REVIEW

Differentiating Frontostriatal and Fronto-Cerebellar Circuits in Attention-Deficit/Hyperactivity Disorder

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Attention-deficit/hyperactivity disorder (ADHD) has long been conceptualized as a neurobiological disorder of the prefrontal cortex and its connections. Circuits with the prefrontal cortex relevant to ADHD include dorsal frontostriatal, orbitofronto-striatal, and fronto-cerebellar circuits. Dorsal frontostriatal circuitry has been linked to cognitive control, whereas orbitofronto-striatal loops have been related to reward processing. Fronto-cerebellar circuits have been implicated in timing. Neurobiological dysfunction in any of these circuits could lead to symptoms of ADHD, as behavioral control could be disturbed by: 1) deficits in the prefrontal cortex itself; or 2) problems in the circuits relaying information to the prefrontal cortex, leading to reduced signaling for control. This article suggests a model for differentiating between interlinked reciprocal circuits with the prefrontal cortex in ADHD. If such a differentiation can be achieved, it might permit a neurobiological subtyping of ADHD, perhaps by defining "dorsal fronto-striatal," "orbitofronto-striatal," or "fronto-cerebellar" subtypes of ADHD. This could be useful as a template for investigating the neurobiology of ADHD and, ultimately, clinically.

Key Words: ADHD, cognition, neurobiology, neuroimaging, subtypes

Although attention-deficit/hyperactivity disorder (ADHD) has been conceptualized as a disorder of the prefrontal cortex for over 20 years, it is still diagnosed entirely on behavior. The DSM-IV recognizes a hyperactive-impulsive subtype of ADHD, an inattentive subtype, and a combined subtype, all of which are defined on the basis of the presence of a minimum number of symptoms.

One of the prime functions of the prefrontal cortex is to exert control over behavior (for review, see Badre) (1), and it was perhaps the observation that behavioral control is compromised in ADHD that first led to a model of ADHD as a disorder of the prefrontal cortex and its connections (2). Of the reciprocal circuits with the frontal cortex in the brain, it is the frontostriatal circuits that have been most convincingly implicated in ADHD. Functionally, dorsal frontostriatal connections have been linked to cognitive control, whereas loops between ventral striatum and orbitofrontal cortex have been linked to reward and motivation (3). The fronto-cerebellar circuit has also been implicated in ADHD, in particular in timing and building temporal expectations (e.g., Durston *et al.*) (4).

It has been suggested that neurobiological dysfunction in any of these circuits can lead to symptoms of ADHD: 1) deficits in the prefrontal cortex could affect control systems directly, or 2) problems in the circuits relaying information to the prefrontal cortex could lead to reduced signaling for control (5,6). In both scenarios, behavioral control would be compromised, leading to behavioral changes, such as impulsive and inattentive behavior. If it is indeed the case that symptoms of ADHD arise from discrete neurobiological deficits and these deficits can be reliably detected, this could lay the basis for a neurobiological subtyping of ADHD, where individuals could be diagnosed with, for example, "dorsal fronto-striatal" or "fronto-cerebellar" ADHD. Such a subtyping of ADHD would be a helpful template for investigating the neurobiology of ADHD and might ultimately be useful to clinicians. For example, such subtypes might differ in terms of their responsiveness to treatment, where individuals with a form of ADHD that involves striatal loops might be more responsive to stimulant medication (because this is the prime site of action of stimulants) than individuals with a form of ADHD that does not directly involve these circuits.

This review investigates three circuits of interlinking reciprocal connections with the prefrontal cortex. It investigates whether it might be possible to differentiate between these in ADHD to allow a neurobiological subtyping of affected individuals. To this end, we begin with a brief discussion of the neuroanatomical substrates for these three circuits implicated in ADHD. We then give a brief description of the neuropsychological functions supported by them. This is followed by a discussion of the evidence implicating each of these circuits in ADHD. Finally, we suggest a model for dissociating these circuits to define neurobiological subtypes of ADHD.

Neuroanatomical Substrate for Links Among Prefrontal Cortex, Striatum, and Cerebellum

In 1986, Alexander *et al.* (3) published a seminal article where they proposed that there were at least five parallel loops between the striatum and cortex. Each loop includes discrete areas in the striatum, globus pallidus, substantia nigra, thalamus, and cortex and is structured in a parallel manner: Cortical inputs to the striatum are passed through the basal ganglia to the thalamus and from there back to a single cortical area. Each circuit receives multiple inputs only from cortical areas that are functionally related and usually interconnected (3). The five circuits originally described were named the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate circuits after their cortical targets. The motor circuit involves the putamen and supplementary motor cortex; the oculomotor circuit involves the caudate nucleus and the frontal eye fields; the dorsolateral prefrontal circuit involves the dorsolateral caudate nucleus and the dorsolateral prefrontal cortex; the lateral orbitofrontal circuit involves the ventromedial caudate nucleus and the lateral orbitofrontal cortex; the anterior cingulate circuit involves the ventral striatum and the anterior cingulate cortex.

Since 1986, additional corticostriatal circuits have been described (e.g., Middleton and Strick) (7), as have connections between these loops: ventral corticostriatal loops influence more dorsal loops through spiraling striato-nigrostriatal projections, where projections from the ventral striatum to the substantia nigra are fed back into the striatum to the same but also adjacent more dorsal areas (8). There appear to be far fewer connections feeding infor-

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mation forward through these spiraling loops than there are projecting back within the same loop (8). Nonetheless, this ventral-to-dorsal organization provides a neuroanatomical basis for putative influences of motivation and reward on cognition.

The cerebellum was long-considered a center for motor control and coordination. However, recently it has become increasingly clear that this structure also has a role in many other domains, including cognitive functions and learning (9). Neuroanatomical evidence shows that it has projections via the thalamus to many areas of the cortex, including the prefrontal cortex, in closed loops (10). Furthermore, there is mounting evidence that the basal ganglia and the cerebellum might be more directly linked than via their connections to cortex: recent evidence shows that they also project directly to one another (11,12). Here again, the projections connecting these circuits appear to be far fewer in number than the connections within each circuit.

In addition to subcortical connections between these circuits, there are connections between them at the cortical level (13). Studies in primates have shown that each architectonically distinct area of the prefrontal cortex has a distinctive pattern of overall cortical connectivity, with a functional distinction between ventral and dorsal prefrontal areas. For example, Brodmann area (BA) 8 in the dorsolateral prefrontal cortex receives inputs from limbic, visuo- and audiospatial, and visual cortex. The BA 44 in the inferior frontal cortex receives input largely from somato-sensory and parietal association cortex, whereas the adjacent BA 45 receives inputs largely from auditory association cortex and limbic areas.

In sum, there are neuroanatomical connections to support relatively closed circuits between the prefrontal cortex and striatum and cerebellum respectively. There is a neurobiological substrate for crosstalk between these circuits. However, the number of connections supporting such crosstalk is fewer than the number of connections within each circuit, suggesting that their function might be relatively separable.

Linking Neuroanatomy to Brain Function

The prefrontal cortex is critical to cognitive control, the ability to flexibly adjust behavior to changing circumstances (5). Cognitive control has also been called "behavioral control" or simply "control." Functions typically covered by this umbrella term include response inhibition, motor inhibition, switching, and sometimes planning. Tasks used to assess cognitive control include the go/no-go task, stop task, Stroop task, Wisconsin Card Sorting Test, and many others. To give but one example, in the go/no-go task, subjects are asked to press a button as quickly as possible in response to a frequent and predictable stimulus. On the rare no-go trials (typically no more than 25% of trials), the subjects are instructed to withhold their response. The predictable and typically rapid presentation of go-trials makes it difficult to override the dominant pattern of button presses and to exert behavioral control by suppressing this response. Other tasks use variations of this type of behavior to look at similar (though not necessarily identical) processes. The common denominator among these tasks is that all involve suppressing behavior (ongoing, planned, or otherwise) and sometimes switching to another. Functional imaging studies have shown that cognitive control relies on activity in the prefrontal cortex, usually in regions of the dorsolateral, ventrolateral, or dorsal anterior cingulate cortex, depending on which task is used (14,15). Other brain systems can affect cognitive control, such as reward systems and timing systems in the brain.

Motivation is an important factor in being able to engage cognitive control. One mechanism by which to enhance motivation is through reward (either anticipated or actual). Reward processing is supported in part by the orbitofrontal circuit previously discussed. One task that is often used to assess reward processing is the monetary incentive delay task (16). Here, a cue indicates to subjects whether they will be rewarded on the upcoming trial or not. On rewarded trials, subjects earn a predetermined amount of money by pressing the button in time to a target stimulus. Reward anticipation can be separated from reward evaluation and reward error processing by manipulating the time between the cue and the target and the feedback as well as the error rate. Functional magnetic resonance imaging (fMRI) studies have shown that ventral striatum is sensitive to anticipating rewards, where medial prefrontal and orbitofrontal cortex are involved in assessing reward outcome (17). Spiraling loops through the striatum and substantia nigra provide a potential neurobiological pathway for reward to influence cognition and ultimately behavior (e.g., Haber) (8).

Cognitive control is engaged when other brain systems signal to the prefrontal cortex that control is needed (5). This relies on, among other factors, the ability to predict when events are going to occur in the environment, so that violations of these predictions can be detected. For the detection of temporal violations, this ability therefore depends critically on timing (6). As such, the ability to predict the occurrence of events depends on fronto-cerebellar circuits (18,19) in addition to frontostriatal circuitry (20–22). Indeed, activation in frontostriatal regions has been associated with violations of what to expect, whereas activation in fronto-cerebellar areas has been associated with violations in the timing of events (23).

Frontostriatal Circuits in ADHD

Cognitive Control and Dorsal Frontostriatal Connections

The frontostriatal circuit, which comprises reciprocal connections among the striatum, thalamus, and prefrontal areas, is critical to cognitive control. Deficits in this ability have even been suggested to be the core deficit in ADHD, underlying other cognitive differences (24). However, meta-analyses have shown that most children with ADHD do not have a measurable deficit in cognitive control, suggesting that it is not central to ADHD symptoms, at least not for all children (25).

According to the model of segregated corticostriatal loops described by Alexander *et al.*, deficits in cognitive control should correspond to dysfunction in the dorsolateral prefrontal circuit (see preceding text). Functional imaging studies have indeed shown differences in dorsal frontostriatal activity during cognitive control tasks (for review, Dickstein *et al.* [26] and Durston *et al.* [27]). Attenuated activity in prefrontal control regions in ADHD has been related to ADHD, even when poorer task performance is accounted for (28). Recent work has highlighted the importance of the long-range connections between the striatum and the prefrontal cortex in these differences: work on the typical development of frontostriatal white matter has already shown that greater microstructural organization of these tracts predicted developmental improvements in cognitive control (29). Recently, we used diffusion tensor imaging (DTI) and magnetization transfer imaging to investigate white matter tracts connecting the prefrontal cortex to the striatum in ADHD. In DTI, the directional diffusion of water in white matter is measured to give an index of its structural integrity. In magnetization transfer imaging, the magnetization transfer ratio is calculated. This is an index of the proportion of protons bound by macromolecules and in white matter gives an index of myelination. We found that children with ADHD showed less directional diffusion than control children but not less magnetization transfer in frontostriatal

tracts, suggesting that differences in connectivity of these areas in ADHD are related to microstructural organization rather than myelination per se (De Zeeuw P, Mandl RCW, van Engeland H, Durston S, Changes in frontostriatal connectivity in ADHD assessed using diffusion tensor and magnetization transfer imaging, unpublished data, 2010). Other studies of white matter structure in ADHD have not assessed the frontostriatal tract directly but have shown changes in DTI-derived measures of directional diffusion in areas proximal to our findings (30–33).

Reward Processing and Orbitofronto-Striatal Connections

Reward processing has been implicated in the pathophysiology of ADHD: it has been suggested that differences in sensitivity to reinforcement might lead to changes in motivation, in turn resulting in ADHD symptoms (34,35). Indeed, three fMRI studies have now reported decreased ventral striatal activation in both adolescents and adults with ADHD in anticipation of reward (36–38). Hypo-responsiveness of ventral striatum to anticipated reward might provoke increased impulsive reward-seeking behavior to compensate for lower basal levels of ventral striatal activation (39).

Furthermore, the existence of spiraling striato–nigro–striatal loops provides a neuroanatomical basis for activity in ventral frontostriatal circuits to influence activity in more dorsal circuits (see preceding text). As such, this suggests a biological mechanism for improving cognitive function in ADHD through reward systems. Here, reward might stimulate activity in ventral striatum, compensating for baseline hypo-activation in ADHD, and lead to improvements in cognitive performance.

Fronto-Cerebellar Circuits in ADHD

Traditionally, much attention has been paid to the role of the prefrontal cortex and its links with the striatum in ADHD research. However, the cerebellum is another prime candidate for involvement in this disorder. It has a protracted development, is sexually dimorphic, and is susceptible to environmental influences (40). This tentatively provides support for a possible role in ADHD, because this disorder is usually diagnosed in middle childhood, when the cerebellum is still developing; is more common in boys than girls; and has been shown to not be solely genetic but rather in part caused by environmental factors (41–43, but see also 44). The cerebellum has outputs to both the prefrontal cortex and the basal ganglia (see preceding text) (10) and, as such, is in a position to influence activity in circuits already implicated in ADHD.

Magnetic resonance imaging studies investigating the cerebellum in ADHD have reported reduced volumes (45–48), both of the vermis and its subdivisions (46,49–52) and the cerebellar lobules (49,52,53). In fact, in one of the largest studies to date, the cerebellum was the only region that was significantly reduced in ADHD after correction for total cerebral volume (47). Whole-brain voxel-based studies have also shown differences in the cerebellum (54,55). Functional MRI studies have reported attenuated cerebellar activation in ADHD with a host of cognitive tasks, including those tapping cognitive control (56,57), working memory (58), and timing (59–61) as well as in resting state fMRI (62,63). Furthermore, recent work has shown reduced connectivity between the cerebellum and the prefrontal cortex in adults with ADHD (64).

In addition to its role in the pathophysiology of ADHD, there is some evidence that the cerebellum might be involved in the outcome of this disorder. A cognitive training program for ADHD was shown to enhance activity in frontal areas for a cognitive control paradigm and in the cerebellum for an attention paradigm (65). Studies of the effects of stimulant treatment have shown that an acute dose of methylphenidate normalized activity in frontostriatal circuits and cerebellum in youths with ADHD (66) and that the area of the vermis was normal in chronically treated children with ADHD but smaller in those who were treatment-naive (67). Furthermore, children with ADHD and worse outcome have been shown to have smaller cerebellar hemispheres than children with ADHD and better outcome. (51). Not many studies have yet been conducted in this area, and as such these findings should be considered preliminary. However, these results do lend further credibility to a role for the cerebellum and its connections with the prefrontal cortex in ADHD.

Genetic Influences on Frontostriatal and Fronto-Cerebellar Circuits in ADHD

Attention-deficit/hyperactivity disorder is a disorder with a genetic component: 70%–80% of the phenotypic variance is estimated to be heritable (68). Differences in frontostriatal circuits in ADHD have indeed been shown to be under genetic influences: the unaffected siblings of boys with ADHD share reductions in prefrontal gray matter volume (48) and prefrontal activity during cognitive control (69). Furthermore, established risk genes for ADHD (DRD4 and DAT1) are related to both structure and function of these circuits (70–75). As such, some of the genetic effects in ADHD seem to be carried by frontostriatal pathways.

Are there also genetic influences on fronto-cerebellar circuits in ADHD? In 2004, we reported that there were familial influences on brain volume in ADHD. Regions that were smaller in boys with ADHD than in typically developing boys were also reduced in volume for the unaffected brothers of boys with ADHD. The one exception was the cerebellum, which was smaller for boys with ADHD but not for their unaffected brothers (48). At the time, we interpreted this as an indication that the cerebellum might be more susceptible to environmental influences, in line with evidence that it is the least heritable brain area (76,77).

However, genetic effects do also play a role in the cerebellum, even if their influence is not as great as elsewhere in the brain. We found that activity in the cerebellum was sensitive to familial influences. We used a go/no-go paradigm where we manipulated the timing of events in addition to the manipulation of stimulus identity (4,23). Activity in the cerebellum was attenuated on trials that were temporally unpredictable (78). As such, changes in cerebellar activity to manipulations of timing showed familial effects, similar to prefrontal activity. In addition, we recently found that functional connectivity between anterior cingulate gyrus and the cerebellum was sensitive to familial risk for ADHD: both subjects with ADHD and their unaffected siblings had lower functional connectivity than typical control subjects, whereas connectivity for unaffected siblings was intermediate between that of subjects with ADHD and control subjects (79). Of course, establishing that familial risk affects the cerebellum does not inform us whether the mechanism by which it does so is genetic (shared environment could also play a role) or which genes are involved.

Work on candidate genes for ADHD has often focused on dopamine systems (80). Interestingly, some of the genes to be implicated in the fronto-cerebellar pathway seem to be the same as those implicated in the frontostriatal circuit. The DRD4-genotype has been shown to be related to prefrontal volume, whereas the DAT1-genotype is related to volume and activity of the striatum (for review, see Durston[80]). However, both genes have been shown to also be related to the cerebellum: DAT1-genotype is related to cerebellar activity patterns during a cognitive control task (73), whereas DRD4-genotype is related to the volume of the cerebellar cortex in adult ADHD (74).

Other genetic systems are also likely to be involved. For example, studies of a taq1 polymorphism in the promoter region of the dopamine β hydroxylase gene potentially implicate noradrenergic genes in ADHD. Dopamine β hydroxylase is an enzyme that is involved in converting dopamine to norepinephrine, and the genetic mutation is associated with lower norepinephrine production (81). Noradrenaline function is highly relevant to both prefrontal and cerebellar function and has also been implicated in ADHD (81). Carriers of the genetic mutation have poor impulse control (82) and poor sustained attention (83). Furthermore, this mutation has been associated with impairments in neuropsychological function (84). No studies have yet investigated its impact on brain structure or function.

Dissociating Circuits with Prefrontal Cortex in ADHD

As discussed previously, dorsal frontostriatal, orbitofronto-striatal, and fronto-cerebellar circuits are involved in ADHD. These circuits interact through spiraling loops in the striatum and connections from the cerebellum to the prefrontal cortex and the striatum, although there are more connections within than between circuits. Dysfunction in any of these circuits might cause symptoms of ADHD: Dysfunction of the prefrontal cortex is likely to result in a reduced ability to exert control (5). Dysfunction in dorsal striatum might lead to differences in the ability to predict what events are going to occur, whereas dysfunction in ventral striatum is more likely to lead to deficits in motivation and reward processing. Dysfunction of the cerebellum is likely associated with problems in the ability to predict when events are going to occur and other problems with timing. The implication of this is that, although this wide range of neurobiological differences can lead to symptoms of ADHD, the cognitive effects of dysfunction at the various levels might be quite different (Figure 1). If this is indeed the case, we might be able to use this to define subtypes of ADHD on the basis of deficits in one of these circuits. This would be useful in terms of ADHD research and ultimately clinically. However, before this can be achieved, much more work is necessary to investigate whether these circuits are indeed dissociable at this level.

Preliminary evidence that such dissociation might be possible comes from Sonuga-Barke *et al.* (85). They recently used principal-component analysis to show that three separable components contributed to the variance in their neuropsychological task battery. These components corresponded to timing, cognitive control (termed inhibition in their report), and reward (termed delay aversion). Of the 77 children with ADHD included in this study, 55 could be identified as having a deficit on one of these components, and the overlap between components was no greater than would be expected by chance. This suggests that these components might indeed rely on neurobiologically separable systems. However, these data were based on computer testing only, so no direct measures of neurobiology were available. Nonetheless, the cognitive areas with which these components are related suggest they might map onto the three circuits described in this report: timing is associated with fronto-cerebellar loops, cognitive control with dorsal frontostriatal loops, and reward with orbitofronto-striatal loops.

Further support comes from our own recent findings. We have found components similar to those reported by Sonuga-Barke with principal-component analysis on data from a very different task battery in 200 children (De Zeeuw P, Weusten JMH, van Dijk S, van Belle J, Durston S, Dissociable Cognit subtypes in ADHD, unpublished data, 2010). Our battery includes far fewer tasks than the one used by Sonuga-Barke and takes $<$ 1 hour to administer. The components we found include those that correspond to cognitive control, reward processing, and timing, similar to Sonuga-Barke *et al*. In our data, 60% of subjects with ADHD had a detectable deficit on one of the three factors. Of these, 68% had a deficit in cognitive control, 21% had a deficit in timing, and 7% had a deficit on reward. Only 3% of subjects with ADHD had a deficit on more than one factor.

Many children with ADHD do not have a deficit on any of the components found by us (40%) or Sonuga-Barke (29%). As such, there might be other pathways to ADHD than the three circuits discussed here. Imaging studies have sometimes reported neural changes even in children with ADHD without a detectable deficit at the cognitive level (28,69). This might be related to the fact that in these studies children with ADHD have been traditionally grouped together by diagnosis, regardless of their cognitive performance. As such, these studies might have inadvertently grouped together children with and without a deficit in the systems under investigation. fMRI likely has more power than neuropsychological testing to pick up small differences at the group level.

A related issue is that unaffected brothers and sisters of children with ADHD have been shown to share some of the cognitive deficits of their affected siblings, even in the absence of ADHD symptoms (e.g., Slaats-Willemse *et al.* [86]). As such, these subtypes might show clearer patterns of familiarity than the diagnosis. This fits with the idea that these subtypes might be closer to the neurobiology of ADHD and, as such, might follow clearer patterns of inheritance. The relation between cognitive deficits and ADHD symptoms is entirely unclear and will require careful investigation if the existence of neurobiological subtypes can be established in larger studies. Another point that will be highly relevant to differentiating between neurobiological subtypes is their developmental trajectories. For example, if certain subtypes are related to delayed cortical maturation in ADHD, they might improve over development.

Although the aforementioned is—of necessity—speculative and the presence of separable neurobiological subtypes in ADHD remains to be established, that such similar components were found by Sonuga-Barke and by us with very different neuropsychological tests suggests that these might indeed represent something central to ADHD. A particular advantage of our task battery is that the tasks are fMRI-compatible. As such, we can use the same tasks in the imaging environment to link the components we found to a neurobiological substrate.

One example is that we have used one of our tasks to show that deficits in timing and cognitive control associated with ADHD were separable in the brain. In this study, the predictability of stimulus type and stimulus timing were manipulated in a go/no-go paradigm. There were both expected and unexpected events in terms of stimulus identity to engage cognitive control (go and no-go trials). Furthermore, stimuli were presented at expected or unexpected times to engage timing systems in the brain (4,23). In two independent samples, we showed differences in the performance of subjects with ADHD, both in terms of cognitive control and in benefitting from events being predictable (i.e., occurring at the expected time). Violations of stimulus timing were related to diminished activation in the cerebellum, whereas violations of stimulus identity were related to diminished prefrontal activity (4). Although these data should be considered preliminary and we need more studies to address the separability of these systems directly, they do provide some support that these systems might indeed be separable.

The neuropsychological work described in the preceding text suggests that there might be at least three neurobiological pathways to ADHD, involving disruption of dorsal frontostriatal, orbitofronto-striatal, or fronto-cerebellar circuits. However, there might be other circuits involved. For example, amygdala has reciprocal

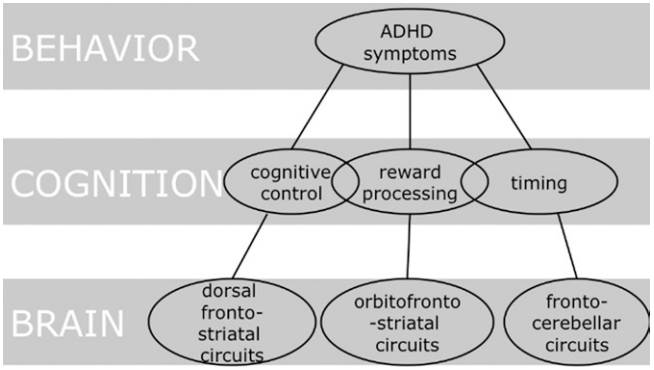

Figure 1. Model showing how distinct neurobiological pathways might lead to overlapping but separable cognitive profiles and similar behavioral patterns. ADHD, attention-deficit/hyperactivity disorder.

connections with the prefrontal cortex and has been suggested to play a role in ADHD (6). Fronto-amygdalar circuits could be involved in attributing emotional value to events, and inputs from amygdala could affect the recruitment of prefrontal control. Only indirect evidence of the involvement of this circuitry in ADHD comes from the observation of differences in medial temporal lobe structures in ADHD (45,54,87,88) and the rate of anxiety disorders in children with this disorder (89).

Where Next in ADHD Research?

The work described in the preceding text shows that we, as a field, are preparing to take the next step in ADHD research. To date, studies in ADHD have typically grouped children on the basis of symptoms and behavioral assessments. For example, in imaging genetics studies, the effect of candidate genes on the brain has been investigated in large samples of individuals with ADHD, categorized by their clinical diagnosis. As such, we have effectively ignored the fact that there might be multiple biological pathways that lead to ADHD. By grouping subjects together at the symptom level, we might not be able to detect subtle neurobiological differences that occur in only one pathway. We are now ready to do the reverse: cognitive batteries such as those developed by us and Sonuga-Barke *et al.* might be useful to subtype individuals with ADHD on the basis of their cognitive profiles. Neuroimaging can then be used to investigate the neurobiological substrate of cognitive deficits, allowing us to map different biological pathways to ADHD. This opens up possibilities for linking neurobiological subtypes to risk genotypes, behavioral profiles, risk for comorbidities, and so forth. In short, by beginning to tease apart neurobiological pathways to ADHD, we can move closer to understanding how the ADHD phenotype comes about in an individual case.

Conclusions

In conclusion, there are multiple circuits with the prefrontal cortex that play a role in the pathophysiology of ADHD. Dorsal frontostriatal pathways are implicated in deficits in cognitive control, orbitofronto-striatal circuits relate to differences in reward processing, and fronto-cerebellar pathways are linked to problems with timing and building temporal predictions. Recent work suggests that it might be possible to dissociate these circuits at the cognitive level and use them for neurobiological subtyping of ADHD. Neuroimaging and genetic techniques can then be employed to investigate the neurobiology of such subtypes.

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