled studies in pre-school-age children, and concern about potential long-term adverse effects[4], stimulant medications are increasingly being administered to children as young as two years of age[5]. The 'initial phase' of research into ADHD has been descriptive by design, but it has also been driven by adult-based models from psychiatry, psychology and neuroscience. Our purpose here is to highlight the crucial studies and perspectives that have guided clinical investigations of ADHD, which form the basis for new integrative and multidisciplinary approaches that incorporate a developmental perspective. We argue that the field is now poised to build on the insights gleaned from descriptive symptom-based approaches by developing endophenotypes of ADHD that are grounded in neuroscience. Endophenotypes are heritable quantitative traits that index an individual's liability to develop or manifest a given disease, and they are thought to be more directly related than dichotomous diagnostic categories to aetiological factors[6,7].

Research into ADHD has been hampered by confusion over nomenclature and diagnostic criteria. The many terms that have been applied to ADHD include attention-deficit disorder (ADD), hyperactivity, hyperkinesis, hyperkinetic syndrome, minimal brain dysfunction and minimal brain damage[8]. The current criteria for the diagnosis of ADHD (BOX 1), published by the American Psychiatric Association in the 1994 *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition; DSM-IV), are the most widely used and form our starting point[8]. Other proposed criteria include those for the *International Statistical Classification of Diseases and Related Health Problems* (tenth revision; ICD-10) diagnosis of hyperkinetic disorder, which represents a more severe and 'refined' subset of DSM-IV ADHD[9], but which does not recognize the DSM-IV predominantly inattentive subtype, and those for the conjunction of disorders of attention, motor control and perception (DAMP)[10], which have been primarily used in Scandinavia.

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doi:10.1038/nrn896

The search for a single theory of ADHD

Partly in response to controversy about the validity of ADHD[1] and legitimate concern about an apparent rapid increase in its prevalence in the 1990s, investigators have unsuccessfully attempted to formulate a single theory of ADHD[11] that would facilitate the development of an objective diagnostic test. These single-cause theories have appealed to psychological constructs such as response inhibition[12], regulation of arousal/activation[13] and delay aversion (the avoidance of delay, often expressed as the choice of smaller, earlier rewards over larger, later rewards)[11]. These theories have clearly

Box 1 | **Diagnostic criteria for attention-deficit/hyperactivity disorder**

The following criteria for attention-deficit/hyperactivity disorder (ADHD) are reproduced, with permission, from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition; DSM-IV)[8].

A. Either (1) or (2):

(1) six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities

(b) often has difficulty sustaining attention in tasks or play activities

(c) often does not seem to listen when spoken to directly

(d) often does not follow through on instructions and fails to finish schoolwork, chores, duties in the workplace (not due to oppositional behaviour or failure to understand instructions)

(e) often has difficulty organizing tasks and activities

(f) often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

(g) often loses things necessary for tasks or activities (for example, toys, school assignments, pencils, books or tools)

(h) is often easily distracted by external stimuli

(i) is often forgetful in daily activities

(2) six (or more) of the following symptoms of hyperactivity–impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is expected

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) often has difficulty playing or engaging in leisure activities quietly

(e) is often 'on the go' or often acts as if 'driven by a motor'

(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (for example, butts into conversations or games)

B. Some hyperactive–impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (for example, at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia or other Psychotic Disorder, and are not better accounted for by another mental disorder (for example, Mood Disorder, Anxiety Disorder, Dissociative Disorder or a Personality Disorder).

Code based on type:

314.01 — Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria Al and A2 are met for the past 6 months

314.00 — Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion Al is met but Criterion A2 is not met for the past 6 months

314.01 — Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive–Impulsive Type: if Criterion A2 is met but Criterion Al is not met for the past 6 months

ADHD is often associated with other disruptive behaviours and with specific learning disorders[8]. Although DSM-IV established three behavioural subtypes, there is evidence that they do not 'breed true', in contrast to empirically derived subtypes that are obtained by performing a type of factor analysis on parental ratings[128]. The empirical approach might offer a better categorization of ADHD, particularly for genetic studies. However, parent ratings are more likely than teacher ratings to be biased[129,130].

Symptom scales have been clinically useful and have formed the bulwark of ADHD research[131], but apart from problems of bias and subjectivity, they yield highly skewed distributions, as symptoms are typically measured as absent, slightly present, and so on. Swanson's seven-point Likert (SWAN) scale, which remedied this flaw, is being used in several large studies (see ADHD.net online).

Neither DSM-IV nor ICD-10 (another diagnostic algorithm) gives guidelines for combining information from multiple informants, which is problematic, because parents and teachers often disagree[123]. Another challenge is that neither of these diagnostic algorithms provides operational definitions of the specific symptoms of inattention and hyperactivity/impulsivity, so that one behaviour (such as 'frequently leaves seat') can be misinterpreted as evidence for several symptoms (for example, often leaves seat; easily distracted by external stimuli; difficulty sustaining attention). So, it is not surprising that one of the inattentive items ('is often easily distracted by extraneous stimuli') was found to load more highly on the hyperactivity/impulsivity factor than on inattention in a factor analysis of teacher ratings of primary-school children (T. Sagvolden, personal communication). Moreover, although the symptoms of ADHD are not equal in their ability to predict the diagnosis[132], DSM-IV and ICD-10 treat every item equally in making diagnostic decisions. The development of assessment tools that attempt to provide operational definitions for each symptom[133], and the use of alternative algorithms that limit the diagnosis to clusters of symptoms that predict impairment[134], are likely to increase the validity and precision of the ADHD diagnosis.

advanced our understanding of ADHD by vigorously stimulating new research[14,15]. However, the unintended consequence has been that ADHD has been reified "as an ontological and psychological reality, rather than just a useful clinical construct"[11], with the result that relatively little progress has been made towards elucidating its pathophysiology, despite a burgeoning literature that is summarized in BOX 2.

Aetiological factors

Symptom-based descriptive diagnostic criteria were adopted for psychiatric disorders in reaction to the psychoanalytic categories that dominated from the 1920s to the 1970s. The universal use of DSM-IV, at least in research settings, has put the reliability of psychiatric diagnoses on a par with those of other complex medical conditions[1], which is a prerequisite for aetiological explorations. The increasing success of the Human Genome Project has engendered enthusiasm for discovering the genetic causative factors of common, complex conditions such as ADHD. However, aetiological factors include not only genetic variations or mutations, but also environmental factors and, most importantly and most difficult to identify, interactions between genes, and between genes and the environment[16]. These factors are the initial causes of the multiple conditions that manifest symptomatically as ADHD, and their eventual identification should be accorded high priority.

Genetic factors. A range of family, adoption and twin studies has provided compelling evidence that genetic factors contribute to a substantial portion of the phenotypic variance in the expression of ADHD, with most estimates of heritability exceeding 0.70 (reviewed in REFS 17–19). Nearly all molecular-genetic studies have focused on testing candidate genes that are linked to dopaminergic[20] or noradrenergic pathways[21] (see below for further discussion of the importance of dopaminergic mechanisms in ADHD). However, in the only genome-wide scan to be published so far[22], both the dopamine receptor D4 locus (*DRD4*) and the dopamine transporter (DAT) locus (*DAT1* or *SLC6A3*) were excluded as representing major genes that contribute to ADHD susceptibility, because loci that doubled the risk of ADHD in gene carriers should have been detected. However, small gene effects, such as those reported for these loci (BOX 2), could not be excluded. Interestingly, two linkage peaks, at chromosomal locations 2q24 and 16p13, coincided with loci that were linked to autism in another study[22,23], consistent with the idea that susceptibility genes cut across psychiatric disorders.

Environmental factors. Environmental aetiologies for the *de novo* development of ADHD include traumatic brain injury[24] and stroke, particularly when the putamen is affected[24,25]. Other environmental risk factors include severe early deprivation[26], family psychosocial adversity[27] and maternal smoking during pregnancy[28], although the last two factors might also interact with parental genotype. For example, mothers who have ADHD are more likely to smoke and to use other drugs of abuse. Nevertheless, accumulating evidence points to prenatal nicotine exposure as an important independent contributor to deleterious early brain development. First, nicotinic acetylcholine receptor proteins (nAChRs) and gene transcripts are expressed very early in the human brain, indicating that they might be important in modulating dendritic outgrowth and establishing neuronal connections during development[29]. Second, prenatal and perinatal exposure to nicotine influences cells in the hippocampus and somatosensory cortex[30], affects glutamate release and reuptake in developing cerebellar cells in culture[31], and produces enduring changes in catecholaminergic systems and in locomotor activity[32]. Finally, both animal and human studies indicate that these neurobiological effects of nicotine can, in turn, impair cognitive function, particularly WORKING MEMORY (and, in younger individuals, response inhibition)[33]. Presumably, specific genotypes that have yet to be discovered confer even greater vulnerability to the deleterious effects of nicotine on brain development. The question is how best to detect these genotypic vulnerabilities.

Putative endophenotypes and behaviour

ADHD, similar to all studied psychiatric disorders, fails to follow Mendelian patterns of inheritance and is classified as a complex genetic disorder. Nearly two decades of unsuccessful efforts in psychiatric genetics have led to the conclusion that symptom-based diagnostic classification systems do not facilitate (and can actively obstruct) mapping between susceptibility genes and behavioural outcomes[34]. So, there is great interest in discovering quantitative indices of disease liability or risk, termed endophenotypes, that predict the risk of ADHD in the same way that serum cholesterol predicts the risk of cardiovascular disease[7]. Such endophenotypes should be continuously quantifiable, should predict disorder probabilistically, and should be closer to the site of the primary causative agent (whether genetic or environmental) than to diagnostic categories[7]. To these three requirements, we add a fourth: priority should be given to endophenotypes that are based or anchored in neuroscience. In this way, the power of experimental control across model organisms and systems can be most effectively brought to bear on clinically relevant questions. We review some candidate endophenotypes that should be considered for collaborative[11,21] and comprehensive large-scale studies. First, we discuss the most easily discerned symptom of ADHD — locomotor hyperactivity — and the attempts that have been made to uncover its neurobiological bases.

Locomotor hyperactivity and dopamine

All rating scales for ADHD include items that relate to motoric hyperactivity, but these ratings can be confounded by aggression and oppositionality[35]. In a small preliminary study, objectively confirmed hyperactivity during cognitive testing[36] predicted the ability of optimal clinical doses of the psychostimulant methylphenidate (BOX 3) to normalize blood flow in the BASAL GANGLIA[37] and cerebellar vermis[38] in boys who met the DSM-IV

WORKING MEMORY
The representation of items held in consciousness during experiences or after retrieval of memories. Working memory is short-lasting and associated with the active rehearsal or manipulation of information.

BASAL GANGLIA
A group of interconnected subcortical nuclei in the forebrain and midbrain that includes the striatum, globus pallidus, subthalamic nucleus, ventral tegmental area and substantia nigra.

Box 2 | **Aetiological studies**

The present state of aetiological studies of attention-deficit/hyperactivity disorder (ADHD) is presented schematically as an incomplete version of the Morton–Frith causal developmental model[6]. Most studies have been primarily descriptive, with the aim of examining differences between patients and control subjects. Because of the expense of obtaining representative samples, all neurobiological studies have used convenience samples, which are conditioned by referral patterns. Most studies either fail to differentiate subtypes of ADHD, or enrol mainly subjects with combined-type ADHD.

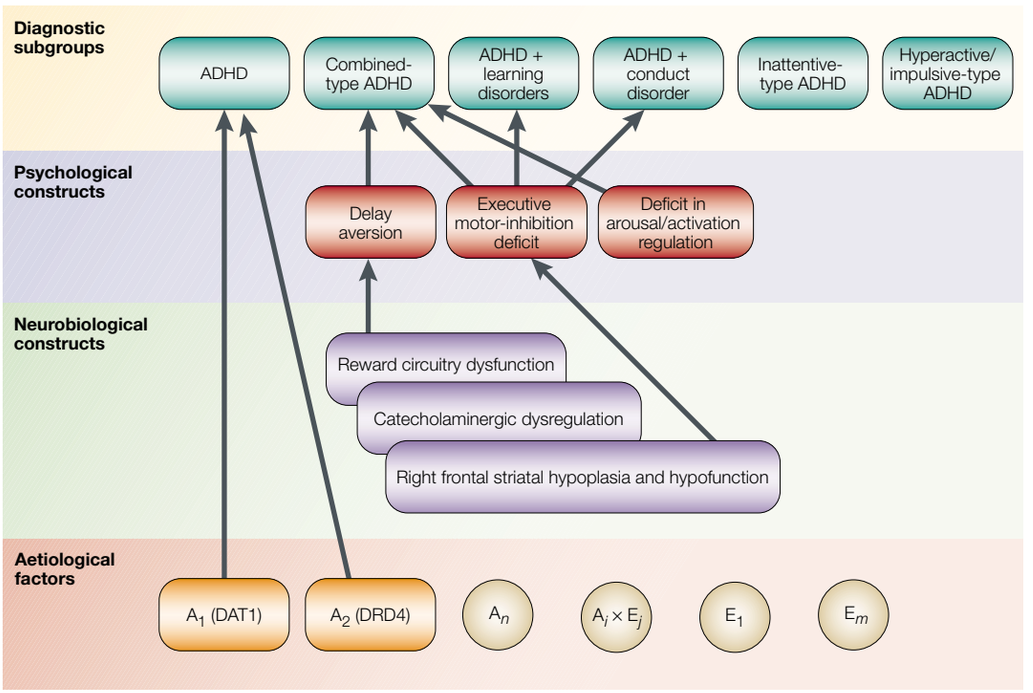
A loosely formulated dopamine hypothesis (reviewed in REF. 54) motivated candidate-gene studies that have been surprisingly productive. For example, the reported biased transmission of a ten-repeat allele of an untranscribed variable tandem-repeat region in the dopamine transporter gene (*DAT1*) in probands with ADHD[135] has been replicated in independent samples and continues to be studied. Although this allele does not alter the structure of the transporter protein, it might affect the expression and, therefore, the density of the transporter, abnormalities of which have been associated with ADHD in functional imaging studies[68].

A case–control association between the seven-repeat allele of dopamine receptor D4 and ADHD has been more extensively confirmed[136]. However, the estimated EFFECT SIZES that are associated with these candidate alleles are modest, with current estimates of the odds ratios for both genes in the range of 1.2–1.4 (I. Waldman, personal communication). That is, the risk of manifesting ADHD seems to be increased by about 20–40% for individuals that carry the putative susceptibility alleles. Collaborative analyses are investigating whether these genes interact additively or multiplicatively, although preliminary results have been negative[21].

The construct validity of the competing psychological theories of delay aversion[11], deficits in response inhibition[12] and deficits in arousal/activation regulation[13], are being addressed by contrasting them with each other[11,137]. Subtyping of subjects has been limited to the diagnostic level. For example, studies of delay aversion have been carried out only in the case of combined-type ADHD. Inhibition deficits do not clearly differentiate children with ADHD from those with conduct disorder or with ADHD and comorbid conduct disorder[59], and are also associated with reading disorder[138].

Current neurobiological constructs are based on neuroimaging techniques, including anatomical[139] and functional magnetic resonance imaging (MRI)[140]; positron emission tomography (PET) and single-photon emission computed tomography (SPECT); quantitative electroencephalography (EEG) and evoked response potentials[117]. Anatomical MRI studies have found reduced volumes, mainly supporting the idea that a distributed circuit that includes the right prefrontal cortex, the caudate nucleus, the cerebellar hemispheres and a subregion of the cerebellar vermis, underlies ADHD[117]. These findings are consistent with results from functional imaging studies, although the latter should be considered preliminary because of small sample sizes and a lack of truly replicated findings. Electrophysiological studies also agree that ADHD involves hypofunction of catecholaminergic circuits, particularly those that project to the prefrontal cortex[48]. However, all these studies have been descriptive, the primary goal being to establish differences between subjects with ADHD and controls. The resulting neurobiological constructs are shown as overlapping, because they have been formulated in too vague a manner to be definitively falsifiable.

A_{1-n}, additive genetic factors; DAT1, dopamine transporter (ten-repeat polymorphism); DRD4, dopamine receptor D4 (seven-repeat polymorphism); $A_i \times E_j$, gene–environment interactions; E_{1-m}, environmental factors.



EFFECT SIZE
A measure of effect that is adopted when different scales are used to measure an outcome. It is usually defined as the difference in means between the experimental and control groups, divided by the standard deviation of the control or both groups. As effect size is a standardized measure, it allows us to compare and/or combine the effects found in different studies of the same phenomenon.

Box 3 | **Stimulant treatment in attention-deficit/hyperactivity disorder**

Much of the controversy linked to attention-deficit/hyperactivity disorder (ADHD) has arisen because the pharmacological treatments of choice are the psychostimulants methylphenidate (Ritalin) and amphetamine, which can produce abuse and dependence[1]. However, these drugs are extraordinarily efficacious for the short-term treatment of the behavioural symptoms of ADHD, as confirmed by hundreds of randomized, double-blind, placebo-controlled clinical trials (for a review, see REF. 15). Methylphenidate and the amphetamines both increase synaptic catecholamines, albeit by different mechanisms. Methylphenidate, the drug that is most commonly used to treat ADHD, blocks the reuptake of dopamine and noradrenaline by their respective transporters. Amphetamines can also stabilize dopamine and noradrenaline transporters in channel configurations, reverse flow through intracellular vesicular monoamine transporters, and cause internalization of dopamine transporters[141]. Despite these differences in basic mechanisms of action, most children with combined-type ADHD respond well to either drug type, with rapid decreases in behavioural symptoms that begin about 30 min after oral ingestion and peak 60–90 min after administration of immediate-release formulations[142]. (Most of the 20–30% of children who are not classified as good responders to one type of stimulant do respond well to the other[143].) These time courses parallel the kinetics of brain uptake of the drugs, as shown by Volkow and colleagues using positron emission tomography (PET) in humans[144].

Studies by the Volkow group also highlight the crucial nature of the kinetics of administration of these drugs. Adult volunteers who experienced intravenous injections of methylphenidate reported euphoric experiences that were indistinguishable from those of intravenous cocaine, whereas those who attained equivalent striatal concentrations through oral administration did not[144]. This distinction is relevant because most neuroscience investigations of the stimulants have focused on understanding the mechanisms of substance abuse and dependence. Fortunately, a few laboratories are now beginning to examine the effects of clinically relevant doses of methylphenidate and amphetamine, administered by enteral routes (with training, the drugs can be administered in drinking water, or by gavage) and, most importantly, in juvenile animals[4,145]. These studies should yield important insights into the basic mechanisms of these widely used pharmacological agents.

criteria for ADHD. An early study found that children with ADHD are more active than age-matched controls, even during sleep[39], indicating that locomotor hyperactivity is a primary symptom. However, others have found evidence that hyperactivity might compensate for low external stimulation[40], and a recent study failed to confirm greater motor activity during sleep[41]. It is ironic that so fundamental an issue remains unresolved, especially given that nearly all attempts to produce animal models of ADHD begin with locomotor hyperactivity, which itself can confound, for example, continuous exploratory activity, deficiencies in habituation, and disorganized and/or hyperactive grooming (reviewed in REF. 42).

Locomotor hyperactivity has been associated with both hypodopaminergic[43,44] and hyperdopaminergic[45,46] animal models, which might indicate that either extreme can produce behavioural and cognitive dysregulation[47]. Furthermore, most models have not addressed the neurotrophic roles of the monoamines during early brain development[48], or the probable role of compensatory mechanisms. Human functional and structural imaging studies also provide some evidence for dopaminergic dysfunction in ADHD, although the question of whether such dysfunction is specific for finer-grained dimensions of behaviour has not been addressed.

The highest concentrations of dopamine are found in the STRIATUM. Abnormalities of caudate nucleus volume or asymmetry have been reported in ADHD, although findings have been particularly inconsistent regarding laterality or asymmetry differences[49]. These inconsistencies might reflect differences in methodology, comorbidity, statistical power or, probably more importantly, sample composition. For example, in girls with ADHD, differences in asymmetry relative to controls were not found, although affected girls had smaller left and total caudate volumes[50].

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) techniques have been used to quantify DAT density in several recent studies. Striatal DAT density, as indexed by [^{123}I]-altropane binding potential (Bi_{max}/K_d), was elevated in six adults with ADHD who were compared with historical controls[51]. A similar finding was reported in ten adults with ADHD, all of whom were previously untreated, using [Tc-99m]-TRODAT-1, another DAT ligand[52]. However, a third study using [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) failed to find differences in striatal DAT density between controls and nine untreated adults with ADHD[53]. Even if the finding of increased DAT density is confirmed by larger studies, it will be difficult to determine whether higher DAT density in adults with ADHD represents a primary abnormality that is ameliorated by stimulant treatment (BOX 3), or a secondary compensation, perhaps for excessive dopaminergic stimulation during early development[54].

Developmental differences were highlighted by a pair of positron emission tomography (PET) studies that used 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]-fluorodopa or [^{18}F]F-DOPA) to label catecholamine terminals. In the first, [^{18}F]F-DOPA uptake was significantly diminished in the left and medial prefrontal cortex (relative to occipital uptake) of 17 unmedicated adults with ADHD compared with 23 controls, with no differences in the striatum or midbrain regions[55]. By contrast, in ten adolescents with ADHD, [^{18}F]F-DOPA uptake in the right midbrain was significantly elevated compared with ten controls[56]. However, as the authors acknowledge, the fluorodopa

STRIATUM
Part of the subpallidum and one of the components of the striatopallidal complex. It comprises deep (caudate nucleus, putamen and nucleus accumbens) and superficial (olfactory tubercle) parts.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY
A method in which images are generated by using radionuclides that emit single photons of a given energy. Images are captured at multiple positions by rotating the sensor around the subject; the three-dimensional distribution of radionuclides is then used to reconstruct the images. SPECT can be used to observe biochemical and physiological processes, as well as the size and volume of structures. Unlike positron emission tomography, SPECT uses many fewer detectors, resulting in the loss of many available photons and the degradation of the image.

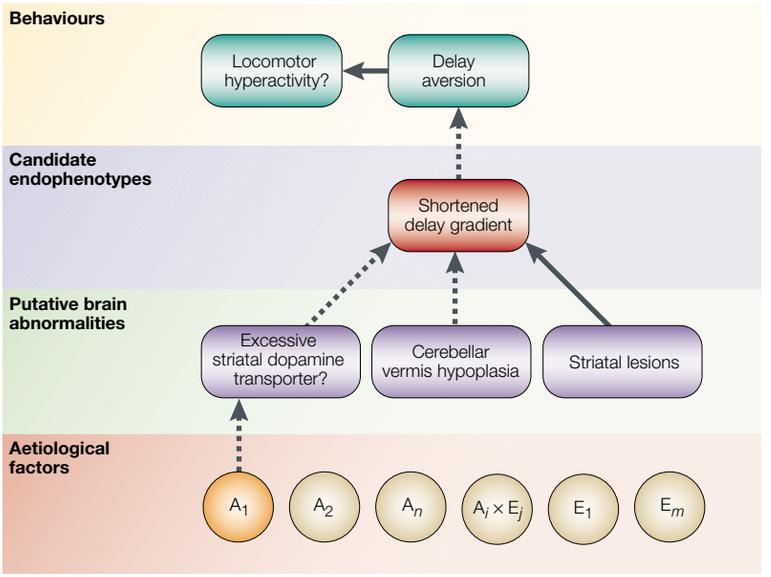


Figure 1 | **Causal model of shortened delay gradient as a candidate endophenotype.** The figure shows a causal developmental model, with shortened delay gradient as the candidate endophenotype, delay aversion as the primary behavioural manifestation, and at least three possible causative brain abnormalities. Most of the proposed links have yet to be tested, except that lesions in the core of the nucleus accumbens produce a preference for small, immediate rewards over larger, delayed rewards[44]. Anatomical studies have not been able to measure the volume of the nucleus accumbens in attention-deficit/hyperactivity disorder (ADHD), but striatal abnormalities have been detected in both primary[49,50] and secondary (lesion-associated)[24,25] ADHD. FIGS 1, 3 and 4 are based on the Morton–Frith approach[6]. Broken arrows indicate untested proposed causal links; A_1 represents the dopamine transporter (*DAT1*) polymorphism, which might be linked to differences in striatal transporter density. A_{2-n}, additive genetic factors; $A_i \times E_j$, gene–environment interactions; E_{1-m}, environmental factors.

signal is noisy in regions of low dopaminergic neuronal density, such as the medial prefrontal cortex, where the signal magnitude in affected adults is less than 10% of that in the striatum[55]. Still, these preliminary results, together with those from candidate-gene studies mentioned earlier, support the idea that catecholamine dysregulation is involved in the pathophysiology of at least some neurobiological types of ADHD. They also support the proposition that dopaminergic and noradrenergic systems cannot be understood completely without taking developmental effects into account (reviewed in REF. 54).

Unfortunately, ethical and practical constraints prevent the application of the most instructive techniques to paediatric controls, because they involve tracer quantities of radioactive ligands. Despite this important limitation, quantitative work is proceeding on stimulant-evoked and basal dopamine release, and on the densities of the DAT and dopamine receptors D1 and D2, in carefully selected adults with ADHD (N. Volkow, personal communication). Pending the results of these studies, more precise specification of putative dopaminergic abnormalities is unlikely to emerge from neuroimaging. So, we now turn to candidate endophenotypes for ADHD in which developmental issues can be addressed directly.

EXECUTIVE FUNCTION
A cluster of high-order capacities, which include selective attention, behavioural planning and response inhibition, and the manipulation of information in problem-solving tasks.

ANTISACCADE TASKS
Tasks in which subjects are required to suppress the automatic response of making a saccade towards a target and, instead, produce an eye movement in the opposite direction.

GO/NO-GO TASK
A task in which the subject must produce a motor response for one class of stimulus while ignoring others.

Response inhibition

Numerous authors have highlighted the putative role of EXECUTIVE dysfunction in ADHD[57]. Barkley proposed that response inhibition, which is integral to virtually all behavioural regulation and executive function, is the primary deficit in ADHD[12]. Nigg differentiated inhibition tasks into those that are primarily executive (requiring deliberate suppression of a response to achieve a later, internally represented goal), motivational (motivated by fear of punishment) and automatic. Executive inhibition can be further characterized on the basis of whether the responses to be inhibited are primarily motor, cognitive or pertaining to response conflicts[58]. Nigg concluded that, at least for combined-type ADHD, the evidence supports an executive response-inhibition deficit, as detected by the ANTISACCADE, GO/NO-GO and stop-signal tasks[14]. In the stop-signal task, subjects are asked to respond as quickly as they can to a 'go' signal, but to inhibit their response when presented with a 'stop' signal. The intervals between the onsets of the go and stop signals are varied to allow an estimation of the 'stop-signal reaction time'. Most studies find longer stop-signal reaction times in ADHD patients[58].

Despite the robust effects that have been detected[14,59], the stop-signal task has several features that make it problematic for the investigation of aetiological factors. The task assumes independence of the stop and go processes, and assumes that subjects use the same strategy. The latter assumption is not supported by the surprisingly large numbers of subjects whose data must be discarded because of excessive omissions or insufficient inhibitions[60]. Such exclusions are necessary because the primary measure of response inhibition cannot be obtained directly (as successful inhibition is manifested overtly by the omission of a response), but rather is a theoretically based and derived estimate of the latency of the postulated inhibitory process, the robustness of which depends, in part, on performance in the go task and at least a minimal ability to inhibit[61]. The model does not provide a way of estimating the variability of the postulated inhibitory process, which is of concern, given the typically slow and highly variable response times of subjects with ADHD in the go task. So, the findings of slow and variable responses in the go task, and the slow estimated stop-signal reaction times, are consistent with a generalized slowness of information processing (consistent with the arousal/activation theory)[13] and/or with difficulties in matching responses to the temporal parameters of the task. Not surprisingly, given the complexity of the stop-signal task and its many variants, this phenomenon has not been explored in animal models. However, the finding of slowed response inhibition in ADHD has been replicated by several research groups, which, together with preliminary evidence that poor stop-task inhibition in children with ADHD is associated with an increased frequency of ADHD in first-degree relatives[62], leads us to agree with other investigators that deficient response inhibition (at least as measured by this task) meets several of the criteria for a candidate endophenotype[14,62]. Notably, recent evidence that inattention, and not

POLYMORPHISM
The simultaneous existence in the same population of two or more genotypes in frequencies that cannot be explained by recurrent mutations.

VENTRAL TEGMENTAL AREA
A nucleus of the midbrain. The main supplier of dopamine to the cortex.

LOCUS COERULEUS
A nucleus of the brainstem. The main supplier of noradrenaline to the brain.

hyperactivity/impulsivity, is the strongest predictor of slowed response inhibition[63], raises the possibility that impaired stop-signal inhibition could be an endophenotype for the inattention symptom cluster rather than for ADHD *per se*. Below, we propose several further candidate endophenotypes that are better grounded in neuroscience.

Shortened delay gradient

The stop-signal response-inhibition model was recently compared with an alternative cognitive theory — delay aversion — in a collaborative multi-site study that should serve as a model for future work in the field[11,60]. Delay aversion refers to the intolerance for waiting that can manifest as a tendency to select an immediate reward over a larger reward for which the subject has to wait[11]. For example, children with ADHD are more likely than controls to select a small, immediate reward (1 point after 3 s) rather than a larger, delayed one (2 points after 30 s)[11]. When subjects were tested, both delay aversion and deficits in stop-signal inhibition were found, but the differences between control subjects and those with ADHD were more pronounced in the case of delay aversion. More importantly, these differences did not correlate within subjects[60], indicating that multiple pathways lead to the behavioural symptoms of ADHD[11]. Sonuga-Barke[11] argues that delay aversion is an acquired characteristic that is based on more fundamental abnormalities in reward mechanisms[64] that have been extensively studied in model systems[65]. In particular, a faster decline in the effectiveness of reinforcement as the delay between the behaviour and reward increases (a shortened delay gradient) has been found in both a rat model of ADHD and children with ADHD on analogous tasks[66] (see also REF. 67). Also, as predicted by this model, greater locomotor activity in subjects with ADHD than in controls was found only when delays became unavoidable[40], indicating that hyperactive and fidgety behaviours might represent compensatory responses.

A causal developmental model with shortened delay gradient as the candidate endophenotype, delay aversion as the primary behavioural manifestation, and at least three possible causative brain abnormalities, is shown in FIG. 1. Although anatomical studies have not been able to measure the volume of the nucleus accumbens in ADHD, other striatal abnormalities have been detected in both primary[49,50] and secondary (lesion-associated)[24,25] ADHD. Excessive striatal DAT density[51–53], if confirmed, could be linked to a POLYMORPHISM in *DAT1* (REF. 68), and should lead to shortened delay gradients by rapidly removing synaptic dopamine. Interestingly, while anticipating a monetary reward, normal adults who were scanned by functional magnetic resonance imaging (fMRI) showed selective activation not only in the nucleus accumbens, but also in the cerebellar vermis[69] (FIG. 2). In children with ADHD, the most prominent decreases in volume have been in the posterior–inferior lobules of the cerebellar vermis (lobules VIII–X)[50,70,71]. The potential relevance of the posterior–inferior vermis for ADHD was further highlighted in non-human primates, by the selective finding of DAT immunoreactivity in the ventral cerebellar vermis, particularly in lobules VIII–X, but not elsewhere in the cerebellum[72]. The function and origins of these putatively dopaminergic fibres are not known, but they might form the afferent portion of a cerebellar circuit that has been proposed to influence the VENTRAL TEGMENTAL AREA and the LOCUS COERULEUS[73,74]. Finally, human functional brain-imaging studies have documented the sensitivity of the cerebellum, and particularly the vermis, to the effects of psychostimulants[38,75,76].

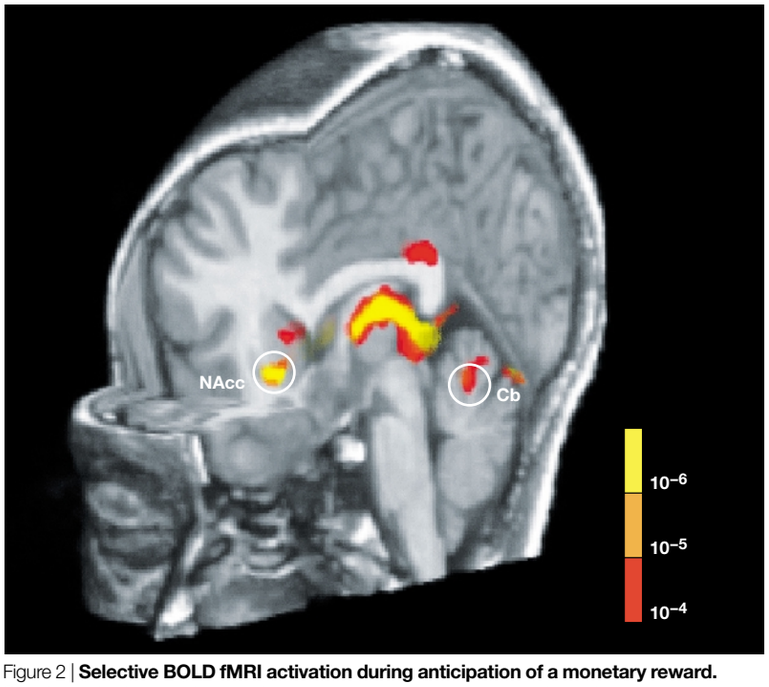


Figure 2 | **Selective BOLD fMRI activation during anticipation of a monetary reward.** Selective activation was found in the nucleus accumbens (NAcc) and the anterior cerebellar vermis (Cb) of eight normal adults in a study using blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI)[69]. The colours indicate the statistical significance of those regions that responded during the anticipation of $5.00 versus $0.20. The caudate, thalamus and posterior cingulate were also activated. Image courtesy of B. Knutson, Stanford University.

Temporal processing

Although groups of children with ADHD nearly always perform more poorly than comparison subjects on tasks that require sustained vigilance (for example, continuous-performance tests[77]), inconsistencies in sample selection criteria and task parameters, and the nonspecificity of results for ADHD, preclude the conclusion that patients with ADHD have a fundamental deficit in sustained attention[77,78]. Results from this work have also been disappointing because methods have been derived from neuropsychological models based on lesions in adults[79], rather than from developmental psychology. Moreover, emphasis has been placed on inter-individual variability and global measures of performance (mean response times or total errors) at the expense of trial-by-trial or intra-individual variability, which reflect the moment-by-moment process of task performance, in which individuals with ADHD have problems.

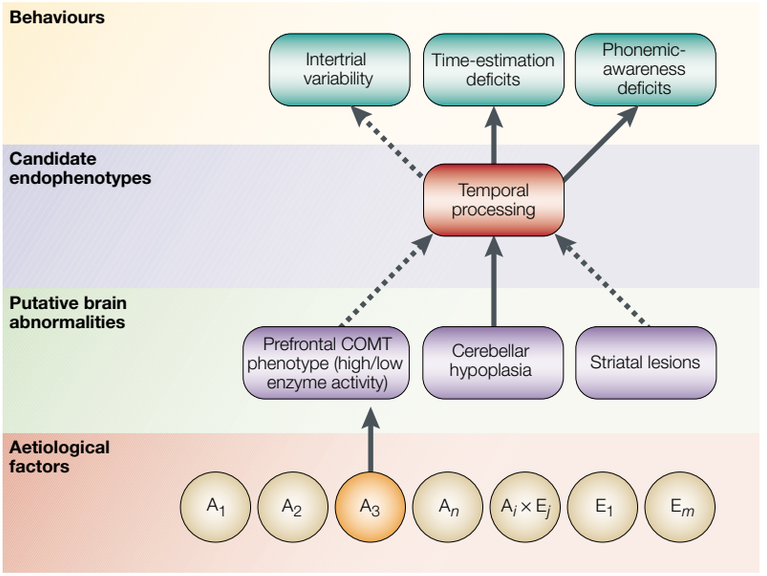


Figure 3 | **Causal model of temporal processing as a candidate endophenotype.** Deficits in temporal processing in attention-deficit/hyperactivity disorder (ADHD) are proposed to be linked to key deficits in time estimation and time production. Cerebellar dysfunction might be linked to high response variability. Broken arrows indicate untested proposed causal links; A_3 represents the catechol-*O*-methyl transferase (COMT) Val/Met polymorphism. A_1, dopamine transporter (*DAT1*) polymorphism; A_{2-n}, additive genetic factors; $A_i \times E_j$, gene–environment interactions; E_{1-m}, environmental factors.

Perhaps the most striking clinical characteristics of ADHD include the transient but frequent lapses of intention and attention, and the moment-to-moment variability and inconsistency in performance, which are described by parents, teachers, spouses and those who receive a diagnosis of ADHD. Ironically, the thresholds for determining symptom presence and severity have been criticized because they are expressed in imprecise terms such as 'often', 'frequently', 'pretty much' and 'most of the time', without further specification. But these terms might capture the essence of ADHD: temporal and contextual variability in symptom expression. Moreover, response variability is the one ubiquitous finding in ADHD research across a variety of speeded-reaction-time tasks, laboratories and cultures[80–82]. Response variability reflects a high frequency of slow responses, as well as a high frequency of fast anticipatory responses when these are permitted by the scoring algorithms (A.-C. Bedard *et al.*, unpublished observations)[64,80].

Abnormalities in reproducing temporal durations have been documented in children[83], adults[84] and adolescents with ADHD[67], albeit at relatively long time intervals (2–60 s). Such intervals are believed to require cortical mediation and rehearsal in working memory[85]. By contrast, performance for intervals of less than 1 s is dependent on subcortical circuits (the basal ganglia and cerebellum)[86,87]. A recent study using intermediate durations (1,000 and 1,300 ms) also detected an isolated time-perception deficit in subjects with ADHD[88]. Tannock *et al.* have carried out a pair of studies of time estimation and time reproduction with intervals as brief as 400 ms in children and adolescents with ADHD. In both studies, ADHD groups were impaired in duration discrimination, and in the precision and reliability with which they reproduced the intervals, particularly for the 400-ms intervals; no impairments were found in the control task of frequency discrimination. ADHD participants also showed high variability in their performance on the reproduction task. Finally, working memory measures and teacher ratings of behaviour were found to differentially predict performance on the measures of time perception (M. Toplak *et al.*, unpublished observations).

As shown in FIG. 3, we propose that the candidate endophenotype of temporal processing is linked to these deficits in time estimation and time production. Temporal-processing deficits, whether associated with the observed response variability in ADHD, the phonemic-awareness deficits in developmental dyslexia, or the time-estimation deficits in both ADHD and developmental dyslexia[89], could be linked to cerebellar dysfunction. Cerebellar hemispheric volumes are significantly smaller in ADHD patients[90,91], and neocerebellar circuits are crucial for representing precise temporal relationships, whether they be motor responses[86] or sensory anticipation[92]. Functional imaging studies are ideally suited for differentiating prefrontal, striatal and cerebellar sources of temporal-processing abnormalities. Such techniques have been used to probe prefrontal working memory mechanisms that are modified by differences in catechol-*O*-methyltransferase (COMT) enzymatic activity[93]. For example, homozygosity for the low-activity *met* allele results in an enzyme that is only one-quarter as active in degrading prefrontal dopamine, and the presence of the *met* allele predicts more focused and efficient cerebrovascular responses during a working memory task[93]. Determining the effect of this genotype on the processing of a range of time intervals will probably be instructive. However, we must also remember that abnormalities in precise temporal representations might contribute to response variability through multiple mechanisms (including multisecond oscillations observed in single-unit recordings from basal ganglia output neurons that are exquisitely sensitive to dopaminergic agonists[94,95]), which might also account for some attentional lapses[96,97] in ADHD.

Working memory

Working memory is a non-unitary system of processes and mechanisms that allow task-relevant information to be maintained temporarily (for a few seconds) in an active state for further processing or recall, in the service of complex cognition, including novel or familiar skilled tasks[98]. This internal and continuously updated 'on-line' record of relevant information, rather than the immediate sensory cues in the environment, controls attention and guides decision making and behaviour moment by moment during an activity[99,100]. Animal and human studies have shown that working memory (particularly visual–spatial working memory) is mediated by the prefrontal cortex[101,102], and modulated by the catecholamines dopamine and noradrenaline (reviewed in REF. 103; see also REF. 104).

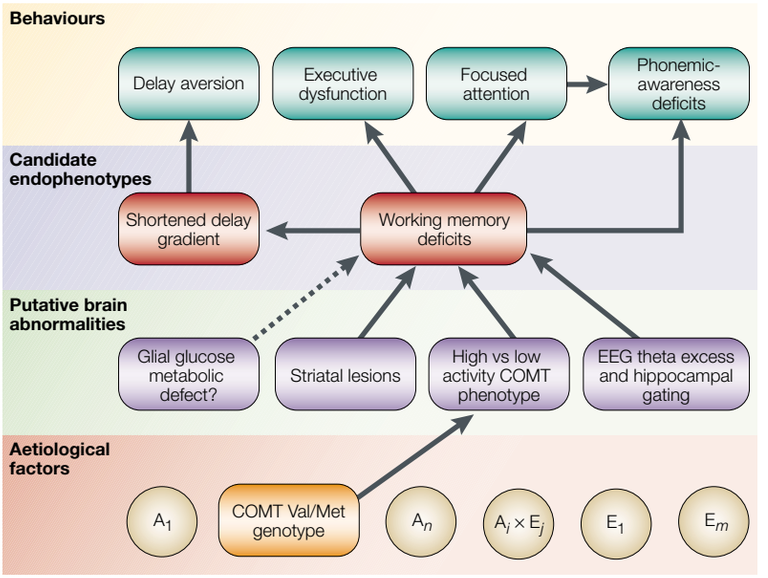


Figure 4 | **Causal model of working memory deficits as a candidate endophenotype.** Such deficits might arise as a result of brain abnormalities, including striatal lesions and alterations in catechol-*O*-methyl transferase (COMT) activity. Attention-deficit/hyperactivity disorder (ADHD)-associated behaviours that are influenced by working memory might include attentional processes and learning disorders. Broken arrows indicate untested proposed causal links; A_1, dopamine transporter (*DAT1*) polymorphism; A_{2-n}, additive genetic factors; A_3, catechol-*O*-methyl transferase (COMT) Val/Met polymorphism; $A_i \times E_j$, gene–environment interactions; EEG, electroencephalogram; E_{1-m}, environmental factors.

Working memory impairments are prominent in current psychological models of ADHD[12,105], which is not surprising, given the growing consensus that catecholaminergic dysregulation and prefrontal dysfunction are central to the pathophysiology of ADHD. However, the number of controlled empirical investigations is limited, and their findings remain equivocal, leading some authors to conclude that working memory is not impaired in ADHD[57,106]. Such conclusions might be premature, because they were based primarily on findings from studies of auditory–verbal working memory that relied solely on behavioural measures derived from neuropsychological tasks. Moreover, as the cluster of inattention symptoms has been found to be more strongly associated than the hyperactive/impulsive symptom cluster with cognitive and academic impairments[63], it is possible that only individuals with severe inattention (rather than ADHD *per se*) show significant visual–spatial working memory impairments.

More compelling evidence of impairments in working memory in ADHD is provided by studies of visual–spatial working memory. These studies found impairments even after controlling for comorbid conditions (dyslexia and language impairments), which are also associated with working memory deficits[107–109]. Further evidence comes from electrophysiological studies of the P300 COMPONENT, which provides a sensitive index of the attentional and working memory demands of a task, although findings are not always consistent[18]. Moreover, one recent study indicates that narrowing the phenotype by examining individual differences within the inattention dimension could reveal ADHD subgroups that differ meaningfully in visual–spatial working memory, cognitive response to stimulant medication, and family history of ADHD in first-degree relatives (R. Martinussen *et al.*, unpublished observations). Furthermore, preliminary evidence indicates that individuals with ADHD and control subjects might not activate the same brain regions or use the same approach when performing auditory–verbal working memory tasks[110].

Dopaminergic modulation of prefrontal neurons is important in working memory performance[111]. Variations in drug response might reflect individual differences in monoaminergic tone, which, in turn, might be related to allelic variations in genes related to the dopaminergic system[112]. Therefore, it is reasonable to propose that genetic polymorphisms that influence dopaminergic and/or noradrenergic function (such as the DAT or dopamine receptors) might be associated with this endophenotype in ADHD (FIG. 4). The functional polymorphism in the *COMT* gene, which results in a fourfold difference in dopamine-catabolic efficiency, predicts working memory performance and cerebral activation patterns[93]. The *COMT* polymorphism has been linked to the diagnosis of ADHD in one sample[113], but not in several others[114–116]. However, these genetic studies did not measure working memory or other executive functions.

The extensive electrophysiological literature on ADHD[117] has not been addressed here owing to lack of space, but it is worth noting that the THETA/BETA POWER RATIO in the electroencephalogram (EEG) is strongly related to age and the diagnosis of ADHD[118,119]. Similarly, increased absolute theta activity (not just in anterior regions) was detected in a group of 54 adolescent males with ADHD when compared with an equal number of matched controls[120]. The possible relationship between abnormalities in theta rhythm and the 'gating' of theta oscillations in association with hippocampal activation during working memory performance[121,122] should be explored in subjects with ADHD.

Conclusions

The symptom-based, atheoretical approach to the classification of psychiatric diseases has been successful in improving diagnostic reliability. It has also provided the initial conditions for integrative explorations of the interplay of causal factors that are embedded in development and manifested in heterogeneous conditions such as ADHD. The approach we advocate builds on previous conceptual work[7,11–14,66], and allows us to side-step apparently intractable problems such as how to integrate symptom reports from informants who disagree[123]. Simply put, establishing a diagnosis of ADHD is a useful starting point, but it needs to be followed by the quantitative determination of strengths and weaknesses on a finite set of dimensional measures that can serve as endophenotypes. We acknowledge that this review has been selective rather than exhaustive, and that we have focused most heavily on the criterion that a potential endophenotype be well

P300 COMPONENT
A positive-going waveform in the electroencephalogram that occurs approximately 300 ms after the onset of a stimulus, and is related to the attentional and working memory demands of a task.

THETA/BETA POWER RATIO
A ratio that compares the power output in the theta (4–8 Hz) versus the beta (13–21 Hz) frequency bands of the electroencephalogram.

grounded in neuroscience. This is the primary reason, for example, for our preference of shortened delay gradient as an endophenotype rather than response inhibition, even though the latter has been the most frequently studied in ADHD. However, we believe that the complexity of paradigms such as the stop-signal task, and the multiplicity of operational definitions of response inhibition, represent a significant problem. Likewise, our enthusiasm for the endophenotype of working memory derives from the extensive understanding of spatial working memory in the non-human primate, and the ready extension of that work to functional imaging, as well as the intriguing link to that rarity — a genetic variation that clearly affects neuronal function[93,112].

The most tentative of our proposals is the link between variability *per se* and temporal processing. Once again, we believe that our approach 'turns vice into virtue'. Variability and inconsistency in such apparently straightforward tasks as visual fixation on a central stimulus in an otherwise dark room[124] have thwarted the development of trait markers that might have objectively validated the diagnosis of ADHD. At the same time, variability on reaction-time tasks is highly heritable[81] and temporal processing has been shown to be abnormal in subjects with ADHD across a wide range of intervals. However, our hypothesis that temporal-processing abnormalities underlie behavioural variability is admittedly speculative.

Obviously, much work remains to be done before candidate endophenotypes such as those discussed above (and others now being developed[125–127]) will be ready for the multi-site collaborative projects that will eventually be needed. Fortunately, this need is being acknowledged by agencies such as the US National Institute of Mental Health, which is increasingly recognizing the importance of funding integrative multi-disciplinary approaches to ADHD. In this way, the extraordinary insights that are emerging from the neurosciences can be combined synergistically with molecular-genetic perspectives to delineate the complex causal pathways of ADHD.

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