“Cool” Inferior Frontostriatal Dysfunction in Attention-Deficit/Hyperactivity Disorder Versus “Hot” Ventromedial Orbitofrontal-Limbic Dysfunction in Conduct Disorder: A Review

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Attention-deficit/hyperactivity disorder (ADHD) and conduct disorder overlap behaviorally, clinically, and cognitively. An important question of potential future clinical relevance is whether these two overlapping disorders are mediated by similar or distinct underlying brain substrates. This article reviews the modern neuroimaging literature on brain structure, function, and connectivity in both disorders, shaping out commonalities and differences. Findings show that ADHD is characterized predominantly by abnormalities in inferior frontal, striatal, parietotemporal, and cerebellar regions and networks that mediate “cool”-cognitive, i.e., inhibitory, attention and timing functions associated with the disorder. Conduct disorder, by contrast, has consistently been associated with abnormalities of the “hot” paralimbic system that regulates motivation and affect, comprising lateral orbital and ventromedial prefrontal cortices, superior temporal lobes, and underlying limbic structures, most prominently the amygdala. Direct comparisons in functional imaging show that these associations of cool inferior fronto-striato-cerebellar dysfunction in ADHD and of hot orbitofrontal-paralimbic dysfunction in conduct disorder are disorder-specific. There is, hence, evidence for dissociated underlying pathophysiologies for these two disorders that may have implications for future anatomy-based differential diagnosis and prevention and intervention.

Key Words: ADHD, attention-deficit/hyperactive disorder, CD, conduct disorder, executive functions, fMRI, frontal lobe, functional magnetic resonance imaging, motivation

Attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms of age-inappropriate inattentiveness, impulsiveness, and hyperactivity (DSM-IV) (1). It disrupts academic and social development and is associated with significant psychiatric comorbidities (2) and mental health problems in adult life (3,4).

Conduct disorder (CD) is defined by the violation of the rights of others and societal rules and the persistent display of antisocial behaviors such as deception, theft, vandalism, and violence within a 6- to 12-month period before age 18 (DSM-IV) (1). Conduct disorder is considered a risk factor for various psychiatric conditions beginning in adolescence or adulthood, including antisocial personality disorder and mood disorders (5–13). Oppositional defiant disorder (ODD) is characterized by recurrent patterns of negativistic, defiant, disobedient, and hostile behavior toward authority figures. Oppositional defiant disorder is often comorbid with CD and has been considered a less severe subtype, although there is empirical evidence to distinguish the two disorders. In the DSM-IV, a diagnosis of CD is given if an individual meets criteria for both CD and ODD. The lower age of onset of CD before age 10 has been associated with a worse outcome, such as a greater risk for adult antisocial behavior and for emotional and behavioral dysregulation (14). A more pervasive subtype of CD is seen in those with callous-unemotional (CU) traits, defined as low fearfulness and a lack of empathy, guilt, and emotion (15), present in approximately 25% of cases of child-onset conduct disorder (16,17). This subtype is associated with poorer outcomes compared with non-CU CD groups, including substance use disorders, criminality, violent offending, and increased risk of psychopathy, as well as higher genetic risk factors (15,16,18–20).

Neuropsychological Findings

Attention-deficit/hyperactivity disorder is associated most consistently with neuropsychological deficits in tasks of motor response and cognitive inhibition (such as tasks of interference inhibition or cognitive switching), sustained attention, and timing functions (21–23). Children with CD have also shown deficits in tasks of motor and cognitive inhibition (24–27). Furthermore, like ADHD patients, they are also impaired in tasks of cognitive switching and reversal (28–31), as well as of sustained attention (32–37). However, studies have included comorbidity with ADHD, and the evidence for impairment in CD without comorbid ADHD compared with control subjects is less consistent; in fact, several studies found no independent deficits from ADHD for these tasks (37–43).

An exception, however, is in functions of motivation control, where children with CD seem as impaired or more impaired than children with ADHD. Thus, children with CD or psychopathy are consistently impaired in reversal tasks, where previously valid and learned rewarded stimulus-response contingencies change and are no longer rewarded or even punished (28,44). This seems to be due to a reduced sensitivity to punishment in children with CD compared with control subjects or children with ADHD. In fact, response perseveration (i.e., hyposensitivity to increasing punishment) using the Newman Card Playing Task paradigm (45) or other task variants has been found to be independently related to CD but not “noncomorbid” ADHD (39,46,47). In gambling tasks that measure reward-related long-term advantageous decision making versus impulsive short-term decisions, both pathologies have been shown to be impaired, although none of these studies excluded comorbidity with the other disorder (48–50). Regression analyses, however, showed that the antisocial behavior traits were responsible for the impulsive reward-related choice pattern in this task, whereas ADHD traits accounted for the “cool” executive function deficits in tasks of motor inhibition and attention (50).
Cool and Hot Executive Functions and Their Underlying Neurobiology

Recent developmental theorists have proposed the distinction between cool cognitive executive functions such as attention, working memory, planning, and inhibition that are known to be mediated by lateral inferior and dorsolateral frontostriatal and frontoparietal networks (51–54) and “hot” executive functions that involve incentives and motivation (55) and are mediated by the paralimbic orbitomedial and ventromedial frontolimbic structures (51,56–60).

Emotion regulation and motivation are mediated by lateral orbitofrontal and ventromedial frontal regions, including the anterior cingulate, amygdala, insula, hippocampus and hypothalamus, the ventral striatum, and other connected areas (61,62). The amygdala is important for the processing of negative affect and threat and together with ventral striatum mediates stimulus-reward associations and motivation functions (63–66). Orbitofrontal and temporal lobes have been associated with impulsivity and aggression in lesion, animal, and imaging studies (67–69). Together with ventromedial frontal cortex, including anterior cingulate, they mediate top-down affect regulation in their interconnection to underlying limbic areas (61,62,65,66). These networks of affect regulation and motivation have been shown to be implicated in hot executive functions (70).

Cool higher level cognitive processes are mediated by frontostriato-temporo-parietal and frontocerebellar circuitries in children and adults (51–54). Higher order temporal and parietal sensory cortices mediate bottom-up attention based on stimulus salience, with the temporoparietal junction being crucial for visual-spatial and executive attention functions (71–73). The prefrontal cortex (PFC) provides goal-directed top-down attention and cognitive control through several functions: inhibitory control of irrelevant acts and attention to irrelevant stimuli; sustaining, dividing, and selecting attention; working memory; and cognitive flexibility, as well as timing functions such as temporal foresight (74–76). Frontal, temporal, and parietal cortical areas are reciprocally interconnected with each other and project to basal ganglia and thalamus, as well as cerebellum in fronto-parieto-striatal and corticocerebellar circuitries that, in concert, mediate these attention and cognitive control functions (65,66,72,73).

It thus seems that the neuropsychological evidence shows deficits in children with ADHD in cool executive function tasks mediated by fronto-striato-cerebellar and frontoparietal neural networks, while children with CD appear to be more prominently impaired in tasks of affect and motivation control, such as gambling, or stimulus-response contingency reversal tasks that are mediated by ventromedial and orbitofrontal limbic neural networks. The association between motivation control deficits and antisocial behaviors is in line with behavioral studies showing that contingency association learning involving reward and punishment is strongly implicated in the development and maintenance of antisocial behaviors (77).

Comorbidity Between ADHD and CD

Conduct disorder and ODD overlap clinically, behaviorally, and cognitively with ADHD. The odds ratio for comorbidity with ADHD in children with CD is over 40, while this increases to 79 in children with ODD (78,79). Comorbid patients are often considered severe cases of ADHD (28) and the notion of a separate neurobiological basis for CD has been debated (80). Comorbid cases have a more severe clinical outcome than the individual diagnoses (81,82).

An important question yet to be addressed is whether these two similar and often clinically and neuropsychologically overlapping disorders differ in their underlying etiopathophysiology. The separation of associated neural networks for each disorder would potentially be very helpful for the development of a more objective differential diagnosis and of disorder-specific prevention and interventions.

Structural and Functional Neuroimaging of ADHD

Structural Studies

Neuroimaging studies in children with ADHD have shown consistent abnormalities relative to control subjects in late-developing inferior frontostriatal and frontocerebellar circuitries that mediate these cognitive control functions that are impaired in the disorder. Thus, structural magnetic resonance imaging (MRI) studies found reduced volume and cortical thickness in inferior prefrontal cortex (IFC) but also other frontal brain regions, as well as parietotemporal regions, the basal ganglia, the splenium of the corpus callosum, and the cerebellum (83–86). Two recent meta-analyses of structural data in childhood ADHD have been published. The first meta-analysis was conducted on region of interest studies showing the greatest significant reductions relative to control subjects in posterior inferior vermis of the cerebellum, the splenium of the corpus callosum, total and right cerebral volumes, right caudate, and various frontal regions (87). The other meta-analysis was of whole-brain voxel-based morphometry imaging studies, avoiding the a priori bias of region selection, and identified a significant regional gray matter reduction in ADHD children compared with control subjects in right putamen and globus pallidus (88). Diffusion tensor imaging studies have furthermore provided evidence for abnormalities at the neural network level, showing abnormalities in multiple white matter tracts in cingulate and frontostriatal, as well as frontoparietal, frontocerebellar, and parieto-occipital white matter tracts, in children, as well as adults, with ADHD compared with control subjects (89–92). Longitudinal imaging studies have provided evidence that the structural abnormalities in these late-developing fronto-striato-cerebellar and frontoparietal systems are due to a late structural maturation of these regions (86,93). Thus, the peak of cortical thickness maturation has been shown to be delayed in children with ADHD compared with healthy peers by an average of 3 years, with some regions, including frontal and temporal areas, being delayed in their cortical maturation by up to 4 to 5 years (93).

Functional Imaging Studies

In line with the frontostriatal hypothesis of ADHD, functional imaging studies have shown reduced activation compared with control subjects, in particular in the IFC, anterior cingulate, and caudate, but also in temporoparietal regions, during tasks of motor response inhibition (69,94–100), interference inhibition (101–103), and of sustained, selective, and flexible attention (100,102,104–111) (for meta-analysis, see [112]). Furthermore, ADHD children have also shown reduced activation in dorsal and ventrolateral prefrontal, cingulate, and cerebellar brain regions during temporal processes, including tasks of motor timing, time discrimination, and temporal foresight (94,113–115), as well as temporal unpredictability (116). The cerebellum has furthermore been shown to be dysfunctional in children with ADHD relative to healthy control subjects during tasks of attention and timing functions (108,109,114,116). A few recent studies have also tested for neurofunctional deficits in children with ADHD relative to healthy control subjects during tasks of motivation, finding abnormalities in ventral striatum, orbitofrontal, and cingulate cortices during reward-related processes (108,109,114,117).

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More recent functional imaging studies have tested for deficits in interregional functional connectivity. During the resting state, children with ADHD have been shown to have reduced functional connectivity relative to healthy control subjects in frontostriatal, frontoparietal, temporoparietal, and frontocerebellar networks \((118 - 120)\), although increased interregional connectivity between anterior cingulate, striatum, and temporocerebellar regions has also been reported \((118,121 - 123)\). In the context of cognitive tasks, I am only aware of two published papers in childhood ADHD. One found a reduced degree of functional connectivity relative to healthy control subjects between IFC and the basal ganglia, parietal lobes, and cerebellum, as well as between cerebellum and parietal and striatal brain regions during sustained attention \((108)\); the other study found reduced connectivity between frontoparietal and frontocerebellar regions during interference inhibition and time estimation, respectively \((124)\). These findings suggest that the dysfunctions observed in ADHD patients not only affect isolated brain regions but also the functional interregional interconnectivity between affected regions, thus demonstrating deficits in frontostriato-cerebellar and frontoparietal neural networks.

Relatively fewer studies have been conducted in adult ADHD and findings have been more inconsistent. This is likely due to the fact that confounding factors are more pronounced in adults compared with childhood ADHD imaging studies, such as the inclusion of small sample sizes, the elevated rate of comorbid conditions in adult ADHD, long-term medication history, and the need for retrospective diagnosis \((125)\). Structural imaging studies in adult ADHD observed abnormalities in the volumes of left orbitofrontal cortex \((126)\); in overall cortical gray matter, right anterior cingulate, and left superior/dorsolateral prefrontal cortex \((127)\); and cortical thickness in bilateral dorsolateral and orbitofrontal cortices, anterior and posterior cingulate, and in the temporoparietal junction \((128)\), as well as reduced structural connectivity between these regions \((91)\). Functional underactivation has been observed in adult ADHD relative to healthy control subjects in orbital and dorsolateral prefrontal cortices and striatal, anterior cingulate, cerebellar, and parietotemporal brain regions, with, however, also some evidence for compensatory increased activation in some of these regions in some studies (for review, see \(125)\). Functional task-related connectivity studies show deficits in interregional connectivity relative to healthy control subjects during motor response inhibition between right and left IFC cortices and between the right inferior frontal lobe and other areas, including basal ganglia, anterior and posterior cingulate, and parietotemporal and cerebellar areas \((129)\), which was also observed by another study in adult ADHD patients during working memory \((130)\). However, in the study of Wolf et al. \((130)\), compensatory-increased connectivity was also observed between left dorsal anterior cingulate, superior frontal lobe, and cerebellum. Rest-associated functional connectivity studies have found abnormal functional connectivity between anterior and posterior cingulate \((91,131,132)\).

Conclusions

In summary, childhood ADHD is characterized by structural and functional deficits compared with healthy children in predominantly inferior but also medial and dorsolateral prefrontal cortices, anterior cingulate, the basal ganglia, cerebellum, and temporoparietal brain regions and their functional and structural interconnectivity, causing poor top-down control over inhibitory, attention, and timing functions. An important caveat, however, is that the majority of imaging studies in children with ADHD have not excluded comorbidity with ODD or CD. The extent to which antisocial problems may have confounded the neuroimaging literature of ADHD can therefore not be assessed.

Structural and Functional Neuroimaging of CD

Structural Imaging Studies

Unfortunately, the imaging literature in CD is very confounded by ADHD comorbidity. Very few imaging studies have tested children with CD independently of ADHD. A small, underpowered structural study compared 7 comorbid children with ADHD + CD, 5 children with noncomorbid ADHD, and 19 healthy control subjects \((133)\). While the children with noncomorbid ADHD did not differ from those with comorbid ADHD and CD, both groups differed from control subjects in the volume of the left and total posterior superior and inferior lobes of the cerebellar vermis \((133)\) (Table 1). More recent structural studies found reduced volume and gray matter concentration/thickness of temporal lobes and other limbic and paralimbic regions in childhood-onset CD relative to healthy control subjects \((134,135)\). In the study of Krueger et al. \((134)\), all children had lower IQ and a history of ADHD, with 6 out of 10 children having current ADHD and 4 having substance abuse. Patients relative to control subjects showed reduced total temporal lobe and reduced right temporal gray matter volumes, and findings remained after controlling for IQ and substance abuse. Attention-deficit/hyperactivity disorder, however, was not controlled for in the study. In the study of Huebner et al. \((135)\), most CD patients were comorbid with ADHD (17 of 23 patients) but had no affective disorder. They showed reduced total gray matter volumes relative to control subjects, in particular in bilateral temporal lobes, left amygdala and hippocampus, and orbitofrontal and ventromedial frontal regions, but increased gray matter in bilateral cerebellum. Although the majority of CD children also had ADHD, regression analyses within patients revealed significant associations between CD symptoms and gray matter reductions in temporal, limbic (amygdala, hippocampus), cerebellar, medial, and mesial frontal gray matter, while hyperactivity/impulsiveness symptoms correlated inversely with gray matter reductions in left inferior frontal and parietal cortices and bilateral temporo-occipital regions \((135)\). A study by Sterzer et al. \((136)\) scanned 10 patients with CD; 7 of the patients also met criteria for ADHD and scored high for anxiety and depression. Reduced gray matter volumes were observed relative to healthy control subjects in bilateral insula and left amygdala, both of which correlated with aggressive and inattentive but not anxiety/depression symptoms. A study by DeRito et al. \((137)\) compared 23 community adolescent boys with no psychiatric abnormalities or mood or anxiety problems but high levels of callous-unemotional (CD-CU), as well as CD and ADHD problems, with their healthy twins. Covarying for both inattentive-hyperactivity symptoms and IQ, they found that gray matter concentration was increased compared with control boys in posterior medial orbitofrontal cortex, dorsal and rostral anterior cingulate, as well as in gray matter concentration and volumes in superior parietotemporal and superior frontal regions, cerebellum, insula, posterior cingulate, and hippocampus. The most interesting finding of their study was a significant deviation in CD-CU children from the norm-typical negative correlation between age and cortical thickness in orbitofrontal and left dorsal anterior cingulate. The fact that patients, unlike control subjects, showed no negative age correlation in this measure could potentially indicate a delay of normal brain maturation \((137)\), similar to that observed in ADHD \((93)\). Longitudinal studies will be needed, however, to corroborate this observation based on cross-sectional data.

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<thead>
<tr>
<th>Study</th>
<th>Imaging Method</th>
<th>Task</th>
<th>WB/ROI</th>
<th>Subjects</th>
<th>F/M</th>
<th>Age Range</th>
<th>Med/Med History</th>
<th>Results</th>
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<td>Bussing et al.</td>
<td>sMRI</td>
<td>—</td>
<td>WB</td>
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<td>CD/ADHD and ADHD alone versus control subjects: reduced mean volumes in total and L posterior superior and inferior cerebellar vermis. No differences between the pure and the comorbid groups. No group differences in cerebral hemispheres or caudate.</td>
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| Rubia et al.     | fMRI           | Stop task              | WB     | 20 ADHD                           | M   | 9 – 17     | No              | 3-group interaction effects:  
  a) Successful stop: ADHD versus CD and versus control subjects: reduced activation in L DLPFC/IFC  
  b) Failed stop: CD versus ADHD and versus control subjects: reduced activation in L and R IPL and R STL  
  Both patient groups versus control subjects: reduced activation in L and R PCC/precuneus. |
| Rubia et al.     | fMRI           | Rewarded CPT            | WB     | 18 ADHD                           | M   | 9 – 17     | No              | 3-group interaction effects:  
  CPT: ADHD versus CD and control subjects: reduced L and R IFC and enhanced L and R Cb/hippocampus/PCC activation.  
  L and R IFC activation was correlated with omission errors that were enhanced at trend level in ADHD.  
  CD versus ADHD and control subjects: reduced activation in R insula, hippocampus, PMC, ACC.  
  Reward effect: CD versus ADHD and control subjects: reduced activation in R ventromedial OFC.  
  ADHD versus CD and control subjects: reduced activation in precuneus and PCC. |
| Rubia et al.     | fMRI           | Simon and oddball tasks | ROI    | 8 ADHD                            | M   | 10 – 17    | No              | 3-group interaction effects:  
  Oddball: ADHD versus CD and control subjects: reduced activation in L DLPFC/IFC.  
  ADHD and CD versus control subjects: reduced activation in R DLPFC but no differences between patient groups.  
  Simon: ADHD and CD versus control subjects: reduced activation in R STL and MTL and R precuneus but no differences between patient groups. |
| Rubia et al.     | fMRI           | Switch task            | WB     | 14 ADHD                           | M   | 9 – 17     | No              | 3-group interaction effects:  
  ADHD versus CD and control subjects: reduced activation in L and R IFC/ DLPFC.  
  2-group comparisons:  
  CD versus control subjects: reduced activation in L and R IPL and R STL/precuneus but no differences between patient groups. |
| Marsh et al.     | fMRI           | Neutral, fearful, and angry faces | ROI    | 12 ADHD/CD/ODD + CU             | M   | 10 – 17    | Yes             | Group by expression effect:  
  ADHD/CD/ODD + CU versus ADHD pure and control subjects: reduced R amygdala activation for fearful faces (trend). Also reduced functional connectivity between R amygdala and R OFC.  
  Connectivity abnormalities correlated with CU severity. No group differences for angry or neutral faces. |
In conclusion, the structural evidence, therefore, points toward abnormalities in CD of the paralimbic system, comprising the orbitofrontal cortex (OFC), anterior cingulate, superior temporal lobes, and underlying limbic structures that are known to mediate motivation and affect (29,138). So far, however, there are no studies of structural connectivity in CD that have tested for potential disturbance of white matter tracts belonging to the paralimbic system to confirm a neural network disturbance.

Functional Imaging Studies

Functional imaging studies in children with CD have been consistent with the structural evidence, finding abnormalities in the ventromedial orbitofrontal temporolimbic system in CD. The majority of functional magnetic resonance imaging (fMRI) studies in CD have used emotion processing tasks. A study by Sterzer et al. (139) found more pronounced deactivation in right anterior cingulate gyrus in children with CD relative to healthy control subjects during the viewing of pictures with negative valence, which was interpreted by the authors as reduced inhibition of emotional behavior. Although 62% of patients also met criteria for ADHD and the group scored high on depression-anxiety, the anterior cingulate deactivation correlated negatively with the aggressive behavior scores and remained when controlling for attention, depression/anxiety scores, and IQ (139). This is in line with the notion of reduced emotion processing as the basis of aggression, given that the amygdala is a key region for the processing of negative affect (140). A subsequent correlation analysis on the same dataset found a correlation between abnormal functioning of anterior cingulate and sensation seeking (141). A later study on a group of 22 children with CD with no affective disorder, 16 of which had ADHD, found enhanced left amygdala activation compared with healthy control subjects to the same negative affect stimulation, suggesting emotional hyperresponsivity. The effect remained when controlling for affective/depressive symptoms and was not observed in a patient control group with ADHD only (142). Although the findings remained when covaried for affective symptoms, the group was characterized by high symptoms of emotion and anxiety, which could, at least partly, explain the enhanced amygdala activation that is typically enhanced in anxiety in relation to negative emotions such as fear (143).

A recent fMRI study in children with early-onset childhood CD, 88% of which also met criteria for ADHD, found abnormal activation compared with control subjects in relation to empathy and sympathy. Children with CD had reduced activation in the somatosensory pain matrix, typically activated in healthy children in response to the observation of pictures showing humans undergoing accidental body harm, but enhanced activation in anterior midcingulate, left amygdala, right caudate, and bilateral temporal pole (144). Furthermore, the extent of prefrontal and amygdala activation to viewing pain in others was significantly positively correlated to their number of aggressive acts and their ratings of daring and sadism score on behavioral questionnaires.

The comparison of pictures showing intentional versus accidental body harm also showed enhanced activation in the antisocial patients compared with healthy control subjects in somatosensory pain regions of left anterior insula, supplementary motor area, and precentral gyrus but decreased activation in lateral IFC, posterior cingulate, and the temporoparietal junction. Furthermore, the activation in the temporoparietal junction and insula correlated with the subjective ratings of the pain experienced by the individuals in the pictures (144). Connectivity analyses showed that pain inflicted by others versus accidental pain led to enhanced connectivity between ventromedial prefrontal cortex and amygdala in control sub-

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projects but not in CD patients (144). The findings suggest that highly aggressive antisocial youth are hypersensitive in their brain response to seeing victims in pain and show diminished regulation of emotion-processing networks, as shown by reduced PFC/amygdala connectivity relative to control subjects. The fact that these activation and connectivity patterns correlated with sadism and antisocial behavioral ratings suggests either that the hypersensitivity reflects greater enjoyment of the other’s pain or enhanced reactivity and reduced control over networks that process negative emotions (144). The correlation findings also suggest that the brain abnormalities are associated with the antisocial core ratings, which is important, given the high comorbidity. Aggression may thus be related to poor regulation over hypersensitive negative affect processing brain regions, resulting in harmful patterns of interpersonal behavior (144–146).

Another more recent fMRI study found reduced activation compared with healthy control subjects in the amygdala in patients with CD and callous-unemotional traits who had elevated ADHD scores but no elevated affective symptoms (147). The findings remained after covarying for ADHD symptoms.

In conclusion, parallel to structural studies, functional imaging studies show evidence that children with CD and CD-CU suffer from a dysregulation of ventromedial prefrontal amygdala regions and networks that mediate affect regulation (29,138).

Overall Conclusion

In conclusion, imaging studies of children with CD show structural and functional abnormalities compared with healthy control subjects in ventromedial and orbital prefrontal, superior temporal, and limbic brain regions that are known to regulate motivation and affect and abnormal functional connectivity within these frontolimbic networks. A caveat is that all studies have included a large proportion of patients that were comorbid with ADHD, with the majority of studies including over 50% comorbidity. The observed abnormalities in brain abnormalities, however, were shown to correlate with antisocial symptoms or to survive covariation for ADHD in several structural (135–137) and functional imaging studies (139,144,148). Some studies, however, did not control for ADHD (136) or found that the main findings correlated with both CD and ADHD symptoms (136) or only presented the correlation with CD, but not ADHD, symptoms (144). Anxiety and depression are other common comorbidities with CD. The majority of studies, however, have either excluded comorbidity with affective disorders and/or covaried for anxiety and depression (139,142,147,148). However, while this suggests that anxiety and depression cannot alone account for the deficits, this does not exclude the possibility that they may have contributed to some extent. Last, all imaging studies focused on children with CD, and ODD was not assessed separately in any study. Future studies will need to investigate the neuroimaging correlates of ODD and whether they differ from those associated with CD.

Structural and Functional Neuroimaging Comparisons Between ADHD and CD

Given the substantial clinical overlap between ADHD and CD symptoms, with between 50% and 90% comorbidity (19,149), the possibility of an objective differentiation through imaging technology is attractive. Modern functional neuroimaging could be an important aid in the differentiation of clinically and behaviorally similar disorders, if it can identify differences in the objectively measurable underlying pathophysiological mechanisms, the biomarkers that underlie overlapping behavior features of these two disorders. Disentangling the disorder-specific underlying pathophysiology of behaviorally and cognitively overlapping disorders will be crucial to develop more objective differential diagnostics and more informed and disorder-specific targeted methods on prevention and early intervention.

Very few studies, however, have directly compared these two disorders in neuroimaging. As mentioned, only one structural imaging study compared whole brain volume abnormalities in small groups of comorbid children with CD and ADHD and noncomorbid ADHD, finding no significant differences between the disorders, whereas both groups showed reduced volumes in the posterior and inferior cerebellar vermis (133) (Table 1).

Few fMRI studies have compared the neurofunctional substrates between the two disorders. Furthermore, few of them have controlled for differences in IQ or tested medication-naive patients with ADHD or CD that were clinically not comorbid. Long-term medication with stimulants appears to have effects on both brain structure (150,151) and brain function development (152), and medication naïvety is, hence, crucial when comparing between child psychiatric disorders.

Comparison Between Noncomorbid Groups of ADHD and CD on Tasks of Executive Functions and Reward

A series of fMRI studies from our group compared well-differentiated, medication-naive IQ-matched groups of children with CD, who had no clinical diagnosis of ADHD and scored significantly lower on ADHD symptoms on a questionnaire of symptom severity (the Strength and Difficulties Questionnaire [153]), with children with ADHD, who had no clinical diagnosis of CD and scored significantly lower on the questionnaire for CD symptoms. Affective disorders and anxiety were excluded and both patient groups did not differ from control subjects in their affective symptom scores. The disorders were compared in their neurofunctional activation during five disorder-relevant executive function tasks, shown to be impaired in both disorders: motor response inhibition, sustained attention, cognitive switching, interference inhibition, and attentional oddball. One of the tasks, the sustained attention task, included an additional motivational aspect, where sustained attention was compared in both rewarded and nonrewarded conditions to assess the effects of motivation on attention networks. Despite the fact that performance measures did not differ between patient groups, in four of the five tasks we observed disorder-specific reduced activation in patients with ADHD compared with both healthy control subjects and CD patients in the IFC (96,102,107,109) (Table 1). The location of disorder-specific abnormality was more dorsolateral for the stop and oddball tasks and more ventrolateral for the sustained attention and switching tasks. Furthermore, the dysfunction was bilateral for the sustained attention and switching tasks (107,109) but left hemispheric for the stop and oddball tasks (96,102) (Figure 1A, Table 1). During the sustained attention condition, we also observed a disorder-dissociated effect in a large posterior activation cluster comprising the cerebellum, hippocampus, and inferior temporal lobe, which was enhanced in activation in children with ADHD but reduced in children with CD compared with each other and healthy control subjects (109) (Figure 1A, Table 1). The cerebellum is an essential part of frontocerebellar networks (72), and in particular, the later-developing anterior cerebellum has been shown to be crucially implicated in attention functions (154,155). We hypothesized that the disorder-specific enhanced cerebellar/temporal activation in children with ADHD was compensatory for the reduced IFC activation during the task, corroborated by the finding of a negative correlation between these two brain regions in ADHD children but not the other two groups.
The disorder-specific reduced IFC activation in ADHD patients across four different tasks is a consistent finding that may suggest that IFC dysfunction is a disorder-specific neurofunctional biomarker for ADHD, at least when compared with CD. This is in line with the fact that we also found disorder-specific reduction in IFC activation in children with ADHD during two tasks, motor response inhibition and switching, when compared with healthy children and children with obsessive-compulsive disorder (156). Obsessive-compulsive disorder patients, in turn, had shared abnormalities with ADHD patients in other prefrontal regions, including the OFC and dorsolateral prefrontal cortex (106,156) (Figure 2). The IFC has been associated with a range of cognitive control processes. It has a prominent role in motor response inhibition, more prominently but not exclusively in the right hemisphere, as demonstrated by fMRI studies of children and adults during motor inhibition tasks (22,52,53,157), as well as lesion (158) and transcranial magnetic resonance imaging studies (159). The IFC, however, is also a key region for other related functions that may share elements of inhibitory control, such as interference inhibition, which has more commonly been found to be mediated by left hemispheric inferior
ventromedial OFC in patients with impulsive aggression and psychopathy during emotional tasks. For example, reduced orbitofrontal activation was observed in patients with impulsive aggression in relation to negative emotional stimuli (171), as well as in patients with psychopathy (172,173).

Furthermore, the lateral and ventromedial orbitofrontal cortex also plays a crucial role in the modulation of paralimbic brain regions that mediate aggression (138,174). As mentioned, the orbitofrontal cortex, together with temporal areas including amygdala and hippocampus, was reduced in gray matter in adolescent boys with CD (135). It has been hypothesized that abnormalities in reward computations mediated by orbitofrontal cortex leading to enhanced frustration could trigger reactive aggression, which would explain the link between aggression, abnormalities with the reward system, and orbitofrontal abnormalities (174). The disorder specificity of the dysfunction of the ventromedial frontal cortex in relation to reward compared with ADHD is also in line with evidence of reduced autonomic response in patients with CD compared with ADHD and healthy control subjects during emotional stimuli (175).

It thus seems that there is a disorder-specific and process-related dissociation in prefrontal lobe deficits, where ADHD children have consistent problems with the recruitment of IFC systems in the context of cool executive inhibitory and attention control across several cognitive domains, while CD children have problems with the recruitment of hot ventromedial OFC systems that mediate motivation in the context of reward processing (109) (Figure 1B, Table 1).

Attention-deficit/hyperactivity disorder children, during the reward contrast, showed disorder-specific reduced activation relative to control and CD children in the posterior cingulate and precuneus, brain regions known to mediate visual-spatial attention processing of saliency (176,177). The posterior cingulate and precuneus are reciprocally connected with the anterior cingulate cortex (ACC) (178), which monitors action outcomes to support learning the value of actions (179), and the parietal cortex, which directs visual attention (180) and has hence been associated with the integration of incentives with attention modulation (181). The posterior cingulate and precuneus are typically reduced in activation in children with ADHD during salient stimuli such as errors (95,96) and frontal cortex (51,53,160–162). It is also involved in cognitive switching, in a typically bilateral location, presumably mediating the inhibition of previously valid but no longer relevant stimulus-response associations (right IFC) and the re-engagement of novel stimulus-response associations (left IFC) (51,53,163). It has also been suggested that the IFC junction may have a more generic role for the update of information in tasks of cognitive control, which could explain its ubiquitous activation across cognitive control tasks (160). Furthermore, the bilateral IFC is also consistently activated in children and adults during tasks of selective and sustained attention (108,164) and attention allocation in oddball tasks (54,110). The finding that IFC may be a disorder-specific neurofunctional biomarker of ADHD, when compared with CD, is in line with neuropsychological findings. Attention-deficit/hyperactivity disorder children have consistent impairment in tasks that are mediated by IFC (21,23,113) and this is more prominent than in children with CD (24). Furthermore, children with CD or ODD are often impaired in tasks when ADHD is controlled for (38 – 43). It is also parallel to regression analyses that show that ADHD, but not CD, traits account for poor performance in these IFC mediated cool executive function tasks (50).

For the reward contrast, however, it was the CD children who showed deficits in the recruitment of task-relevant prefrontal brain regions (109). Children with CD, relative to control subjects and children with ADHD, showed reduced activation in ventromedial OFC, which is known to be crucial for executive reward processing and the mediation of motivation (51,165,166) (Figure 1B, Table 1). The orbitofrontal cortex is thought to be important for holding information in representational memory, as well as incentive motivation (58), and thus mediates stimulus-reinforcement learning (58,167). The ventromedial part, in particular, is associated with reward as opposed to punishment-driven processes (168 – 170). The disorder-specific abnormality in ventromedial PFC for CD is in line with evidence for abnormal activation in ventromedial PFC and OFC in patients with impulsive aggression and psychopathy during emotional tasks. For example, reduced orbitofrontal activation was observed in patients with impulsive aggression in relation to negative emotional stimuli (171), as well as in patients with psychopathy (172,173).
oddball or incongruent targets (102,108,110). Reduced activation in a region of saliency processing is consistent with the catecholamine deficiency hypothesis of ADHD, given that catecholamine deficiency diminishes and catecholamine agonists enhance the saliency of stimuli (182). In fact, methylphenidate, the treatment of choice and an indirect catecholamine agonist, has been shown to upregulate the activation of posterior cingulate in children with ADHD, leading to better attention performance (108). Abnormal cingulate activation in ADHD children may thus be the neurobiological substrate of catecholamine deficiency-related abnormal saliency processing.

Apart from the abnormal ventromedial OFC activation, conduct disorder patients demonstrated disorder-specific reductions of activation compared with control subjects in several other regions of the paralimbic system during all tasks. During the sustained attention task, where ADHD children showed disorder-specific inferior frontal underactivation relative to control and CD children, that furthermore correlated with the main performance indicator (i.e., omission errors), children with CD showed reduced activation relative to ADHD and control children in areas of the limbic system that have been shown to contribute to sustained attention through their mediation of motivation, such as hippocampus, the insula, superior temporal lobe, and the dorsal ACC. Furthermore, they also showed reduced activation relative to control and ADHD children in a cluster comprising the cerebellum, the hippocampus, and the inferior temporal lobes (109) (Figure 1B, Table 1). These regions of the paralimbic system lie at the interface between emotion and cognition. The dorsal anterior cingulate is connected to frontoparietal attentional networks but is also crucial for motivation and arousal (183,184). Hippocampus and insula form part of the limbic system and visuomotor pathways and are an interface between motivation and spatial attention (185). Thus, a more anterior part of the insula has been shown to contribute to sustained attention (164), while the hippocampus plays a role in selective visual attention to targets (186). As mentioned, the cerebellar hemispheres form part of frontocerebellar attention systems (72,154,155,187). The superior and inferior temporal lobes are closely connected to the limbic system and contribute to cognitive functions such as perceptual selective attention (188). Together, it thus appears that CD children show disorder-specific underactivation in subcortical and paralimbic brain regions that lie at the interface between motivation and attention and contribute to attention functions, presumably through their mediating role between motivation and cognition. The key performance measure of omission errors did not differ between patient groups but were lower than those of control subjects, which reached significance for ADHD. This suggests that the underrecruitment of cool IFC networks, as well as the reduced recruitment of motivational paralimbic brain regions, can lead to similar performance underachievement.

In addition, CD children showed disorder-specific underactivation of the superior temporal lobes during failures in the stop task compared with both ADHD children and healthy control subjects (96) (Figure 1B, Table 1). The reduced activation of superior temporal regions after mistakes may reflect reduced recruitment of performance monitoring systems, in line with evidence that CD children care less about their mistakes and respond less to negative feedback than healthy children (39,47). Disorder-specific reduced activation in this brain region was also observed in children with CD compared with control subjects, but not ADHD patients, during cognitive switching (107) and sustained attention (109) (Figure 1B, Table 1).

Dysfunction of the temporal lobes during attention and performance monitoring in patients with CD is in line with evidence for structural abnormalities in this brain region (134,135,137). Furthermore, temporal lobe lesions have been associated with aggression and antisocial behavior (189,190), as well as with empathy (191).

In conclusion, the findings of disorder-specific deficits in these two clinically overlapping disorders suggest distinct underlying neurofunctional abnormalities, both of which may be related to overlapping behavioral features. Attention-deficit/hyperactivity disorder appears to be associated with disorder-specific cool top-down inferior prefrontal and bottom-up cerebellar-posterior cingulate cognitive control/attention networks, presumably causing reduced top-down executive inhibitory and attention control. Conduct disorder, by contrast, appears to be associated with neurofunctional deficits in areas of the paralimbic system, in top-down ventromedial OFC and underlying bottom-up limbic and paralimbic structures (anterior cingulate, superior temporal lobes insula, hippocampus) that together mediate motivation and affect and are known to feed into attention systems (164,183,184,186).

The findings of disorder-specific abnormalities in areas of the paralimbic system in CD are in line with neuropsychological evidence that shows specific impairment in these children in tasks of motivation control compared with children with ADHD. They show hyposensitivity to punishment in reward-related paradigms (39,45–47,192). Furthermore, symptom-regression analyses show that CD/ODD symptoms account for the deficits in hot reward-related gambling tasks, while ADHD symptoms account for deficits in cool executive function tasks (50). This neuropsychological evidence, combined with our imaging findings of disorder-specific paralimbic dysfunction, suggests that impairment in cool executive functions in CD may be related to an underlying pathophysiology of the motivational limbic system—that is different from that of ADHD—that disturbs the normal interaction between motivation and cognition, leading to reduced motivational upregulation of the cool executive system, necessary for normal optimal performance. Given that motivation and reward upregulate cognitive processes (185,193,194), both a dysfunction of the hot motivation system, as appears to be the case in CD, as well as a dysfunction of the cool executive system directly, as observed in ADHD, would lead to cognitive impairment. The difference is that the neurobiological deficit in ADHD is directly affecting the cool cognitive control systems, while the deficit in CD affects these systems indirectly, via a dysregulation of the neuronal interplay between motivation and cognition. The dissociative imaging findings hence show that functional imaging is more sensitive than performance to differentiate between behaviorally and cognitively overlapping patient groups. This is illustrated, in particular, for the sustained attention task, where both disorders shared the same number of omission errors but the underlying disorder-specific dysfunctions were in performance correlated cool IFC frontocerebellar activation in patients with ADHD and in hot paralimbic motivation regions in CD that were not directly related to task performance.

We also observed shared abnormalities in the two disorders. Both disorders showed reduced posterior cingulate and precuneus activation during inhibition failures and during incongruent stimuli compared with control subjects, presumably reflecting shared reduced activation to salience, given that both errors and incongruent trials are salient stimuli (96,102). Another brain region that was reduced in activation in both disorders compared with control subjects was the right medial frontal lobe during visual-spatial attention to oddball stimuli (102) (Table 1). It thus appears that a shared abnormality in both disorders is the recruitment of dorsolateral prefrontal and posterior parietal brain regions that mediate visual-spatial attention to salient events.
Comparisons Between Children with CD-CU and Comorbid ADHD with Noncomorbid Children with ADHD

Two fMRI studies from within the same research group compared children with callous-unemotional traits and either CD or ODD with children with noncomorbid ADHD as well as control subjects (148,195). The groups were not well separated in clinical symptomatology because the group with CD/ODD-CU also had ADHD symptoms (7 out of 12). Hence, the comparison was between children with ADHD and no comorbidities and children with ADHD and/or CD or ODD and CU symptoms and healthy control subjects. Mood and anxiety disorders were excluded. Furthermore, the majority of children with ADHD in either group were medicated with psychostimulants. In the study of Marsh et al. (148), reduced right amygdala activation was found to favorably compared with neutral faces in the group with CD/ODD-CU and ADHD relative to control subjects and relative to noncomorbid ADHD, while the latter groups did not differ from each other (148). No group effects were observed for angry or neutral faces. Furthermore, both control subjects and ADHD patients without CD/ODD-CU had a higher degree of functional connectivity between right amygdala and right ventromedial prefrontal activation during fearful compared with the CD/ODD-CU and ADHD group, which furthermore correlated with the severity of the psychopathy symptom scores (Table 1). The amygdala plays an important role in fear processing and socialization (140), and its abnormal response may be the neural substrate for reduced distress cue processing and socialization problems in psychopathy (29,138,196). The underconnectivity findings are interesting with respect to evidence showing that the closely interconnected ventromedial prefrontal cortex and amygdala (197) are crucial to affect control (198). Together, they mediate appropriate behavioral decision making based on positive and negative feedback (51,199) and moral decision making (200–202). These two structures are also known to regulate reactive aggression (174,203).

The second study by Finger et al. (195), on the same sample, compared 14 children with CD/ODD-CU, allowing for ADHD symptoms, with 14 children with noncomorbid ADHD with low scores on antisocial traits and 14 healthy control subjects in a reversal task. While healthy and ADHD children showed reduced activation in bilateral ventromedial prefrontal cortex and caudate during punished reversal errors compared with rewarded correct responses, this effect was not observed in children with CD-CU who showed enhanced activation in this region during punished reversal errors relative to the other two groups. The disorder-specific abnormalities in ventromedial prefrontal activation in the CD-CU and ADHD group were furthermore correlated with total scores on antisocial and callous-unemotional traits (Table 1). Although some of the patients were medicated, the findings remained when these were excluded from the analysis (195). Both the ADHD only group and the group with psychopathy and CD/ODD/ADHD showed enhanced activation in left precuneus and right superior frontal gyrus relative to control subjects (Table 1). The enhanced activation in the group of ADHD without comorbid CD-CU compared with control subjects in precuneus and medial frontal lobe is unusual and not in line with the underactivation findings of the majority of fMRI studies of ADHD during tasks of cognitive flexibility (100,107) or error processing (95,96,156). The negative findings may potentially be related to the fact that the children in this group had a higher IQ compared with the other two groups. While at first the findings of enhanced ventromedial frontal activation may seem in the opposite direction to our finding of reduced ventromedial OFC activation in children with CD during rewarded attention trials (109), they are, in fact, consistent with each other. The children with psychopathy in the study of Finger et al. (195) also showed reduced ventromedial PFC activation during rewarded correct trials, even though this did not reach significance, but showed enhanced activation in this region during punished error trials relative to control subjects and ADHD patients. It thus may be that reward and punishment result in patients with CD in dissociated abnormal response patterns in ventromedial and orbitofrontal brain regions, showing hypersensitive activation in the context of reward and hypersensitive activation during punishment, suggesting a contingency-sensitive orbitofrontal dysregulation. Alternatively, it is also possible that psychopathy and CD have qualitatively different underlying neural substrates, as demonstrated with evidence with respect to amygdala hyperactivation in CD (139,144) and hypoaivation in CD-CU (148). The disorder-specific abnormality findings in ventromedial prefrontal and amygdala activation in the children with psychopathy compared with control and ADHD children are in line with evidence for dysfunction and dysmorphology of these two structures in adults with psychopathy (29,138,145,204–206).

Another interesting dissociation was found for the caudate activation, which was exclusively enhanced in patients with psychopathy compared with control subjects and ADHD patients for punished reversal errors compared with correct rewarded trials, the opposite pattern as in control subjects. However, the caudate hyperactivation did not differ from ADHD patients (195) (Table 1). The caudate is a key region of typically reduced activation in children with ADHD during tasks of cognitive control (94,97,113,207), including tasks of cognitive flexibility (100,156,208). The finding of enhanced caudate activation in antisocial pathologies compared with ADHD may potentially be related to different dopamine levels in these disorders.

In summary, the disorder-specific functional imaging findings suggest that CD and CD-CU compared with ADHD are associated with disorder-specific abnormalities of the paralimbic system of ventromedial and OFC, the limbic part of the anterior cingulate, the amygdala, hippocampus, and the superior temporal lobes, known to regulate affect and motivation. The disorder-specific dysfunctions in children with ADHD, by contrast, appear to be in brain regions that mediate a more cognitive form of top-down inhibitory and attention control, most prominently in IFC-striatal circuitries.

Genetic Associations

The findings of disorder-specific cool IFC dysfunction in ADHD and disorder-specific hot ventromedial-paralimbic dysfunction in CD is further interesting with respect to the genotypes that have been associated most prominently with each of the two disorders. In ADHD, dopamine dysregulation is thought to play a crucial role and the dopamine genotypes of DAT1 and dopamine receptor D4 (DRD4) 7-repeat allele are most commonly associated with the disorder (209). The DRD4-7-7 genotype has been associated with reduced volume and cortical thickness of the right IFC in normal development, which was, furthermore, particularly pronounced in ADHD children with the genotype (210). The DAT1 genotypes have been associated with abnormal caudate volume, as well as activation in patients with ADHD (211,212). Antisocial behaviors, including psychopathy and CD, have more commonly been associated with serotonin genotypes. Thus, the short allele of the serotonin transporter has been associated with impulsive and antisocial behavior features in alcohol abuse (213,214) and violent crime (215) in adults. In children, the short variant has been associated with antisocial and aggressive behavioral features in adoptees (216) and with childhood aggression (217). Furthermore, the short allele showed an interaction with childhood adversity on later-life violent behavior (218). In healthy adults, the short allele of the serotonin
transporter has consistently been associated with the brain structures that have been associated with CD. It has been related to a dysmorphology and dysregulation of the ventromedial prefrontal cortex, including anterior cingulate and medial frontal cortex, and the amygdala, as well as the functional connectivity between both structures (219–221) (for review, see [222]). Abnormal connectivity between amygdala hyperactivity and orbitofrontal hyporesponsivity in relation to negative emotions has been suggested to underlie impulsive aggression (171). Genetic predisposition, hence, may play a role in the development of the disorder-specific dysregulation of IFC-striatal and ventromedial-limbic neural networks in ADHD and antisocial-aggressive behaviors, respectively.

Conclusion and Future Directions

This review shows that ADHD is most prominently associated with the dysmorphology, dysfunction, and the underconnectivity of cool fronto-striato-cerebellar and frontoparietal neural networks that regulate cognition and attention. Furthermore, these regions, most prominently the IFC, are disorder-specific underfunctioning when compared with CD. Antisocial and aggressive behaviors in the form of CD and CD-CU, by contrast, are associated with structural and functional deficits in areas of the paralimbic system, including the orbitofrontal cortex, superior temporal lobes, and underlying limbic structures, as well as ventromedial frontolimbic underconnectivity. Furthermore, compared with ADHD, this paralimbic system dysfunction and underconnectivity are disorder-specific (Figure 3).

Comorbidity Between Disorders

There are several potential caveats, however, that need to be taken into account. All structural studies have tested children with CD with over 50% comorbidity with ADHD. Consequently, structural abnormality findings apply mostly to the comorbid presentation of CD and ADHD. This is also the case for all functional imaging studies, except for those conducted in my laboratory, where we compared noncomorbid patient groups. Although in the majority of studies, brain structure and function abnormalities correlated with antisocial behaviors or survived covariance with ADHD, it cannot be excluded that the comorbid ADHD features may have contributed to the abnormalities. The fact that the studies from our laboratory, however, were conducted in noncomorbid groups and showed disorder-specific functional brain abnormalities in noncomorbid CD relative to noncomorbid ADHD in paralimbic regions, including superior temporal lobes, orbitofrontal cortex, insula, anterior cingulate, and hippocampus, reinforces the association between these paralimbic functional deficits, also observed in the studies of comorbid cases and antisocial behaviors. However, noncomorbid patient groups may be less representative of the typical CD or ADHD population. According to epidemiological studies, children with noncomorbid CD or noncomorbid ADHD are relatively rare (19,78,149). An epidemiological prevalence study in north England schools showed that while hyperactivity prevalence without CD can be relatively high (30%), CD without ADHD is relatively uncommon (1.5%) (223). Epidemiological data from the British Child Mental Health Survey, however, using diagnostic criteria that elicit a relatively conservative ADHD prevalence of 1.5%, showed that only 23% of children with CD had ADHD comorbidity, while 50% of ADHD children had CD comorbidity (224). In US samples, this ratio appears to be higher, however, with odds ratios of 41.3 for concurrent comorbidity of ADHD given CD and of 79 for ADHD given ODD (78). The comorbid presentation is likely to suffer

Figure 3. Schematic representation of the magnetic resonance imaging evidence for disorder-specific structural and functional brain abnormalities in children with attention-deficit/hyperactivity disorder and those with conduct disorder. The figure is based on evidence for disorder-specific abnormalities from head-to-head functional and structural imaging comparisons between noncomorbid and comorbid disorders. While evidence from individual disorder-control studies may suggest overlapping abnormalities in several of these regions (such as anterior cingulate, dorsolateral prefrontal, or temporal lobes), the figure is focusing on evidence for disorder-specific association findings between regional abnormalities and either attention-deficit/hyperactivity disorder or conduct disorder. ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; PFC, prefrontal cortex.
from a dysregulation of both cool fronto-striato-parieto-cerebellar as well as hot ventromedial fronto-temporo-limbic neural networks. Future studies will need to compare 100% comorbid cases with noncomorbid CD and noncomorbid ADHD patients to elucidate to what extent the comorbid presentation shares the etiopathophysiology of the noncomorbid disorders or whether it is a more complex disorder, characterized by a qualitatively different underlying pathology.

Furthermore, although most studies in ADHD and CD have excluded affective comorbidity and controlled for anxiety and depressive symptoms, it cannot be completely excluded that underlying problems of anxiety and depression may have contributed to the observed brain abnormalities. Future studies are needed to assess the contribution of affective symptomatology on brain abnormalities in these disorders, by comparing children with noncomorbid depression and anxiety with children with noncomorbid ADHD and CD, as well as comorbid presentations of these disorders.

Bias in Structural and Functional Imaging Studies

There has been a bias in structural studies, where regions of interest in ADHD have more commonly targeted frontal and striatal brain regions, while areas of the paralimbic motivation circuitries have more commonly been selected as regions of interest in structural studies in CD. More recent structural imaging studies of ADHD that have selected limbic areas as regions of interest have, in fact, found limbic structural abnormalities in ADHD children. A study by Plessen et al. (225) found enhanced volumes in the head of the hippocampus in 51 children with the combined type of ADHD compared with 63 healthy control subjects. This structural abnormality, however, was associated with fewer ADHD symptoms and hence interpreted as a compensatory plastic hypertrophic response, possibly for reduced prefrontal parts of frontal-hippocampal circuitries. Surface morphology analyses also showed reduced size bilaterally of the basolateral complex of the amygdala in ADHD children relative to control subjects, which correlated with prefrontal cortex size, suggesting reduced frontal-amygdala connectivity. The amygdala surface morphology was negatively associated with inattention but positively associated with hyperactivity symptoms, suggesting distinct associations between amygdala neurobiology and different ADHD symptoms (225). Although there were potential confounds such as history or current symptoms of depression/anxiety, ODD, or medication history and status, these were not associated with the findings. Abnormalities in medial frontal regions and their connections to amygdala and hippocampus could be associated with abnormal performance in some of the hot executive functions associated with ADHD, most typically reward-related decision making in the form of delay aversion or hypersensitivity to immediate rewards, as well as attention and mnemonic processes. Another recent structural study found smaller volume of the pulvinar of the thalamus in 46 children with ADHD compared with healthy control subjects. A dissociation of thalamic volumes with ADHD symptoms was observed, with hyperactivity being associated with smaller left ventrolateral and pulvinar regions and inattention with larger right pulvinar and medial dorsal thalamic regions (226). The pulvinar is part of fronto-parieto-cortico-thalamic networks important for attentional saliency processing (227,228). However, this region is also connected to the limbic system, including the amygdala (229,230), and hence part of an emotional regulation network (228). Moreover, recent postion emission tomography studies that carefully selected noncomorbid adults with ADHD observed abnormal dopamine transporter levels relative to healthy adults in areas of the limbic system including nucleus accumbens and midbrain, amygdala, and hippocampus that furthermore correlated with inattention but not hyperactivity symptoms (231,232).

In fMRI studies of both disorders, there has also been a bias in paradigm selection, where cool cognitive paradigms have been applied in the majority of fMRI studies of ADHD to test the hypothesis of frontostriatal deficits, while hot motivational paradigms have been more commonly chosen for fMRI research of CD. In fact, more recent fMRI studies that have tested for deficits in motivational networks in ADHD using paradigms of emotion processing or reward-related functions have, indeed, found underfunctioning in children and adults with ADHD in limbic brain regions, including orbital and ventromedial prefrontal cortex, amygdala, and ventral striatum (114,117,233–235). Comorbidity with antisocial behaviors, however, was not excluded and could potentially have confounded the results. This, however, also applies to the majority of fMRI studies that observed frontostriatal dysfunctions during cool executive function in ADHD patients and did not exclude comorbid cases with CD. In support of an association with ADHD, however, is the fact that several of these studies found a correlation between activation in limbic regions, such as ventral striatum and amygdala, with hyperactive/impulsive but not inattentive symptoms (117,233,235). In conclusion, given the bias in the neuroimaging literature of ADHD and CD in the selection of regions of interest in structural imaging studies and paradigm selection for fMRI studies, future imaging studies should combine structural and functional analyses in large patient numbers to conduct head-to-head comparisons between children with noncomorbid CD, noncomorbid ADHD, and comorbid cases using whole-brain structural imaging analyses and using fMRI tasks that tap into both hot and cool executive functions.

Potential Overlap Between Disorders in Brain Structure and Function Abnormalities

Ventromedial-limbic circuitries and mesolimbic dopamine reward pathways may potentially be a shared abnormality between both ADHD and CD. The nucleus accumbens is located between and reciprocally connected to both cool frontocortical as well as hot limbic areas and is thought to be a key mediator between motivation and attention functions (64). It is ideally placed to integrate emotional salience and contextual constraints, processed in amygdala and hippocampus, respectively, and goal-directed executive plans from the PFC. The mesolimbic dopamine system maintains the balance between limbic and cortical drive within this region (64). This region is closely interconnected with anterior cingulate, ventromedial frontal cortex, and amygdala, which, in concert, mediate reward-related decision making (67,236,237). Furthermore, abnormalities in these circuitries have been associated with impulsiveness and behavioral disinhibition (67,238), overlapping features between ADHD and CD (28). While orbital and ventromedial frontal cortices, anterior cingulate, amygdala, and hippocampus have been shown to be associated with CD, no structural or functional MRI study, however, has as yet tested for structural abnormalities of nucleus accumbens in children with CD or for potential activation abnormalities in reward-related paradigms that specifically activate this region. It is likely that the ventral striatum, in its role as interface between motivation and attention, is not only impaired in ADHD but also in children with CD, and this should be tested in future studies.

Another area of potential overlap could be the anterior cingulate. This paralimbic area lies at the interface between the frontal lobes and the limbic system and has been associated with several functions, depending on exact location, including performance monitoring, error detection, arousal, motivation, and outcome monitoring to modulate executive attention (157,179,183,184,239).
Both rostral and dorsal anterior cingulate have consistently been found to be abnormal in structural and functional imaging studies of CD (see above). This brain region has also been found to be abnormal in brain structure and function in ADHD children (94,102,110,156,240) and adults (125,127,241,242). Direct comparisons between ADHD and CD, however, point toward more severe abnormalities in this region in CD. Functional MRI comparisons have found dorsal ACC underactivation to be specifically associated with noncomorbid CD when compared with noncomorbid ADHD (109) and dysfunction in this area remained when ADHD was controlled for (139) or correlated specifically with antisocial and CU symptoms (144). Structural studies found ACC to be specifically associated with CD but not ADHD symptoms in regression analyses (135) and to be associated with CD when ADHD was covaried (137). The ACC abnormality may thus be more strongly associated with antisocial behavioral features than ADHD symptoms and abnormality findings in ACC in ADHD patients—more commonly observed in adult than childhood ADHD (for review, see 125)—may potentially be associated with underlying, and mostly uncontrolled, antisocial features.

Lastly, we found that in children with ADHD and emotional dysregulation, both the DRD4 7-repeat allele as well as the short allele of the serotonin transporter have been associated with emotional dysregulation, suggesting that this behavioral feature, which is common in ADHD children and associated with CD and/or ODD behavior, may be mediated by the abnormality of both top-down PFC control systems, the cool executive lateral PFC-striatal control network as well as the hot ventromedial PFC-limbic pathway that controls affect and motivation (243).

In conclusion, there is evidence that some brain regions that intermediate between hot motivation and cool attention functions may be affected in both disorders, but this needs to be further tested in head-to-head comparisons between noncomorbid and comorbid patient groups.

Heterogeneity Within ADHD and CD

Both ADHD and CD are heterogeneous disorders. More effort needs to be undertaken to disentangle the neurobiological substrates within subgroups of these disorders. For example, children with inattention only are likely to suffer from different neurobiological abnormalities than children with the combined type ADHD. Children with inattention are less likely to have oppositional defiant disorder than those with the combined subtype (244), while impulsiveness is a key feature shared between the impulsive-hyperactive subtype of ADHD and CD, in particular the impulsive-aggressive subtype of CD. It has been argued that the inattentive symptoms of ADHD may be associated with deficits in frontostriatal mediated cool EF, whereas hyperactivity/impulsivity symptoms may reflect hot executive function deficits, mediated by paralimbic brain regions (245). This would suggest that the different subtypes of ADHD may be mediated by different brain abnormalities, with the impulsive-hyperactive subtype resembling more CD than the inattentive subtype. This is, however, only in part supported by evidence. In line with this theory, limbic brain abnormalities in orbitofrontal, amygdala, and ventral striatum correlated with impulsive-hyperactive but not inattentive symptoms (117,233,235). Symptoms of inattention, however, and not impulsive-hyperactive symptoms have been shown to correlate with limbic abnormalities in children with ADHD and CD in structural MRI and positron emission tomography studies (136,231). By contrast, hyperactivity/impulsiveness symptoms and not inattention symptoms correlated inversely with gray matter reductions in cool fronto-temporo-parietal brain regions (135). Furthermore, there is some evidence to suggest that children with inattention and sluggish cognitive tempo have more anxiety and depression and fewer externalizing problems (246). This would, by contrast, point toward abnormalities in orbitofrontal-limbic brain regions that are typically associated with depression (72) and that overlap substantially with the observed brain abnormalities in CD. Clearly, large-scale imaging studies that compare children with the inattentive, impulsive-hyperactive, and the combined subtypes are needed to clarify potential differences in the underlying neural substrates of each of the subtypes.

Along the same lines, future imaging studies should investigate subtypes of CD because there are likely to be differences in the underlying neurobiological substrates of CD children with and without callous-unemotional traits or with either reactive or instrumental aggression. Lastly, there are likely to be neurophysiological differences between children with CD and ODD. To my knowledge, however, no imaging studies have as yet investigated the neuroimaging substrates of ODD, independent from CD, or compared between different subtypes of CD.

Need for Longitudinal and Combined Structure-Function Studies

All published studies comparing ADHD and CD have been cross-sectional. Longitudinal imaging studies will be needed to assess differences in the developmental trajectories of the disorders. While in ADHD there is evidence for a maturational delay (93,247), nothing is known on the longitudinal trajectories of CD. Childhood disorders are more likely to differ in the temporal dynamics of their brain abnormalities, i.e., in the onset of their deviance from normal development and/or in their developmental trajectories, rather than at any chosen cross-sectional time point.

Furthermore, no studies have combined structural and functional information. Future, large-scale multimodal imaging studies should compare ADHD and CD in brain structure, brain function, and structural and functional connectivity. Modern multivariate pattern recognition analysis classification systems applied to MRI data, which differentiate cases and control subjects on the basis of quantitative, spatially distributed neural networks rather than isolated brain regions with the ability to make individual classifications (248–250), could potentially be of clinical use by providing a more objective, neuroimaging-based differential diagnosis. A successful classification of these two patient groups based on their underlying neurobiological abnormalities would not only provide a more objective differential diagnosis but also deliver a target for disorder-specific prevention and interventions aimed at normalizing disorder-specific abnormal brain and neurotransmitter systems and their abnormal development.

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