HHS Public Access

Author manuscript

Lancet Psychiatry. Author manuscript; available in PMC 2016 June 06.

Published in final edited form as:

Lancet Psychiatry. 2016 June ; 3(6): 555–567. doi:10.1016/S2215-0366(16)00096-1.

Moving towards causality in attention-deficit hyperactivity disorder: overview of neural and genetic mechanisms

Eduardo F Gallo, PhD and **Jonathan Posner, MD**

Columbia University and New York State Psychiatric Institute, New York, NY, USA

Abstract

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by developmentally inappropriate levels of inattention and hyperactivity or impulsivity. The heterogeneity of its clinical manifestations and the differential responses to treatment and varied prognoses have long suggested myriad underlying causes. Over the past decade, clinical and basic research efforts have uncovered many behavioural and neurobiological alterations associated with ADHD, from genes to higher order neural networks. Here, we review the neurobiology of ADHD by focusing on neural circuits implicated in the disorder and discuss how abnormalities in circuitry relate to symptom presentation and treatment. We summarise the literature on genetic variants that are potentially related to the development of ADHD, and how these, in turn, might affect circuit function and relevant behaviours. Whether these underlying neurobiological factors are causally related to symptom presentation remains unresolved. Therefore, we assess efforts aimed at disentangling issues of causality, and showcase the shifting research landscape towards endophenotype refinement in clinical and preclinical settings. Furthermore, we review approaches being developed to understand the neurobiological underpinnings of this complex disorder including the use of animal models, neuromodulation, and pharmaco-imaging studies.

Clinical overview: prevalence and symptoms

Attention-deficit hyperactivity disorder (ADHD) prevalence has been estimated at 5·0–7·1% in children and adolescents worldwide.[1,2] ADHD is diagnosed more frequently in males than in females (2–4 to 1), but the diagnosis in females typically occurs at an older age than in males and might be more prone to detection failures.[3] Nonetheless, these sex differences appear to be less pronounced after childhood.[3] Although the disorder is typically thought of as a developmental disorder, persistence into adulthood is seen in about 50% of patients.[4] Prospective studies spanning over 30 years have noted the highly impairing consequences of ADHD.[5,6] Diagnosis in childhood is associated with poor educational, occupational, economic, and social outcomes, as well as higher criminality in adulthood.[5,6]

Correspondence to: Dr Eduardo Gallo, Columbia University and New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA, ; Email: GalloEd@nyspi.columbia.edu

Contributors

EFG and JP reviewed the literature, wrote the manuscript, and prepared the figures and tables.

Declaration of interests

JP has received research funding from Shire Pharmaceuticals. EFG declares no competing interests.

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5),[7] a child must present with six or more symptoms in either the inattention or hyperactive and impulsive domains, or both, to be diagnosed with ADHD (panel). Adults (17 years and older) must present at least five symptoms in either domain. With the transition from DSM-IV to DSM-5, the age of onset of symptoms was increased from 7 years to 12 years, allowing more flexibility in diagnosing teenagers and adults. Additionally, DSM-IV subdivided ADHD into three subtypes based on the predominant symptomatology: inattentive, hyperactive and impulsive, or combined. With DSM-5, the term subtype was changed to presentation to reflect that symptom clusters could change over the course of development.

Emotional dysregulation is also frequently observed in ADHD. A recent review largely of clinic-based studies estimated its prevalence at 25–45% in children and 30–70% in adults with ADHD.[8,9] Emotional dysregulation might reflect aggressive behaviour, emotional lability, poor frustration tolerance, and excessive excitability.[8] A longitudinal study of children with ADHD followed into adulthood suggested that emotional dysregulation might confer risk for a host of negative occupational and social outcomes above and beyond the effect of inattentive and hyperactive and impulsive symptoms.[10] Because of its impairing consequences, emotional dysregulation is thought to represent an important clinical feature of ADHD, and is considered an associated feature supporting the diagnosis in DSM-5.[7] Alterations in motivation and processing of reinforcement, which might underlie some of the emotional dysregulation symptoms, have also been reported in ADHD.[8,11] Children with ADHD often prefer immediate over delayed rewards, are generally less sensitive to reinforcement, and their response to a reward might attenuate more rapidly than that of their unaffected peer.[12,13]

Understanding the neurobiological basis of ADHD is complicated by the fact that certain behavioural correlates are not always unique to ADHD. For instance, the deficits in working memory, cognitive flexibility, and attention seen in ADHD are similar to those observed in schizophrenia.[14] Additionally, there is evidence for substantial rates of comorbidity with other disorders such as autism spectrum disorders, substance use disorders, and conduct and mood disorders.[4,15] The subjective nature of symptom assessment and reporting can lead to indistinct diagnoses, which contribute to concerns about the potential over-diagnosis of ADHD.[16] Furthermore, whereas ADHD is a highly heritable disorder, studies have linked ADHD to environmental factors, including exposure to lead[17] and nicotine prenatally.[18] Although we are unable to review the literature of environmental exposures linked to ADHD, detailed reviews on the topic exist.[19] Here we provide an overview of select studies that showcase past and current efforts aimed at uncovering aetiological factors for this complex disorder both at the level of neural circuitry and genetics.

Neural circuits

Neuroimaging studies have implicated several large-scale neural circuits in ADHD with particular emphasis of neural circuits related to sustained attention, inhibitory control, motivation, and emotional regulation. The principal magnetic resonance imaging (MRI) modalities used to study brain structure and function in children and adults with ADHD

include structural MRI, connectivity analyses, and task-based functional MRI (fMRI). Across these modalities, a consistent set of neural circuits has been associated with ADHD including frontoparietal, dorsal frontostriatal, and mesocorticolimbic circuits (figure 1), as well as the default mode and cognitive control networks (figure 2).

Structural MRI studies

Many structural MRI studies have examined volumetric differences in individuals with ADHD relative to healthy controls, and meta-analyses point to a consistent set of findings. In three separate meta-analyses (albeit with considerable overlap in the studies included in these metan-alyses), whole-brain structural MRI data show volumetric reductions in the basal ganglia.[20–22] The basal ganglia, which receive broad input from the cortical mantle, play a crucial role in goal-directed behaviours, motivation and reward processing, and motor control,[23] all of which are putative dysfunctional cognitive domains in ADHD.[24,25] Two of these three meta-analyses examined developmental effects by sampling studies of children and adults with ADHD. In these two studies, a statistically significant effect of age was detected suggesting that the volumetric reductions in the basal ganglia attenuate with development and are no longer detectable by adulthood.[21,22] These findings support a model of ADHD as a disorder of delayed maturation, a hypothesis originally suggested on the basis of the clinical observation that many of the behaviours typical of children with ADHD appear immature in nature and attenuate with development.[26]

In addition to subcortical volumetric abnormities, structural MRI studies have examined cortical thickness in ADHD, and suggest abnormalities in cortical thickness in frontal and parietotemporal brain regions. Longitudinal research suggests that cortical thickness abnormalities in ADHD might reflect a delay, rather than an enduring alteration, in cortical development. A longitudinal study[27] has compared cortical thickness in 223 children with ADHD with 223 age-matched healthy controls studied with structural MRI at up to four timepoints spanning up to 17 years. Growth trajectories suggested that the children with ADHD probably obtain peak cortical thickness similar to that of healthy controls; however, the age at which they were projected to achieve peak cortical thickness was delayed by 2–5 years.[27] Delays in obtaining peak cortical thickness were detected in frontal, parietal, and temporal brain regions, consistent with findings from cross-sectional structural MRI studies showing cortical thickness abnormalities in similar brain regions.[28–30]

Structural MRI studies have revealed consistent volumetric reductions in the basal ganglia in children with ADHD, as well as cortical thickness abnormities in frontal and parietotemporal regions. Collectively, these findings suggest anomalous development within frontoparietal and frontostriatal circuits, which might play an important part in the deficits in attention and executive functions in ADHD. Evidence of delayed maturation of these circuits supports a model of ADHD as a disorder of delayed neural maturation. However, structural MRI abnormalities in ADHD are correlational in nature, and thus attributing them a causal role in ADHD must remain circumspect.

Connectivity analyses

Developments in clinical neuroscience have led to the prominence of neural circuits, rather than isolated brain regions, as the presumed substrates of psychopathology.[31] MRI techniques to examine the topology of neural circuits, or neural connectivity, include a range of sophisticated methodologies. We will focus on the three techniques commonly used to study neural connectivity in ADHD: diffusion MRI (dMRI), resting-state functional connectivity, and task-based functional connectivity. Diffusion MRI examines the diffusion of water molecules as an indicator of tissue architecture and the orientation of white matter fibres.[32] Resting state functional connectivity examines the correlation, or coherence, of neural activity over time across disparate brain regions.[33] The coherence of neural activity is measured during a state of rest when the experimenter provides no explicit cognitive task or demands, typically instructing individuals to allow their minds to wander freely. Brain regions with synchronous neural activity are termed functionally connected with the assumption that synchronous neural activity across disparate brain regions reflects the intrinsic architecture of neural circuits.[34] Task-based functional connectivity is similar; however, the coherence of neural activity is examined in the context of cognitive demands, thereby testing whether connectivity between brain regions is parametrically enhanced or diminished as a function of cognitive load or process.[35]

dMRI studies have implicated several white matter tracts in ADHD. A meta-analysis of nine dMRI studies in ADHD reported decreased fractional anisotropy (a dMRI measure of white matter organisation) within the anterior corona radiata, internal capsule, and forceps minor.[36] Using similar dMRI measures, two studies found reduced orbitofrontal white matter organisation within mesocorticolimbic circuits in children with ADHD.[37,38] Collectively, dMRI studies suggested deficits in white matter organisation in dorsal frontostriatal and frontoparietal circuits, as well as in mesocorticolimbic circuits, which might relate to deficits in motivation. These findings complement those reported with structural MRI suggesting that cortical and subcortical regions with volumetric abnormalities might be connected via white matter tracts with altered myelination or axonal branching.[38]

Many resting state functional connectivity studies have been done in ADHD.[39–42] One of the more commonly reported abnormalities is reduced connectivity within the default mode network (DMN).[39,40,42] Functionally, the DMN, which encompasses the posterior cingulate, medial prefrontal and lateral and inferior parietal cortices, is difficult to characterise but might underlie mental processes such as self-referential cognitions, introspection, and mind-wandering.[43,44] During task-based functional neuroimaging, the DMN shows enhanced activity when individuals are at rest or engaged in introspective tasks such as recovering autobiographical memories and assessing others' perspectives.[43] Conversely, when individuals transition from internally focused cognitions to externally focused, goal-directed tasks, deactivation of the DMN ensues, with stronger deactivations corresponding to increasing attentional demands.[43,44] One influential hypothesis is that persistent DMN activity in ADHD interferes with sustained attention, which manifests as lapses or errors in goal-directed behaviour, although empirical support for this hypothesis remains limited.[45,46]

Several resting state functional connectivity studies have focused on the connectivity of the DMN in ADHD positing that altered connectivity might reflect an inability to properly modulate DMN activity.[40,42,47] Likewise, interactions between the DMN and the cognitive control network (CCN) have also been investigated.[42,48,49] The CCN encompasses the dorsal anterior cingulate, supplementary motor area, dorsolateral prefrontal cortex, inferior frontal junction, anterior insular cortex, and posterior parietal cortex, and is involved in executive functions such as working memory, inhibitory control, and set shifting.[50] The DMN and CCN work in opposing directions in relation to attentional demands—as attentional demands increase, activation of the CCN increases, whereas DMN activation decreases; conversely, during periods of internally focused cognitions, activation in the CCN is reduced, and DMN activation increases.[51–53] The relation between the DMN and CCN is indexed as inversely correlated neural activity, or anti-correlations, in resting state functional connectivity analyses (figure 2).

Resting state functional connectivity studies have reported that individuals with ADHD have weaker connectivity within the DMN.[39,40,42] Additionally, at least five independent studies of children, adolescents, and adults with ADHD, both with and without exposure to previous medication, have found that anti-correlations between the DMN and CCN are either reduced or absent in ADHD.[42,48,49,54,55] Resting state functional connectivity studies have also implicated mesocorticolimbic circuits in ADHD, with studies noting altered connectivity between the nucleus accumbens and the orbitofrontal cortex[41,56] and between the hippocampus and the orbitofrontal cortex.[57] Though fewer studies have examined task-based functional connectivity in ADHD, they suggest reduced functional connectivity within dorsal frontostriatal and DMN circuits during tasks engaging executive functions.[46,58]

Consistent with structural MRI studies, connectivity research in ADHD implicates dorsal frontostriatal and mesocorticolimbic circuits with behavioural and symptom correlates in executive functions and motivational deficits, respectively.[41] Connectivity studies also underscore the DMN and CCN as important loci of investigation with hypotheses suggesting that altered interactions between these circuits might underlie attentional lapses.[45] Although a causal effect is implicit in these hypotheses, caution is warranted given the correlational nature of this research. Indeed, cross-sectional MRI studies cannot discern whether anomalous connectivity leads to symptoms, or whether behavioural and neural adaption to symptoms begets anomalous connectivity. Experimental approaches that directly test the causality implicit in connectivity-based hypotheses are needed.

Task-based fMRI studies

Task-based functional MRI studies in ADHD have largely focused on two neurocognitive domains: inhibitory control (including response inhibition and interference control) and reward processing. Meta-analyses consistently implicate hypoactivation of frontostriatal and frontoparietal circuits in task-based fMRI studies of inhibitory control in ADHD.[59,60] For example, a meta-analysis[59] of 287 individuals with ADHD and 320 healthy controls found that those with ADHD exhibit reduced activation in frontostriatal regions including the right inferior frontal cortex, striatum, and supplemental motor cortex during tasks requiring response inhibition. A meta-analysis[60] of 55 studies of children (n=39) and adults (n=16)

with ADHD reports ADHD-associated hypoactivation in frontoparietal regions including the dorsolateral prefrontal, anterior cingulate, and inferior parietal cortices. Paralleling findings from functional connectivity analyses, task-based fMRI studies also report hyperactivation of DMN regions including the medial prefrontal cortex, and this finding has been confirmed by meta-analysis.[46,60]

Whereas the preponderance of task-based fMRI studies has focused on inhibitory control, motivation is also prominently affected in ADHD. The use of fMRI tasks such as the monetary incentive delay task has facilitated probing subcomponents of reward processing in ADHD, such as reward anticipation and reward receipt. A recent meta-analysis reported that six of seven studies using the monetary incentive delay task (or similar tasks) found hypoactivation of the ventral striatum, a central node within mesocorticolimbic circuitry, in individuals with ADHD relative to healthy controls. This hypoactivation was present during the reward anticipation phase of the task with a moderate effect size (d = 0·48) and was not seen during reward receipt task conditions.[61]

Taken together, MRI studies of ADHD implicated a consistent set of neural circuits with confirmation from several meta-analyses. These circuits include those related to attentional processes and inhibitory control (frontoparietal and dorsal frontostriatal circuits), sustained attention (DMD and DMN–CCN interactions), and motivation (mesocorticolimbic circuits).

Genetics

Overview

ADHD is a highly heritable disorder. Studies of twins, families, and adoptive children or siblings have estimated a heritability ranging from 60% to 90%,[62–64] making it one of the highest among psychiatric disorders.[65] Despite substantial evidence for a genetic origin of ADHD, discoveries of specific genes or sets of genes causally linked to the disorder have yet to be made. Hypothesis-driven candidate gene approaches have linked ADHD to several genes, but inconsistent results and small effect sizes limit their interpretation.[62] A meta-analysis[66] found significant association of a handful of candidate genes with ADHD, but reported small odds ratios ranging from 1·15 to 1·54 and considerable variability in the reported associations. In a recent review, Hawi and colleagues[64] highlighted ten candidate genes for which supportive evidence exists, such as meta-analyses, genome-wide association studies (GWAS), large-scale linkage studies, or animal model research. Many of the described gene products are involved in neurotransmission, with one half playing an important part in monoaminergic function (dopamine and serotonin transporters, and D4, D5, and 5-HT1B receptors). Other corroborated risk loci were mapped to genes involved in different aspects of synaptic transmission (*SNAP25*, *NOS1*, *LPHN3*, and *GIT1*).Table 1 shows hypothesised implications of these genes on behaviours related to ADHD. Although these individual associations remain tentative and probably contribute only minimally to overall ADHD risk, they might nonetheless guide future investigation towards intermediate phenotypes.

Genome-wide association studies

GWAS have become an important tool for identifying common genetic variants of small effect size in a given disorder, without relying on candidate genes. With their unique ability to analyse over 1 million single nucleotide polymorphisms (SNPs) across the entire genome, GWAS have been used to address the difficult task of elucidating the genetic basis of polygenic psychiatric disorders.[65]

However, even with the growing number of GWAS in child and adult ADHD, there has been limited success in showing significant genome-wide associations ($p \leq 5 \times 10^{-8}$).[64,89] Only two loci (within the *CDH13* and the *GFOD1* genes) have exceeded the critical significance threshold for genome-wide associations with quantitative traits of ADHD.[87] *CDH13* encodes cadherin-13, a calcium-dependent protein important in cell–cell adhesion and neural cell growth. This gene appears to be particularly promising because it was also detected in two additional GWAS,[103,104] making it the only ADHD-related variant to be found in independent GWAS. Additionally, SNPs within *CDH13* have been linked to working memory deficits and hyperactivity and impulsivity in individuals with ADHD.[95,96] Cadherin-13 is expressed in the cerebral cortex,[105] and has also been implicated in schizophrenia and other neuropsychiatric disorders.[106] The other gene, *GFOD1*, is expressed in the brain and is putatively involved in electron transport; its implications for ADHD are less clear.[87,89]

The weak genome-wide associations to ADHD, and the limited overlap between independent GWAS findings, might be attributable to the small sample sizes of GWAS done in ADHD compared with those of schizophrenia, which report over 100 genome-wide significant loci.[65] For example, empowered by the findings of large-scale GWAS examining genetic associations with schizophrenia,[107] Sekar and colleagues[108] recently identified a specific functional allele, and provided mechanistic insight into its link to schizophrenia. Despite their limitations, SNP GWAS in ADHD have already identified genetic regions of interest beyond those found through candidate gene approaches.These emerging genes serve diverse neuronal functions ranging from cytoskeletal and extracellular matrix regulation to neurotransmission and neuroplasticity.[103,104] Further research is necessary to confirm their involvement in ADHD and its traits.

Copy number variants

Whereas early GWAS research focused only on common genetic variants, more recent work has addressed possible associations with rare structural chromosomal abnormalities known as copy number variants (CNVs).[65,89] One of the first genome-wide analyses of rare CNVs (>500 kb) in ADHD showed an excess of CNVs in British children with ADHD, a finding that was replicated in Icelandic patients.[101] A contemporaneous study failed to replicate this excess of CNVs in ADHD, but found rare deletions and duplications in genes implicated in other neurodevelopmental psychiatric disorders, such as autism.[109] However, a large-scale genome-wide CNV study by the same group found enrichment of CNVs in various metabotropic glutamate receptor genes in ADHD,[110] supporting a role for glutamatergic dysfunction.

Stergiakouli and colleagues[111] showed statistically significant convergence of CNVs with ADHD-related SNPs on the same biological pathways. These findings suggest that both SNPs and CNVs are relevant to ADHD risk, and bolster the notion that analysing SNPs through large-scale GWAS might be worthwhile.[111] However, because CNVs are inherently rare, further work with larger sample sizes will be necessary to confirm the contribution of CNVs to ADHD.[64] Additionally, whereas different individual genes might be altered among distinct ADHD populations, together these variations could contribute to shared neurobiological mechanisms or pathways underlying the disorder.[112]

Polygenic risk scores

Polygenic risk scores aggregate genetic associations over multiple loci and thus can be particularly useful in understanding the contribution of numerous SNPs and CNVs of small effect size to the overall genetic variance of the disorder.[113] Polygenic risk scores obtained from ADHD case-control GWAS were found to be higher in ADHD cases than in controls, though this effect was principally driven by individuals with comorbid aggression.[114] This work provided initial evidence that common genetic variants contribute to ADHD risk.[114] Common allelic variation in ADHD, as determined by polygenic score analysis, is predictive of attentional and hyperactive and impulsive traits in children who do not have ADHD.[112] Moreover, high polygenic risk scores predict ADHD diagnosis and symptom severity.[115] These findings suggest overlapping genetic risk factors within individuals diagnosed with ADHD and within individuals from the general population with ADHD-related traits.[115] This is consistent with the view that ADHD represents an extreme set of traits that vary dimensionally within the general population.[116] Polygenic that are associated not only with behavioural traits, but also with neural phenotypes might increase the likelihood of understanding processes by which genetic effects influence behaviour.

Substantial progress has been made in clarifying the complex genetic architecture of ADHD, yet the mismatch between the high heritability estimates and weak associations between ADHD and specific genetic markers is puzzling. Sequencing of protein-coding regions of the genome, referred to as exome sequencing, has been particularly useful in autism genetics, and emerging work focused on ADHD families supports its discovery potential.[117,118] A recognised weakness of genetic studies in ADHD thus far is the small sample sizes compared with other psychiatric disorders.[64,65] This weakness is now being addressed through collaborative efforts and multi-site initiatives.[64] Other options for achieving greater statistical power might include the combined analysis of ADHD genetics in the context of quantifiable behavioural traits or brain imaging and electrophysiological endophenotypes.[64,119]

Candidate endophenotypes in ADHD

Given the high polygenicity and overlapping genetics of ADHD with comorbid disorders, it has been proposed that, rather than linking genetic or neurobiological variability to diagnostic symptoms, it might be more useful to analyse discrete quantitative biological traits or endophenotypes.[16,64,120] Although various definitions have been proposed, endophenotypes often reflect distinct, heritable, and quantifiable traits that are thought to lie

on the path between genes and disorder.[120] Thus, endophenotypes are putatively more proximal to genetic influence than the disorder itself, and thereby increase statistical power to identify relevant associations between genes and neurobiological mechanisms. Endophenotypes might provide a promising route to simplifying the genetic architecture and aetiology of psychiatric disorders including ADHD.[16,120]

Endophenotype research in the context of ADHD has been discussed for more than a decade,[16] and continues to expand rapidly through the validation and refinement of new putative cognitive and neural endophenotypes. One of the most reliable candidate endophenotypes is intra-individual reaction-time variability, which refers to the inconsistency in the rate of responding (in the seconds or milliseconds range) during various attentional tasks, including behavioural inhibition, motor speed, and vigilance.[121] Although reaction-time variability is also observed in other clinical disorders, a recent meta-analysis[121] including 319 studies showed a significantly greater occurrence of reaction-time variability in ADHD than in control individuals, and that it is reduced by psychostimulants. The DMN, and its interactions with the CCN, have been implicated in reaction-time variability through its effects on sustained attention.[122,123]

Children and adolescents with ADHD exhibit difficulty in response inhibition, or the withholding or discontinuation of initiated responses.[124] Deficits in response inhibition are heritable and have been associated with reduced activation of inferior prefrontal, striatal, and other dorsal frontostriatal regions.[124] Moreover, unaffected siblings of individuals with ADHD show intermediate effects in response inhibition and associated neural correlates.[84,124,125] This familial component fits one of the defining characteristics of an endophenotype.[120]

Another commonly studied candidate endophenotype of ADHD is working memory. A meta-analysis of 45 studies of working memory in children with ADHD (8–16 years of age) revealed statistically significant, large deficits in visuospatial and verbal working memory,[126] consistent with previous findings from another meta-analysis reviewing largely non-overlapping studies.[127] These deficits might persist into adulthood.[128] Deficits in working memory might underlie the core symptoms of ADHD[129] and are generally thought to be linked to dysfunction within the CCN, particularly within prefrontal cortices. However, deficits in working memory are reported across a range of neuropsychiatric disorders,[130–132] calling into question the specificity of the relation between working memory deficits and ADHD. Working memory might represent a neuropsychological deficit that is trans-diagnostic in nature, as suggested by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative.[133]

In addition to cognitive endophenotypes, alterations in the structure, connectivity, and function of neural circuits, as discussed above, have been consistently implicated in ADHD, yet whether these brain correlates represent neural endophenotypes remains to be established. For example, heritability is an important criterion for candidate endophenotypes, yet the heritability of ADHD-related abnormalities in neural circuits has scarcely been examined. Some electrophysiological measures have also been proposed as neural endophenotypes.[134] Alterations in very low frequency oscillations in

electroencephalograms (EEG), for instance, have been observed in individuals with ADHD,[134] and might be associated with DMN activity.[45] Whereas this phenotype might affect attentional processes,[135] further work is needed to determine the functional significance of this measure in ADHD symptoms and aetiology.[134,135]

As the number of proposed endophenotypes for ADHD expands, continued validation and refinement will become essential.[120] This can be achieved by improving the reliability of the quantitative measures and by doing repeated, longitudinal assessments to determine the stability of putative endophenotypes.[120] Additionally, increased inclusion of twin studies in the analysis of endophenotypes has also been proposed.[63] By reducing the number of candidate traits to only those with the highest familial influence, twin studies can enhance the ability to detect key genetic origins.[63]

Causal modelling

The limitations of correlational research are a perennial concern in biomedical research, and present a difficult issue for chronic, neurodevelopmental disorders such as ADHD. For example, neuroimaging studies reporting hypoactivation of the ventral striatum in ADHD highlight pitfalls inherent to correlational studies. As noted above, hypoactivation of the ventral striatum during reward anticipation appears to be a reliable finding in ADHD and it is correlated with impulsivity. It is tempting to interpret a causal mechanism by which ventral striatal hypoactivation curtails the capacity to delay gratification, leading to the behavioural phenotype of impulsivity. However, this interpretation is complicated by the fact that unaffected, healthy controls display the opposite pattern: impulsivity correlates with increased, not decreased, activation of the ventral striatum.[61] This finding in healthy controls suggests that the hypoactivation seen in ADHD might not represent a causal pathway between neural and behavioural phenotype, but rather a neural adaptation to impulsivity. Children who chronically act impulsively to obtain rewards might, over time, develop an attenuated response to anticipated rewards.[61] Interpreting hypoactivation of the ventral striatum as a consequence, rather than a cause, of ADHD is consistent with the fact that this hypoactivation is noted in adolescents and adults with ADHD, but has not been reported in children. The ambiguities inherent to correlational research call for experimental designs that can more strongly impute causality. Here, we review ongoing efforts aimed at establishing causal relations through the use of animal models, neuromodulation techniques, pharmacoimaging studies, and the use of longitudinal analyses.

Animal models

Decades of work in rodents have shown that it is possible to model many of the behavioural characteristics of ADHD to gain insight into the underlying neurobiology. Rodents have been studied in the greatest detail because of the relative ease with which they can be bred for ADHD-like traits or genetically manipulated to test the role of candidate genes. Several rat and mouse models show face validity, recapitulating the core symptoms of the disorder: hyperactivity, impulsivity, and inattention. In table 2, we present a brief overview of some of these rodent models with a focus on those that have enabled testing of behavioural and neurobiological aspects linked to ADHD, consequences of therapeutic compounds, or

genetic associations. Although extrapolating their features to the disorder in human beings remains tentative, such models have the potential to provide new insight into the mechanisms underlying relevant behavioural traits.

Rodent models of ADHD have helped delineate potential consequences of genes previously associated with ADHD. Moreover, rodent models might also help identify novel ADHD candidate genes.[159] By exploiting the natural variation in behaviours related to the disorder within individual animals and strains, techniques such as quantitative trait loci mapping can help model subtle genetic and phenotypic variation in a population.[159] This approach can enhance the power to detect weak, yet statistically significant associations that might be difficult to detect in GWAS in human beings.[159]

The unveiling of the RDoC initiative[160] by NIMH has sparked new interest in the use of animal models to study specific neural circuits and their related behaviours. Rather than modelling all clinical aspects of a psychiatric disorder, RDoC focuses on specific domains of functioning that cut across psychiatric nosology. Virus-mediated gene transfer technologies are enabling delivery of genes of interest to specific brain regions, circuits, and cell populations. Such strategies have the potential to uncover specific roles of ADHD-related genes or their polymorphisms within distinct neural circuits associated with the disorder. Furthermore, viral approaches can be used to deliver genetically encoded calcium indicators to specific cell populations, enabling quantification of circuit activity in behaving animals. Similarly, optogenetic and chemogenetic tools, such as designer receptors exclusively activated by designer drugs (DREADDs), are now routinely used to directly manipulate activity of specific cells during different phases of behavioural assays. For example, recent work showed a disruption of attentional processing in mice following optogenetic silencing of prefrontal cortical fast-spiking parvalbumin interneurons. Conversely, optogenetic synchronisation of firing in these neurons to gamma frequencies resulted in improved performance.[161] These tools might also prove advantageous when temporally dissecting complex behaviours such as working memory,[162] which involves multiple phases such as encoding, retention, and retrieval.

Targeting select brain regions or circuitry might also enhance the focus on highly relevant behaviours by reducing extraneous behavioural effects seen with genome-wide genetic manipulations, such as knock-out techniques. Viral strategies can, for example, be a powerful tool to study the consequences of genetic alterations in adolescence or adulthood without the potentially confounding effects of developmental adaptions. These tools can thus serve to test emerging hypotheses about circuit dysfunction and disease course, such as the possibility of adult-onset ADHD[163] and offer insight into potential therapies. Initial steps have been taken to test the consequences of virus-mediated genetic strategies in rodent behaviours relevant to ADHD. For example, viral overexpression of SNAP-25 in the dorsal hippocampus of young adult rats increases glutamatergic transmission and is sufficient to mediate substantial cognitive deficits.[164] More recent work has shown that downregulation of SERT in rat hippocampus attenuates locomotor activity and impulsivity, suggesting that increased serotonergic transmission within this brain region could potentially ameliorate some symptoms of ADHD.[165]

Although rodent models will continue to be essential, the study of non-human primates might offer a better model of complex human brain circuitry, particularly in the context of the prefrontal cortical dysfunction seen in ADHD.[24,28] As with non-human primate models of other disorders such as Parkinson's disease,[166] viral gene delivery could open the door to refined manipulations of brain regions and distinct cell populations in these animals for the study of ADHD endophenotypes.

Despite the inevitable limitations of studying the heterogeneous manifestations of ADHD in animals, a combinatorial approach to modelling specific aspects of the disorder across different models and species is a necessary route towards deciphering the aetiological basis of the disorder.

Assessing causality in human beings

Efforts are also underway to test causal relations between neural correlates and ADHD traits in human beings. Methodologically, these efforts have centred on neuromodulation techniques, such as transcranial magnetic stimulation and transcranial direct current stimulation, and longitudinal pharmacoimaging studies, both of which allow investigators to experimentally manipulate neural circuits of interest. By manipulating neural circuits investigators can test whether perturbation of these substrates exacerbates or attenuates ADHD-like behaviours. For example, previous studies have associated dorsal frontostriatal dysfunction with deficits in response inhibition in ADHD. However, lacking experimental manipulation, a gap has remained between these descriptive studies and causal inferences. Pharmacoimaging studies have, to some extent, helped address this gap. This research suggests that baseline abnormalities in frontostriatal circuits are normalised by psychostimulant treatment, relative to placebo, and that this normalisation is associated with improvements in response inhibition.[167] Though informative, some caution in imputing causality on the basis of this research is still warranted as pharmacological probes typically lack the specificity needed to draw firm mechanistic conclusions. Psychostimulants, for example, affect multiple neural systems, and thus normalising frontostriatal circuits might be coincident with their effects on other circuits. Arguably, psychostimulant effects on neural circuits other than frontostriatal circuits could be mediating improvements in response inhibition. Future studies might obtain greater specificity, and thus bolster causal inferences, by comparing pharmacological agents with distinct mechanisms of action. Neuromodulation techniques combined with neuroimaging might also help show causal relations. Although such research has not yet been done in ADHD, Chen and colleagues[168] found that transcranial magnetic stimulation of nodes within the CCN causes inhibition of the DMN. This work provides a mechanistic account of the inverse relations between the CCN and DMN suggested by resting fMRI studies (see above). Future studies could test whether transcranial magnetic stimulation-induced changes in the balance between the CCN and DMN result in changes in sustained attention or ADHD-related symptoms.

Conclusions

ADHD is a heterogeneous neurodevelopmental disorder that impairs the quality of life of millions of children, adolescents, and adults worldwide, yet the neurobiological

underpinnings of the disorder are not well understood. Given the multifactorial origin and complex symptomatology of ADHD, substantial research efforts over the past two decades have used new technologies to investigate genetic and neural alterations associated with ADHD. Although candidate genes and neurotransmitter systems have been implicated in ADHD, genome-wide associations between ADHD and individual genetic variants have yet to be found. Thus, their contributions to our understanding of ADHD aetiology are limited. However, larger-scale, multicentre approaches are now underway, representing one promising avenue towards deciphering the genetic architecture of this polygenic disorder. Additionally, much progress has been made in identifying key brain circuits and regions whose structure, function, and connectivity are impaired in ADHD. One of the greatest challenges still to be met is establishing causal relations between these neural alterations and the disorder. A deeper understanding of neural circuits and their function will probably require improved neuroimaging methods combined with experimental manipulations, such as refined neuromodulation and pharmacological approaches. Furthermore, relying on well characterised animal models and powerful technologies, such as *in vivo* optogenetics, might enable selective manipulations of the implicated circuitry during ADHD-related tasks. A crucial future direction for ADHD research is to triangulate at causality by coupling studies of human beings and animals. Continued examination of reliable endophenotypes might also bridge the gap from genes to behaviour and provide a useful convergence point for ADHD research across species. Mapping causal pathways from genes to neural circuits to symptoms is essential to isolating targets for novel interventions and preventive strategies to curtail the effects of this remarkably common and impairing condition.

Acknowledgments

This work was supported in part by NIH K01MH107648 to EFG and by the Edwin S Webster Foundation to JP.

References

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007; 164:942–48. [PubMed: 17541055]
2. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics. 2012; 9:490–99. [PubMed: 22976615]
3. Davies W. Sex differences in attention Deficit Hyperactivity Disorder: candidate genetic and endocrine mechanisms. Front Neuroendocrinol. 2014; 35:331–46. [PubMed: 24680800]
4. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. J Pediatr Psychol. 2007; 32:631–42. [PubMed: 17556405]
5. Klein RG, Mannuzza S, Olazagasti MA, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch Gen Psychiatry. 2012; 69:1295–303. [PubMed: 23070149]
6. Satterfield JH, Faller KJ, Crinella FM, Schell AM, Swanson JM, Homer LD. A 30-year prospective follow-up study of hyperactive boys with conduct problems: adult criminality. J Am Acad Child Adolesc Psychiatry. 2007; 46:601–10. [PubMed: 17450051]
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association; 2013.
8. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. Am J Psychiatry. 2014; 171:276–93. [PubMed: 24480998]

9. Posner J, Kass E, Hulvershorn L. Using stimulants to treat ADHD-related emotional lability. Curr Psychiatry Rep. 2014; 16:478. [PubMed: 25135778]
10. Barkley RA, Fischer M. The unique contribution of emotional impulsiveness to impairment in major life activities in hyperactive children as adults. J Am Acad Child Adolesc Psychiatry. 2010; 49:503–13. [PubMed: 20431470]
11. Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009; 57:579–89. [PubMed: 19627998]
12. Luman M, Oosterlaan J, Sergeant JA. The impact of reinforcement contingencies on AD/HD: a review and theoretical appraisal. Clin Psychol Rev. 2005; 25:183–213. [PubMed: 15642646]
13. Sonuga-Barke EJS, Sergeant JA, Nigg J, Willcutt E. Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: nosologic and diagnostic implications. Child Adolesc Psychiatr Clin N Am. 2008; 17:367–84, ix. [PubMed: 18295151]
14. Banaschewski T, Hollis C, Oosterlaan J, et al. Towards an understanding of unique and shared pathways in the psychopathophysiology of ADHD. Dev Sci. 2005; 8:132–40. [PubMed: 15720371]
15. Antshel KM, Zhang-James Y, Faraone SV. The comorbidity of ADHD and autism spectrum disorder. Expert Rev Neurother. 2013; 13:1117–28. [PubMed: 24117274]
16. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci. 2002; 3:617–28. [PubMed: 12154363]
17. Nigg JT, Nikolas M, Mark Knottnerus G, Cavanagh K, Friderici K. Confirmation and extension of association of blood lead with attention-deficit/hyperactivity disorder (ADHD) and ADHD symptom domains at population-typical exposure levels. J Child Psychol Psychiatry. 2010; 51:58–65. [PubMed: 19941632]
18. Milberger S, Biederman J, Faraone SV, Jones J. Further evidence of an association between maternal smoking during pregnancy and attention deficit hyperactivity disorder: findings from a high-risk sample of siblings. J Clin Child Psychol. 1998; 27:352–58. [PubMed: 9789194]
19. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatr. 2007; 96:1269–74. [PubMed: 17718779]
20. Ellison-Wright I, Ellison-Wright Z, Bullmore E. Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. BMC Psychiatry. 2008; 8:51. [PubMed: 18590567]
21. Nakao T, Radua C, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry. 2011; 168:1154–63. [PubMed: 21865529]
22. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand. 2012; 125:114–26. [PubMed: 22118249]
23. Haber SN. The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat. 2003; 26:317–30. [PubMed: 14729134]
24. Bush G. Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2011; 69:1160–67. [PubMed: 21489409]
25. Sonuga-Barke EJ. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. Biol Psychiatry. 2005; 57:1231–38. [PubMed: 15949993]
26. Rubia K, Alegria A, Brinson H. Imaging the ADHD brain: disorder-specificity, medication effects and clinical translation. Expert Rev Neurother. 2014; 14:519–38. [PubMed: 24738703]
27. Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA. 2007; 104:19649–54. [PubMed: 18024590]
28. Almeida LG, Ricardo-Garcell J, Prado H, et al. Reduced right frontal cortical thickness in children, adolescents and adults with ADHD and its correlation to clinical variables: a cross-sectional study. J Psychiatr Res. 2010; 44:1214–23. [PubMed: 20510424]
29. Montes LGA, Alcántara HP, García RBM, De La Torre LB, Acosta DÁ, Duarte MG. Brain cortical thickness in ADHD: age, sex, and clinical correlations. J Atten Disord. 2012; 17:641–54. [PubMed: 22392552]

30. Rubia K. Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. Proc Natl Acad Sci USA. 2007; 104:19663–64. [PubMed: 18077397]
31. Insel TR. Disruptive insights in psychiatry: transforming a clinical discipline. J Clin Invest. 2009; 119:700–05. [PubMed: 19339761]
32. Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron. 2006; 51:527–39. [PubMed: 16950152]
33. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995; 34:537–41. [PubMed: 8524021]
34. Posner J, Hellerstein DJ, Gat I, et al. Antidepressants normalize the default mode network in patients with dysthymia. JAMA Psychiatry. 2013; 70:373–82. [PubMed: 23389382]
35. Posner J, Nagel B, Maia T, et al. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011; 50:828–37, e3. [PubMed: 21784302]
36. van Ewijk H, Heslenfeld DJ, Zwiers MP, Buitelaar JK, Oosterlaan J. Diffusion tensor imaging in attention deficit/hyperactivity disorder: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2012; 36:1093–106. [PubMed: 22305957]
37. Nagel BJ, Bathula D, Herting M, et al. Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011; 50:283–92. [PubMed: 21334568]
38. Cha J, Fekete T, Siciliano F, et al. Neural correlates of aggression in medication-naive children with ADHD: multivariate analysis of morphometry and tractography. Neuropsychopharmacology. 2015; 40:1717–25. [PubMed: 25645374]
39. Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol Rev. 2014; 24:3–15. [PubMed: 24496902]
40. Fair DA, Posner J, Nagel BJ, et al. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2010; 68:1084–91. [PubMed: 20728873]
41. Posner J, Rauh V, Gruber A, Gat I, Wang Z, Peterson BS. Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. Psychiatry Res. 2013; 213:24–30. [PubMed: 23664625]
42. Castellanos FX, Margulies DS, Kelly C, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry. 2008; 63:332–37. [PubMed: 17888409]
43. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci. 2008; 1124:1–38. [PubMed: 18400922]
44. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. Neuroimage. 2007; 37:1083–90. discussion 1097–99. [PubMed: 17719799]
45. Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev. 2007; 31:977–86. [PubMed: 17445893]
46. Peterson BS, Potenza MN, Wang Z, et al. An FMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. Am J Psychiatry. 2009; 166:1286–94. [PubMed: 19755575]
47. Qiu MG, Ye Z, Li QY, Liu GJ, Xie B, Wang J. Changes of brain structure and function in ADHD children. Brain Topogr. 2011; 24:243–52. [PubMed: 21191807]
48. Sun L, Cao Q, Long X, et al. Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. Psychiatry Res. 2012; 201:120–27. [PubMed: 22424873]
49. Hoekzema E, Carmona S, Ramos-Quiroga JA, et al. An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. Hum Brain Mapp. 2014; 35:1261–72. [PubMed: 23417778]
50. Cole MW, Schneider W. The cognitive control network: integrated cortical regions with dissociable functions. Neuroimage. 2007; 37:343–60. [PubMed: 17553704]

51. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA. 2005; 102:9673–78. [PubMed: 15976020]
52. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA. 2001; 98:676–82. [PubMed: 11209064]
53. Grady CL, Protzner AB, Kovacevic N, et al. A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. Cereb Cortex. 2010; 20:1432–47. [PubMed: 19789183]
54. Sato JR, Hoexter MQ, Castellanos XF, Rohde LA. Abnormal brain connectivity patterns in adults with ADHD: a coherence study. PLoS One. 2012; 7:e45671. [PubMed: 23049834]
55. Cao X, Cao Q, Long X, et al. Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. Brain Res. 2009; 1303:195–206. [PubMed: 19699190]
56. Costa Dias TG, Wilson VB, Bathula DR, et al. Reward circuit connectivity relates to delay discounting in children with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2013; 23:33–45. [PubMed: 23206930]
57. Posner J, Siciliano F, Wang Z, Liu J, Sonuga-Barke E, Greenhill L. A multimodal MRI study of the hippocampus in medication-naive children with ADHD: what connects ADHD and depression? Psychiatry Res. 2014; 224:112–18. [PubMed: 25220159]
58. Rubia K, Halari R, Cubillo A, Mohammad A-M, Brammer M, Taylor E. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. Neuropharmacology. 2009; 57:640–52. [PubMed: 19715709]
59. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry. 2013; 70:185–98. [PubMed: 23247506]
60. Cortese S, Kelly C, Chabernaud C, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry. 2012; 169:1038–55. [PubMed: 22983386]
61. Plichta MM, Scheres A. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. Neurosci Biobehav Rev. 2014; 38:125–34. [PubMed: 23928090]
62. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57:1313–23. [PubMed: 15950004]
63. Wood AC, Neale MC. Twin studies and their implications for molecular genetic studies: endophenotypes integrate quantitative and molecular genetics in ADHD research. J Am Acad Child Adolesc Psychiatry. 2010; 49:874–83. [PubMed: 20732624]
64. Hawi Z, Cummins TD, Tong J, et al. The molecular genetic architecture of attention deficit hyperactivity disorder. Mol Psychiatry. 2015; 20:289–97. [PubMed: 25600112]
65. Geschwind DH, Flint J. Genetics and genomics of psychiatric disease. Science. 2015; 349:1489–94. [PubMed: 26404826]
66. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Hum Genet. 2009; 126:51–90. [PubMed: 19506906]
67. Cook EH Jr, Stein MA, Krasowski MD, et al. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet. 1995; 56:993–98. [PubMed: 7717410]
68. Boonstra AM, Kooij JJ, Buitelaar JK, et al. An exploratory study of the relationship between four candidate genes and neurocognitive performance in adult ADHD. Am J Med Genet B Neuropsychiatr Genet. 2008; 147:397–402. [PubMed: 17886261]
69. Colzato LS, van den Wildenberg WP, Van der Does AJ, Hommel B. Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. Neuroscience. 2010; 170:782–88. [PubMed: 20678555]
70. Bidwell LC, Willcutt EG, McQueen MB, et al. A family based association study of DRD4, DAT1, and 5HTT and continuous traits of attention-deficit hyperactivity disorder. Behav Genet. 2011; 41:165–74. [PubMed: 21207241]

71. Paloyelis Y, Asherson P, Mehta MA, Faraone SV, Kuntsi J. DAT1 and COMT effects on delay discounting and trait impulsivity in male adolescents with attention deficit/hyperactivity disorder and healthy controls. Neuropsychopharmacology. 2010; 35:2414–26. [PubMed: 20736997]

72. LaHoste GJ, Swanson JM, Wigal SB, et al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry. 1996; 1:121–24. [PubMed: 9118321]

73. McCracken JT, Smalley SL, McGough JJ, et al. Evidence for linkage of a tandem duplication polymorphism upstream of the dopamine D4 receptor gene (DRD4) with attention deficit hyperactivity disorder (ADHD). Mol Psychiatry. 2000; 5:531–36. [PubMed: 11032387]

74. Kieling C, Roman T, Doyle AE, Hutz MH, Rohde LA. Association between DRD4 gene and performance of children with ADHD in a test of sustained attention. Biol Psychiatry. 2006; 60:1163–65. [PubMed: 16781678]

75. Lionel AC, Crosbie J, Barbosa N, et al. Rare copy number variation discovery and cross-disorder comparisons identify risk genes for ADHD. Sci Transl Med. 2011; 3:95ra75.

76. Daly G, Hawi Z, Fitzgerald M, Gill M. Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Mol Psychiatry. 1999; 4:192–96. [PubMed: 10208453]

77. Lowe N, Kirley A, Hawi Z, et al. Joint analysis of the DRD5 marker concludes association with attention-deficit/hyperactivity disorder confined to the predominantly inattentive and combined subtypes. Am J Hum Genet. 2004; 74:348–56. [PubMed: 14732906]

78. Manor I, Corbex M, Eisenberg J, et al. Association of the dopamine D5 receptor with attention deficit hyperactivity disorder (ADHD) and scores on a continuous performance test (TOVA). Am J Med Genet B Neuropsychiatr Genet. 2004; 127B:73–77. [PubMed: 15108184]

79. Manor I, Eisenberg J, Tyano S, et al. Family-based association study of the serotonin transporter promoter region polymorphism (5-HTTLPR) in attention deficit hyperactivity disorder. Am J Med Genet. 2001; 105:91–95. [PubMed: 11425009]

80. Seeger G, Schloss P, Schmidt MH. Functional polymorphism within the promotor of the serotonin transporter gene is associated with severe hyperkinetic disorders. Mol Psychiatry. 2001; 6:235–38. [PubMed: 11317229]

81. Sonuga-Barke EJ, Kumsta R, Schlotz W, et al. A functional variant of the serotonin transporter gene (SLC6A4) moderates impulsive choice in attention-deficit/hyperactivity disorder boys and siblings. Biol Psychiatry. 2011; 70:230–36. [PubMed: 21497794]

82. Hawi Z, Dring M, Kirley A, et al. Serotonergic system and attention deficit hyperactivity disorder (ADHD): a potential susceptibility locus at the 5-HT(1B) receptor gene in 273 nuclear families from a multi-centre sample. Mol Psychiatry. 2002; 7:718–25. [PubMed: 12192616]

83. Smoller JW, Biederman J, Arbeitman L, et al. Association between the 5HT1B receptor gene (HTR1B) and the inattentive subtype of ADHD. Biol Psychiatry. 2006; 59:460–67. [PubMed: 16197923]

84. van Rooij D, Hoekstra PJ, Mennes M, et al. Distinguishing adolescents with ADHD from their unaffected siblings and healthy comparison subjects by neural activation patterns during response inhibition. Am J Psychiatry. 2015; 172:674–83. [PubMed: 25615565]

85. Brophy K, Hawi Z, Kirley A, Fitzgerald M, Gill M. Synaptosomal-associated protein 25 (SNAP-25) and attention deficit hyperactivity disorder (ADHD): evidence of linkage and association in the Irish population. Mol Psychiatry. 2002; 7:913–17. [PubMed: 12232787]

86. Bruno KJ, Freet CS, Twining RC, Egami K, Grigson PS, Hess EJ. Abnormal latent inhibition and impulsivity in coloboma mice, a model of ADHD. Neurobiol Dis. 2007; 25:206–16. [PubMed: 17064920]

87. Lasky-Su J, Neale BM, Franke B, et al. Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations. Am J Med Genet B Neuropsychiatr Genet. 2008; 147B:1345–54. [PubMed: 18821565]

88. Reif A, Jacob CP, Rujescu D, et al. Influence of functional variant of neuronal nitric oxide synthase on impulsive behaviors in humans. Arch Gen Psychiatry. 2009; 66:41–50. [PubMed: 19124687]

89. Franke B, Neale BM, Faraone SV. Genome-wide association studies in ADHD. Hum Genet. 2009; 126:13–50. [PubMed: 19384554]

90. de Silva MG, Elliott K, Dahl HH, et al. Disruption of a novel member of a sodium/hydrogen exchanger family and DOCK3 is associated with an attention deficit hyperactivity disorder-like phenotype. J Med Genet. 2003; 40:733–40. [PubMed: 14569117]

91. Markunas CA, Quinn KS, Collins AL, et al. Genetic variants in SLC9A9 are associated with measures of attention-deficit/hyperactivity disorder symptoms in families. Psychiatr Genet. 2010; 20:73–81. [PubMed: 20032819]

92. Arcos-Burgos M, Jain M, Acosta MT, et al. A common variant of the latrophilin 3 gene, LPHN3, confers susceptibility to ADHD and predicts effectiveness of stimulant medication. Mol Psychiatry. 2010; 15:1053–66. [PubMed: 20157310]

93. Fallgatter AJ, Ehlis AC, Dresler T, et al. Influence of a latrophilin 3 (LPHN3) risk haplotype on event-related potential measures of cognitive response control in attention-deficit hyperactivity disorder (ADHD). Eur Neuropsychopharmacol. 2013; 23:458–68. [PubMed: 23245769]

94. Won H, Mah W, Kim E, et al. GIT1 is associated with ADHD in humans and ADHD-like behaviors in mice. Nat Med. 2011; 17:566–72. [PubMed: 21499268]

95. Arias-Vásquez A, Altink ME, Rommelse NN, et al. CDH13 is associated with working memory performance in attention deficit/hyperactivity disorder. Genes Brain Behav. 2011; 10:844–51. [PubMed: 21815997]

96. Salatino-Oliveira A, Genro JP, Polanczyk G, et al. Cadherin-13 gene is associated with hyperactive/impulsive symptoms in attention/deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 2015; 168B:162–69. [PubMed: 25739828]

97. Ogdie MN, Fisher SE, Yang M, et al. Attention deficit hyperactivity disorder: fine mapping supports linkage to 5p13, 6q12, 16p13, and 17p11. Am J Hum Genet. 2004; 75:661–68. [PubMed: 15297934]

98. Lu AT, Ogdie MN, Järvelin MR, et al. Association of the cannabinoid receptor gene (CNR1) with ADHD and post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet. 2008; 147B: 1488–94. [PubMed: 18213623]

99. Ehlers CL, Slutske WS, Lind PA, Wilhelmsen KC. Association between single nucleotide polymorphisms in the cannabinoid receptor gene (CNR1) and impulsivity in southwest California Indians. Twin Res Hum Genet. 2007; 10:805–11. [PubMed: 18179391]

100. López-Moreno JA, Echeverry-Alzate V, Bühler KM. The genetic basis of the endocannabinoid system and drug addiction in humans. J Psychopharmacol. 2012; 26:133–43. [PubMed: 21937688]

101. Williams NM, Zaharieva I, Martin A, et al. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. Lancet. 2010; 376:1401–08. [PubMed: 20888040]

102. Young JW, Crawford N, Kelly JS, et al. Impaired attention is central to the cognitive deficits observed in alpha 7 deficient mice. Eur Neuropsychopharmacol. 2007; 17:145–55. [PubMed: 16650968]

103. Lesch KP, Timmesfeld N, Renner TJ, et al. Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. J Neural Transm (Vienna). 2008; 115:1573–85. [PubMed: 18839057]

104. Neale BM, Medland S, Ripke S, The IMAGE II Consortium Group. Case-control genome-wide association study of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2010; 49:906–20. [PubMed: 20732627]

105. Takeuchi T, Misaki A, Liang SB, et al. Expression of T-cadherin (CDH13, H-Cadherin) in human brain and its characteristics as a negative growth regulator of epidermal growth factor in neuroblastoma cells. J Neurochem. 2000; 74:1489–97. [PubMed: 10737605]

106. Børglum AD, Demontis D, Grove J, et al. The GROUP investigators. Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. Mol Psychiatry. 2014; 19:325–33. [PubMed: 23358160]

107. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511:421–27. [PubMed: 25056061]

108. Sekar A, Bialas AR, de Rivera H, et al. The Schizophrenia Working Group of the Psychiatric Genomics Consortium. Schizophrenia risk from complex variation of complement component 4. Nature. 2016; 530:177–83. [PubMed: 26814963]
109. Elia J, Gai X, Xie HM, et al. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry. 2010; 15:637–46. [PubMed: 19546859]
110. Elia J, Glessner JT, Wang K, et al. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. Nat Genet. 2012; 44:78–84. [PubMed: 22138692]
111. Stergiakouli E, Hamshere M, Holmans P, et al. The deCODE Genetics, and the Psychiatric GWAS Consortium. Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD. Am J Psychiatry. 2012; 169:186–94. [PubMed: 22420046]
112. Martin J, O'Donovan MC, Thapar A, Langley K, Williams N. The relative contribution of common and rare genetic variants to ADHD. Transl Psychiatr. 2015; 5:e506.
113. Plomin R, Deary IJ. Genetics and intelligence differences: five special findings. Mol Psychiatry. 2015; 20:98–108. [PubMed: 25224258]
114. Hamshere ML, Langley K, Martin J, et al. High loading of polygenic risk for ADHD in children with comorbid aggression. Am J Psychiatry. 2013; 170:909–16. [PubMed: 23599091]
115. Stergiakouli E, Martin J, Hamshere ML, et al. Shared genetic influences between attention-deficit/hyperactivity disorder (ADHD) traits in children and clinical ADHD. J Am Acad Child Adolesc Psychiatry. 2015; 54:322–27. [PubMed: 25791149]
116. Levy F, Hay DA, McStephen M, Wood C, Waldman I. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. J Am Acad Child Adolesc Psychiatry. 1997; 36:737–44. [PubMed: 9183127]
117. Krumm N, O'Roak BJ, Shendure J, Eichler EE. A de novo convergence of autism genetics and molecular neuroscience. Trends Neurosci. 2014; 37:95–105. [PubMed: 24387789]
118. Lyon GJ, Jiang T, Van Wijk R, et al. Exome sequencing and unrelated findings in the context of complex disease research: ethical and clinical implications. Discov Med. 2011; 12:41–55. [PubMed: 21794208]
119. Baroni A, Castellanos FX. Neuroanatomic and cognitive abnormalities in attention-deficit/hyperactivity disorder in the era of 'high definition' neuroimaging. Curr Opin Neurobiol. 2015; 30:1–8. [PubMed: 25212469]
120. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. Mol Psychiatry. 2010; 15:789–97. [PubMed: 20142819]
121. Kofler MJ, Rapport MD, Sarver DE, et al. Reaction time variability in ADHD: a meta-analytic review of 319 studies. Clin Psychol Rev. 2013; 33:795–811. [PubMed: 23872284]
122. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. Brain. 2014; 137:12–32. [PubMed: 23869106]
123. Karalunas SL, Geurts HM, Konrad K, Bender S, Nigg JT. Annual research review: Reaction time variability in ADHD and autism spectrum disorders: measurement and mechanisms of a proposed trans-diagnostic phenotype. J Child Psychol Psychiatry. 2014; 55:685–710. [PubMed: 24628425]
124. Crosbie J, Pérusse D, Barr CL, Schachar RJ. Validating psychiatric endophenotypes: inhibitory control and attention deficit hyperactivity disorder. Neurosci Biobehav Rev. 2008; 32:40–55. [PubMed: 17976721]
125. Durston S, Mulder M, Casey BJ, Ziermans T, van Engeland H. Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. Biol Psychiatry. 2006; 60:1062–70. [PubMed: 16712804]
126. Kasper LJ, Alderson RM, Hudec KL. Moderators of working memory deficits in children with attention-deficit/hyperactivity disorder (ADHD): a meta-analytic review. Clin Psychol Rev. 2012; 32:605–17. [PubMed: 22917740]
127. Martinussen R, Hayden J, Hogg-Johnson S, Tannock R. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2005; 44:377–84. [PubMed: 15782085]

128. Alderson RM, Kasper LJ, Hudec KL, Patros CH. Attention-deficit/hyperactivity disorder (ADHD) and working memory in adults: a meta-analytic review. Neuropsychology. 2013; 27:287–302. [PubMed: 23688211]

129. Rapport MD, Chung K-M, Shore G, Isaacs P. A conceptual model of child psychopathology: implications for understanding attention deficit hyperactivity disorder and treatment efficacy. J Clin Child Psychol. 2001; 30:48–58. [PubMed: 11294077]

130. Park S, Holzman PS. Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry. 1992; 49:975–82. [PubMed: 1449384]

131. Harvey PO, Le Bastard G, Pochon JB, et al. Executive functions and updating of the contents of working memory in unipolar depression. J Psychiatr Res. 2004; 38:567–76. [PubMed: 15458852]

132. Thompson JM, Gray JM, Hughes JH, Watson S, Young AH, Ferrier IN. Impaired working memory monitoring in euthymic bipolar patients. Bipolar Disord. 2007; 9:478–89. [PubMed: 17680918]

133. Cuthbert BN, Kozak MJ. Constructing constructs for psychopathology: the NIMH research domain criteria. J Abnorm Psychol. 2013; 122:928–37. [PubMed: 24016027]

134. Tye C, McLoughlin G, Kuntsi J, Asherson P. Electrophysiological markers of genetic risk for attention deficit hyperactivity disorder. Expert Rev Mol Med. 2011; 13:e9. [PubMed: 21426626]

135. Helps SK, Broyd SJ, James CJ, Karl A, Chen W, Sonuga-Barke EJS. Altered spontaneous low frequency brain activity in attention deficit/hyperactivity disorder. Brain Res. 2010; 1322:134–43. [PubMed: 20117101]

136. Okamoto K, Aoki K. Development of a strain of spontaneously hypertensive rats. Jpn Circ J. 1963; 27:282–93. [PubMed: 13939773]

137. Sagvolden T, Russell VA, Aase H, Johansen EB, Farshbaf M. Rodent models of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57:1239–47. [PubMed: 15949994]

138. Bizot JC, Chenault N, Houzé B, et al. Methylphenidate reduces impulsive behaviour in juvenile Wistar rats, but not in adult Wistar, SHR and WKY rats. Psychopharmacology (Berl). 2007; 193:215–23. [PubMed: 17406857]

139. Russell VA. Neurobiology of animal models of attention-deficit hyperactivity disorder. J Neurosci Methods. 2007; 161:185–98. [PubMed: 17275916]

140. Dalley JW, Fryer TD, Brichard L, et al. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science. 2007; 315:1267–70. [PubMed: 17332411]

141. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron. 2011; 69:680–94. [PubMed: 21338879]

142. Giros B, Jaber M, Jones SR, Wightman RM, Caron MG. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature. 1996; 379:606–12. [PubMed: 8628395]

143. Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG. Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science. 1999; 283:397–401. [PubMed: 9888856]

144. Weiss S, Nosten-Bertrand M, McIntosh JM, Giros B, Martres M-P. Nicotine improves cognitive deficits of dopamine transporter knockout mice without long-term tolerance. Neuropsychopharmacology. 2007; 32:2465–78. [PubMed: 17375139]

145. Gainetdinov RR, Jones SR, Caron MG. Functional hyperdopaminergia in dopamine transporter knock-out mice. Biol Psychiatry. 1999; 46:303–11. [PubMed: 10435196]

146. Shaywitz BA, Yager RD, Klopper JH. Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. Science. 1976; 191:305–08. [PubMed: 942800]

147. Avale ME, Falzone TL, Gelman DM, Low MJ, Grandy DK, Rubinstein M. The dopamine D4 receptor is essential for hyperactivity and impaired behavioral inhibition in a mouse model of attention deficit/hyperactivity disorder. Mol Psychiatry. 2004; 9:718–26. [PubMed: 14699433]

148. Davids E, Zhang K, Kula NS, Tarazi FI, Baldessarini RJ. Effects of norepinephrine and serotonin transporter inhibitors on hyperactivity induced by neonatal 6-hydroxydopamine lesioning in rats. J Pharmacol Exp Ther. 2002; 301:1097–102. [PubMed: 12023542]

149. Braz BY, Galiñanes GL, Taravini IR, Belforte JE, Murer MG. Altered corticostriatal connectivity and exploration/exploitation imbalance emerge as intermediate phenotypes for a neonatal dopamine dysfunction. Neuropsychopharmacology. 2015; 40:2576–87. [PubMed: 25872916]

150. Luthman J, Fredriksson A, Lewander T, Jonsson G, Archer T. Effects of d-amphetamine and methylphenidate on hyperactivity produced by neonatal 6-hydroxydopamine treatment. Psychopharmacology (Berl). 1989; 99:550–57. [PubMed: 2594922]

151. Hess EJ, Jinnah HA, Kozak CA, Wilson MC. Spontaneous locomotor hyperactivity in a mouse mutant with a deletion including the Snap gene on chromosome 2. J Neurosci. 1992; 12:2865–74. [PubMed: 1613559]

152. Raber J, Mehta PP, Kreifeldt M, et al. Coloboma hyperactive mutant mice exhibit regional and transmitter-specific deficits in neurotransmission. J Neurochem. 1997; 68:176–86. [PubMed: 8978724]

153. Menon P, Deane R, Sagare A, et al. Impaired spine formation and learning in GPCR kinase 2 interacting protein-1 (GIT1) knockout mice. Brain Res. 2010; 1317:218–26. [PubMed: 20043896]

154. Huang PL, Dawson TM, Bredt DS, Snyder SH, Fishman MC. Targeted disruption of the neuronal nitric oxide synthase gene. Cell. 1993; 75:1273–86. [PubMed: 7505721]

155. Nelson RJ, Demas GE, Huang PL, et al. Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase. Nature. 1995; 378:383–86. [PubMed: 7477374]

156. Gao Y, Heldt SA. Lack of neuronal nitric oxide synthase results in attention deficit hyperactivity disorder-like behaviors in mice. Behav Neurosci. 2015; 129:50–61. [PubMed: 25621792]

157. Gallo EF, Iadecola C. Neuronal nitric oxide contributes to neuroplasticity-associated protein expression through cGMP, protein kinase G, and extracellular signal-regulated kinase. J Neurosci. 2011; 31:6947–55. [PubMed: 21562256]

158. O'Dell TJ, Hawkins RD, Kandel ER, Arancio O. Tests of the roles of two diffusible substances in long-term potentiation: evidence for nitric oxide as a possible early retrograde messenger. Proc Natl Acad Sci USA. 1991; 88:11285–89. [PubMed: 1684863]

159. Mill J. Rodent models: utility for candidate gene studies in human attention-deficit hyperactivity disorder (ADHD). J Neurosci Methods. 2007; 166:294–305. [PubMed: 17234273]

160. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167:748–51. [PubMed: 20595427]

161. Kim H, Ährlund-Richter S, Wang X, Deisseroth K, Carlén M. Prefrontal parvalbumin neurons in control of attention. Cell. 2016; 164:208–18. [PubMed: 26771492]

162. Baddeley A. Working memory: looking back and looking forward. Nat Rev Neurosci. 2003; 4:829–39. [PubMed: 14523382]

163. Moffitt TE, Houts R, Asherson P, et al. Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a four-decade longitudinal cohort study. Am J Psychiatry. 2015; 172:967–77. [PubMed: 25998281]

164. McKee AG, Loscher JS, O'Sullivan NC, et al. AAV-mediated chronic over-expression of SNAP-25 in adult rat dorsal hippocampus impairs memory-associated synaptic plasticity. J Neurochem. 2010; 112:991–1004. [PubMed: 20002519]

165. Zoratto F, Tringle AL, Bellenchi G, et al. Impulsivity and home-cage activity are decreased by lentivirus-mediated silencing of serotonin transporter in the rat hippocampus. Neurosci Lett. 2013; 548:38–43. [PubMed: 23769733]

166. Hadaczek P, Kohutnicka M, Krauze MT, et al. Convection-enhanced delivery of adeno-associated virus type 2 (AAV2) into the striatum and transport of AAV2 within monkey brain. Hum Gene Ther. 2006; 17:291–302. [PubMed: 16544978]

167. Rubia K, Alegria AA, Cubillo AI, Smith AB, Brammer MJ, Radua J. Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Biol Psychiatry. 2014; 76:616–28. [PubMed: 24314347]

168. Chen AC, Oathes DJ, Chang C, et al. Causal interactions between fronto-parietal central executive and default-mode networks in humans. Proc Natl Acad Sci USA. 2013; 110:19944–49. [PubMed: 24248372]

Panel: Attention-deficit hyperactivity disorder symptoms (DSM-5)[7]

Inattention

- Fails to give close attention to details or makes careless mistakes in schoolwork, work, or during other activities
- Has difficulty sustaining attention in tasks or play activities
- Does not seem to listen when spoken to directly
- Does not follow through on instructions and fails to finish school work, chores, or duties in the work place
- Has difficulty organising tasks and activities
- Avoids or is reluctant to engage in tasks that require sustained mental effort
- Often loses things necessary for tasks or activities
- Easily distracted by extraneous stimuli or thoughts
- Is often forgetful in daily activities

Hyperactivity and impulsivity

- Fidgets with or taps hands or squirms in seat
- Leaves seat in situations when remaining seated is expected
- Runs about or climbs, or is restless in situations where it is inappropriate
- Unable to play or engage in leisure activities quietly
- Is often on the go acting as if driven by a motor
- Talks excessively
- Blurts out answers before questions have been completed
- Has difficulty awaiting turn
- Interrupts or intrudes on others

Search strategy and selection criteria

We searched PubMed for articles published by Feb 20, 2016, with an emphasis on the previous 10 years (Jan 1, 2006 to Feb 20, 2016). English and non-English language publications were considered in our search. Primary and review articles resulting from these searches, together with relevant references cited within those articles were included. On account of limited space we occasionally cite review papers in place of primary reports. We used the following search terms: “ADHD”, “neurobiolog*”, “neural circuits”, “brain imaging”, “genetics”, “endophenotypes”, and “animal models”.

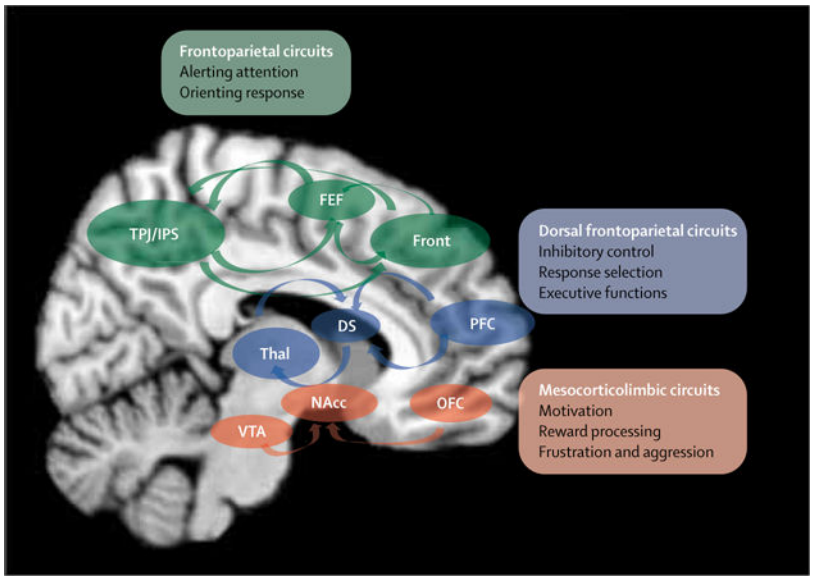

Figure 1. Neural circuits implicated in attention-deficit hyperactivity disorder

Frontoparietal circuits encompass the frontal lobes (front), including the supplemental motor area and frontal eye fields (FEF), and the temporal parietal junction and inferior parietal sulcus (TPJ/IPS). These circuits underlie attentional processes including the altering and orienting of attentional resources. Dorsal frontostriatal circuits encompass the dorsolateral prefrontal cortex (PFC), dorsal striatum (DS), and the thalamus. These circuits underlie inhibitory control including response inhibition and interference control. Mesocorticolimbic circuits encompass the orbitofrontal cortex (OFC), ventral striatum and nucleus accumbens (NAcc), ventral tegmental area (VTA), and anterior hippocampus. These circuits underlie reward and emotional processes including motivation, frustration tolerance, and reward anticipation.

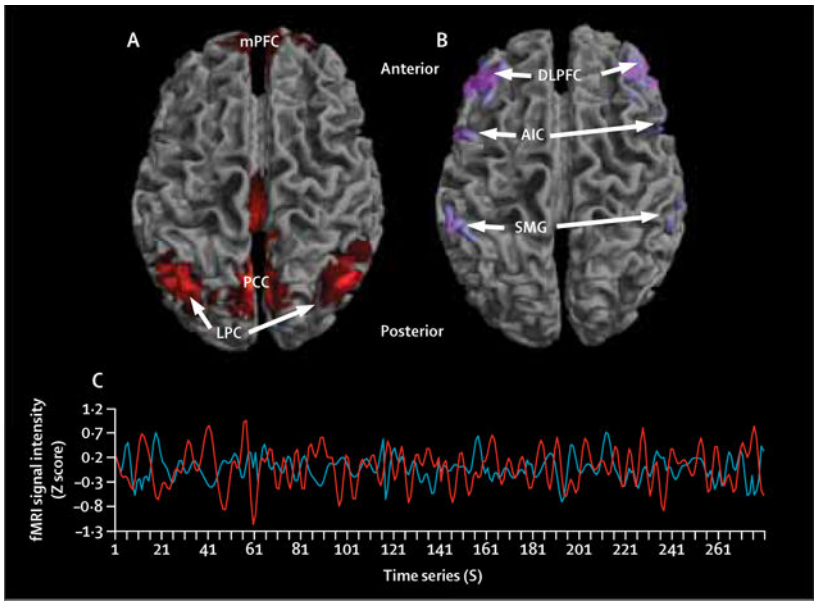

Figure 2. Functional connectivity within the default mode network (DMN) and the cognitive control network (CCN)

(A) Resting state functional connectivity maps of the DMN. Red shows positively correlated functional magnetic resonance imaging (fMRI) signal, or positive connectivity, within regions of the DMN including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and lateral parietal cortex (LPC). (B) Resting state functional connectivity maps of the CCN. Purple shows positively correlated fMRI signal within regions of the CCN including the dorsolateral prefrontal cortex (DLPFC), anterior insular cortex (AIC), and supramarginal gyrus (SMG). (C) Time series data extracted from the DMN (red) and the CCN (blue) show inversely correlated fMRI signal intensity between the DMN and CCN.

Table 1

Selected candidate genes implicated in attention-deficit hyperactivity disorder (ADHD)

	Gene product or function	Method(s) used to show association	Hypothesised links to ADHD-related phenotypes
SLC6A3 (DAT)	Dopamine re-uptake, transporter	Candidate gene[67]	Inhibition,[68] attentional flexibility,[69] inattention,[70] impulsivity[71]
DRD4	Dopamine D4 receptor	Candidate gene, linkage studies[72,73]	Verbal memory skills,[68] inattention,[74] inattention and hyperactivity[70]
DRD5	Dopamine D5 receptor	Candidate gene, GWAS[75,76]	Inattention, response time variability[77,78]
SLC6A4 (SERT)	Serotonin reuptake, transporter	Candidate gene[79,80]	Delay aversion and motivational dysfunction[81]
HTR1B (5HT1B)	Serotonin receptor	Candidate gene[82]	Inattention,[83] response inhibition[84]
SNAP25	Neurotransmission	Candidate gene[85]	Impulsivity, inattention[86]
NOS1	Nitric oxide synthase, neurotransmission, neuroplasticity	Candidate gene, GWAS[87,88]	Impulsivity, aggressivity, hyperactivity[88]
SLC9A9	Ion transport	Linkage, GWAS[89,90]	Impulsivity[91]
LPHN3	GPCR, cell adhesion, signal transduction	Linkage[92]	Inattention[93]
GIT1	GPCR kinase, vesicle trafficking, cell adhesion, cell migration	Candidate gene[94]	Learning deficits[94]
CDH13	Cell-cell adhesion and neural cell growth	GWAS, candidate gene[87,95,96]	Working memory deficits,[95] hyperactivity and impulsivity[96]
GFOD1	Glucose-fructose oxidoreductase-domain containing 1, electron transport	GWAS[87]	Not described
CNR1	Cannabinoid receptor, neurotransmission	Linkage studies, candidate gene[97,98]	Impulsivity,[99] drug abuse[100]
CHRNA7	Nicotinic acetylcholine receptor 7	GWAS[101]	Inattention[114]

GPCR=G protein-coupled receptor. GWAS=genome-wide association studies

Table 2

Rodent models of attention-deficit hyperactivity disorder (ADHD) and selected behavioural and neurobiological abnormalities

	Manipulation	Behavioural phenotypes relevant to ADHD	Associated cellular abnormalities
Spontaneously hypertensive rat[136]	Selective breeding of a spontaneous trait	Hyperactivity in familiar environments, motor impulsivity,[137] sensitivity to delay in reinforcement[138]	Insertion in non-coding region of *DAT* gene, defective dopamine vesicular storage and metabolism[139]
High impulsive rat[140]	Selective breeding of a spontaneous trait	Impulsive behaviour, deficits in premature responding, but not response inhibition[141]	Reduced *Drd2* expression in ventral striatum[140]
DAT KO mouse[142]	Ablation of *DAT* gene	Hyperactivity,[142] which might be sensitive to AMPH, MPH, and serotonergic drugs;[143] impaired learning and memory; heightened sensitivity to pro-cognitive effects of nicotine[144]	Altered dopamine transmission[145]
Neonatal 6- hydroxydopamine (6-OHDA) lesion model in rodents[139,146]	Ablation of dopaminergic neurons in early postnatal life	Hyperactivity that is sensitive to MPH, AMPH and Drd4 antagonists;[147,148] working memory, social behaviour, and learning deficits[149]	Corticostriatal maturation and connectivity alterations,[149] decreased striatal dopamine[150]
Coloboma mutant mouse[151]	Deficient expression of *SNAP-25* gene resulting from chromosomal mutation	Hyperactivity[151] that is sensitive to AMPH; impulsivity; inattention[86]	Impaired glutamatergic and monoaminergic neurotransmission[152]
GIT1 KO mouse[94,153]	Ablation of *GIT1* gene	Hyperactivity, learning and memory impairments[94]	Increased cortical EEG theta range activity,[94] abnormal hippocampal spine formation[153]
NOS1 KO mouse[154]	Ablation of the gene coding for neuronal nitric oxide synthase	Aggression, hyperactivity, impulsivity[155,156]	Impaired glutamatergic signalling and neuroplasticity[157,158]

DAT=dopamine transporter. Drd2=dopamine D2 receptor. KO=knockout. AMPH=amphetamine. MPH=methylphenidate. Drd4=dopamine D4 receptor. GIT1=G protein-coupled receptor kinase-interacting protein-1. EEG=electroencephalogram.