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Chapter 16

Cingulate impairments in ADHD: Comorbidities, connections, and treatment

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Abstract

The entire cingulate cortex is engaged in the structure/function abnormalities found in attention-deficit/hyperactivity disorder (ADHD). In ADHD, which is the most common developmental disease, impaired impulse control and cognition often trace to anterior midcingulate cortex (aMCC) in Go/No-go tests, decoding and reading, the Stroop Color and Word Test, and the Wisconsin Card Sorting Test (WCST), with volume deficits in anterior cingulate cortex (ACC) and posterior midcingulate cortex (pMCC). Volumes in pMCC correlate positively with the WCST and negatively with total and nonperseverative errors on the WCST. Activation and connectivity on *N*-back tests show connections for high and low spatial working memory, but patients have increased activation in PCC and decreased connectivity between MCC and PCC for high load. Students struggle in class due to malfunctioning aMCC, pregenual anterior cingulate cortex (pACC), and dorsal posterior cingulate cortex (dPCC), and to core deficits in response/task switching in aMCC. Gene mutations are found in the DA transporter and DA4 and DA5 receptors. Methylphenidate decreases hyperactivity in aMCC. The DA system is controlled by cholinergic receptors in the daMCC and genetics show nAChR mutations in alpha 3, 4, and 7 receptors. At 25 years, a modified Eriksen flanker/No-go task and voxel-based morphometry (VBM) show prenatal smoking, lifetime smoking at 13 years, and novelty seeking. Prenatal exposure to nicotine exhibits weaker responses in aMCC during cognitive tasks for hyperactivity/impulsiveness but not inattention. AZD1446 (α4β2 nAChR agonist) improves the Groton Maze task due to high nAChR in dPCC/RSC engaged in spatial orientation. Environmental factors associated with childhood ADHD relate to pesticides, organochlorine, and air pollutants. Network connection segregation shows increased amygdala local nodal, but decreased ACC and PCC connections, reflecting emphasis on local periamygdala connections at the expense of cortical connections. Thus, ADHD children/adolescents respond impulsively to the significance of stimuli without having cortical inhibition. Finally, controls show negative relationships between aMCC and the default mode network, and ADHD compromises this relationship, showing decreased connectivity between ACC and precuneus/PCC.

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is one of the most common and complex neurodevelopmental diseases, and a number of reasons exist for considering it in the context of neurologic diseases. First, the role of cingulate cortex in attention is still poorly understood and ADHD may help in understanding it. Second, ADHD is one of the most common childhood disorders (Pennington, 2008) and is estimated to affect 7%–10% of children, with another study reporting an even higher rate of around 30% (Gjevik et al., 2011). ADHD involves difficulty with inattention, hyperactivity, and/or impulsivity (American Psychiatric Association, 2013)

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that encompasses three subtypes: combined hyperactive–impulsive (ADHDC), predominantly inattentive (ADHDI), and mainly hyperactive (ADHDH). Third, the motor and cognitive functions attributed to the rostral cingulate motor area, located mainly in area a24c′ and adjacent cortex, make it a likely site of hyperactivity and it is also a site of cognitive impairment (Bush, 2009). Finally, ADHD comorbidities may help elucidate common impairments such as those in the dopaminergic (DAergic), cholinergic, and noradrenergic (NE) systems that focus treatment strategies.

The goal in this chapter is to localize predominant sites of cingulate damage in ADHD as they relate to symptoms and cognition. However, there are many inconsistencies in the imaging observations. Extreme differences in region-of-interest (ROI) designations mitigate against quantitative data comparison. Finally, while studies often emphasize a cingulate subregion and a limited number of functional deficits, considering the ADHD literature in total shows that the entire cingulate cortex is engaged in different functional impairments and structural abnormalities, i.e., all subregions are impacted depending on how testing and ROIs are defined.

Screening instruments focusing on neurodevelopmental disorders and associated conditions are scarce. The Autism–Tics, ADHD and other Comorbidities inventory (A-TAC) is one. Mårland et al. (2017) showed that the sensitivity and specificity of A-TAC scores for predicting earlier or later clinical diagnoses were good–excellent, with values for clinical diagnosis of autism spectrum disorder (ASD) of 0.98, ADHD 0.93, learning disorder (LD) 0.92, and oppositional defiant disorder (ODD) 0.99. These results support previous claims that A-TAC is a broad screening instrument with a particular strength in assessing ASD, ADHD, LD, and ODD at ages 9–12, and it also provides phenotypic information about other child psychiatric disorders.

Hattori et al. (2006) evaluated the relationship between patients with ADHD and those with pervasive developmental disorders (PDDs) using the high-functioning Autism Spectrum Screening Questionnaire (ASSQ) and the ADHD Rating Scale-IV. The ASSQ scores of PDD and the ADHD groups were significantly higher than controls, with the PDD group scoring higher than the ADHD group. Both groups also showed higher scores than controls in three quantified cognitive domains: restricted and repetitive behavior, social interaction, and communication problems. The PDD and ADHD groups showed no differences in the domains of communication problems and restricted and repetitive behaviors. The PDD group had a higher score than the ADHD group only in social interaction. In the total score for inattention and hyperactivity/impulsivity on the ADHD Rating Scale-IV, both groups were higher than controls. Between the ADHD and the PDD groups, there were no differences in the three scores. The patients with strictly diagnosed ADHD had many PDD symptoms, and patients with PDD had many ADHD symptoms. It therefore is difficult to make a distinction between ADHD and PDD by using the criteria in the DSM-IV and each patient needs to be assessed with both sets of criteria. Lee and Ousley (2006) performed a study using a chart review to determine the frequency of ADHD in a clinical sample of children and adolescents with ASD compared to ADHD, Asperger's disorder, and PDD. Criteria for ADHD in the DSM-IV were met by 78%. ADHDI scores were greater in patients with ASD than other ASDs. Thus, ADHD symptoms are pervasive in clinically referred children and adolescents with ASD.

Finally, Volpe et al. (2009) devised an effective brief rating scale for ADHD by examining both a factor-analytic and an individualized approach to creating short progress-monitoring measures from the longer ADHD-Symptom Checklist-4 (ADHD-SC4). In one of their studies, teacher ratings on items of the ADHD: inattentive (IA) and ADHD hyperactive–impulsive (HI) scales of the ADHD-SC4 were factor analyzed in a normative data sample in students aged 5–12. Items with the highest factor loadings were then selected to create abbreviated IA and HI scales for a second study, in which the psychometric characteristics of two shortened progress-monitoring measures and individualized and original IA and HI scales of the ADHD-SC4 were examined in students aged 4–17 years in a medication titration study with three doses of methylphenidate. Comparable psychometrics was found across the original and abbreviated versions of the IA and HI scales.

Symptom overlap between ADHD, PDD, and ASD likely influences studies seeking to identify sites of structural and functional damage associated with ADHD. The question arises as to whether the previous nosology reflects "pure" ADHD subtypes and can serve as the basis for neurobiologic investigations. Also, imaging studies focus on individual or a few functions for obvious reasons; however, this has led to a number of misconceptions that will be noted throughout this chapter. For example, focus on the DAergic system has substantial support from genetics and success with methylphenidate treatment; however, this is not the only system involved in ADHD and it appears to be driven by cholinergic input to the ventral tegmental area (VTA).

ADHD is one of a number of developmental disorders. Chien et al. (2015) observed that youths with ASD had worse school, peer, and home functions than controls. In general, comorbid psychiatric conditions mediated the link between autistic symptoms and different domains of social adjustment. Additionally, specific mediating effects were noted for anxiety/depression and

inattention on school functions, anxiety/depression on peer relationships, and ODD behaviors on home behaviors. Gjevik et al. (2011) studied ASD in children and adolescents and showed 72% had at least one comorbid disorder with anxiety (41%) with ADHD (31%) being the most prevalent. Obsessive–compulsive disorder (OCD) was more common in older children and ODD/conduct disorder was also present. In another study, youths with ASD show a high rate of behavioral problems, especially ADHD and ODD symptoms (Lecavalier et al., 2009). Apart from the core symptoms of ASD, the prevalence of ADHD symptoms, attention deficits, and impulsivity have long been noted in ASD.

Neurodevelopmental disorders should be considered as different patterns of symptoms or impairments of a common underlying continuum. Several percent of the general population of children have marked autistic features judged to qualify for a medical diagnosis of ASD. Waterhouse and Gillberg (2014) state that unitary models of ASD dysfunction have not adequately addressed conflicting evidence, and efforts to find a single unifying brain dysfunction have led the field away from exploring individual variation and microsubgroups. Autism must be taken apart to find treatment targets and the belief that there is a single defining ASD brain dysfunction must be relinquished. Researchers need to explore individual variation in brain measures within autism, and some have proposed that in early years it is comorbid conditions that move individuals from one with autistic features to a status of autism, particularly when autism diagnoses are growing over time (Nygren et al., 2012). Thus the diagnosis of autism is determined to a large extent by the presence or not of intellectual and developmental disabilities, LDs, epilepsy, or other medical conditions. Also, executive dysfunction, slow processing, and ADHD contribute to the worst outcomes (Hagberg et al., 2013). Moreover, many parents and siblings of children with autistic features are often successful without major problems in adult life.

Regarding the relationship between patients with ADHD and those with PDD, results from the ASSQ and ADHD Rating Scale-IV have showed that the ASSQ scores of PDD and ADHD were higher than controls. Furthermore, the PDD group scored higher than the ADHD group. Both groups also showed higher scores than controls in all three domains: restricted and repetitive behavior, social interaction, and communication problems. The PDD and ADHD groups showed no difference in the domains of communication problems and restricted and repetitive behavior. PDD had a higher score than the ADHD group only in social interaction. In total score of inattention and hyperactivity/impulsivity on the ADHD Rating Scale-IV, both groups were higher than controls. Patients strictly diagnosed with ADHD had many PDD-related symptoms, and the patients with PDD had many ADHD symptoms (Hattori et al., 2006). It therefore seems difficult to make a distinction between ADHD and PDD by using present diagnostic criteria in the DSM-IV. Each patient should be evaluated in terms of both sets of criteria. Finally, Lee et al. (2006) used a chart review to assess ADHD symptoms in comparison to Asperger's disorder and PDD and the correlation between ADHD Rating Scale scores and age. Of 83 children and adolescents, 78% fulfilled DSM-IV criteria for ADHD. Hyperactivity–impulsivity scores were greater in individuals with other ASDs. Thus, ADHD symptoms are pervasive in clinically referred children and adolescents with ASD.

CINGULATE CORTEX STRUCTURAL AND FUNCTIONAL/COGNITIVE DAMAGE IN ADHD

To the extent that students with ADHD develop cognitively at a slower pace than healthy classmates, it is not surprising that they struggle in classes, at least up to the 10th grade. The main sites of damage are in anterior midcingulate cortex (aMCC) but are also found in pregenual anterior cingulate cortex (pACC) and dorsal posterior cingulate cortex (dPCC). Following are some of the studies supporting this view.

Plourde et al. (2015) documented the phenotypic and genetic associations between reading comprehension and ADHD dimensions of inattention and hyperactivity/impulsivity in early schooling compared to those with decoding skills. Reading was assessed with all measures in second or third grade. Teachers assessed ADHD dimensions in kindergarten and first grade. Both decoding and reading comprehension were correlated with ADHD dimensions in a similar way: associations with inattention remained after controlling for other ADHD factors, such as behavioral disorder symptoms and nonverbal abilities, whereas associations with hyperactivity/impulsivity did not. Genetic modeling showed that decoding and comprehension largely shared the same genetic etiology at this age and that their associations with inattention were mostly explained by shared genetic influences. Thus reading comprehension and decoding are uniquely associated with inattention through a shared genetic etiology.

There is little doubt that ADHD has an impact on the structure and functions of cingulate cortex. Fig. 16.1 shows some of the support for this. Seidman et al. (2011; Fig. 16.1A) showed a reduced volume of aMCC with voxel-based measurement (VBM) in adults with ADHD. Interestingly, the site they showed was mainly in the rostral cingulate premotor area (rCPMA; gray matter area in the depths of the cingulate sulcus) that has links to dopamine receptor (DAR) density (below). They also showed a VBM increase in ACC, possibly reflecting amplified emotional and autonomic responses. He et al.

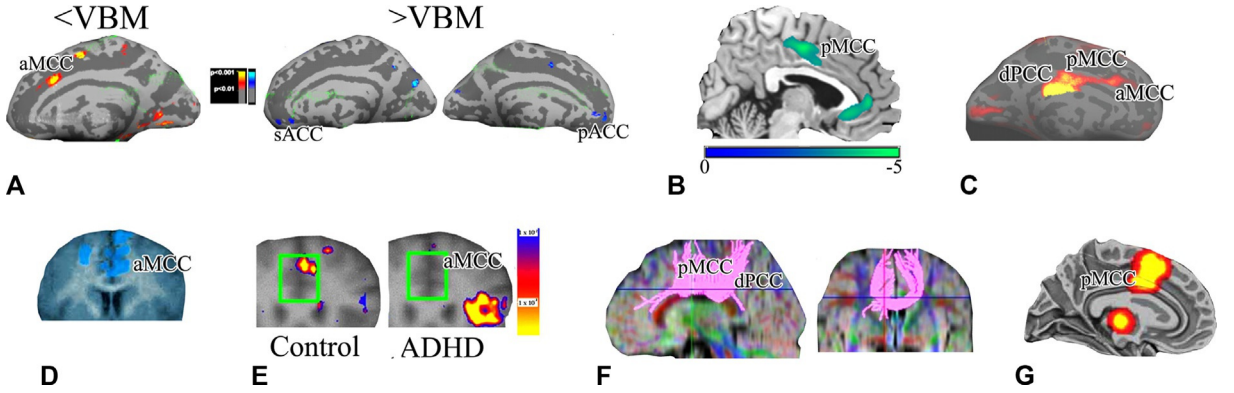

Fig.16.1. Images from various methods that show changes in cingulate cortex in ADHD. (A) Seidman et al. (2011), (B) He et al. (2015), (C) Makris et al. (2007), (D) Tamm et al. (2004), (E) Bush et al. (1999), (F) Basay et al. (2016), and (G) Hart et al. (2013). Abbreviation: *VBM*, voxel-based measurement. For each cingulate subregion refer to Chapter 1.

(2015; Fig. 16.1B) evaluated VBM in male children and adolescents with ADHD and controls and executive function using the Stroop Color-Word Test and Wisconsin Card Sorting Test (WCST). VBM gray matter volume differences between the ADHD and controls were correlated with deficits in executive dysfunctions, ACC and pMCC volumes, among other areas. In patients, volumes of the pMCC were positively correlated with the WCST and negatively correlated with the total and nonperseverative errors on the WCST. Changes in ACC confirmed the findings of He et al. (2015). Further evidence for localized cingulate structural alterations in dPCC and pMCC with a small extension into the aMCC were observed by Makris et al. (2007; Fig. 16.1C).

Functional impairments in cingulate cortex were assessed by Tamm et al. (2004; Fig. 16.1D) and Bush et al. (1999; Fig. 16.1E) and findings were consistent between the two studies. The former study used event-related fMRI in adolescent boys diagnosed with ADHDC and typically developing controls that completed a Go/No-go task. The ADHD group made more errors of omission and commission than controls. Further, the ADHD group showed marked abnormalities in activation during response inhibition, including hypoactivation of the anterior MCC (aMCC) and hyperactivation of the temporal gyrus. This suggests that underactivation in frontal regions reflect a core deficit in response/task switching abilities for ADHD. The latter study by Bush et al. (1999) used fMRI to examine the functional integrity of aMCC in ADHD in unmedicated adults and controls who performed the Counting Stroop during fMRI. While both groups showed an interference effect, the ADHD group, in contrast to controls, failed to activate aMCC. Direct comparisons showed aMCC activity was higher in controls. The previous assessments emphasize the pivotal role of MCC damage in ADHD, be it in adolescents or adults. Failure to activate this region appears to be diagnostic of ADHD and its cognitive impairments. However, other regions are also impaired.

GENETIC PREDISPOSITIONS, DOPAMINE AND METHYLPHENIDATE, AND SEROTONIN SYSTEM

ADHD heritability indicates a genetic basis in 70%–90% of cases (Faraone et al., 2005; Klein et al., 2017) and links to key symptoms. The latter review concluded that it has a complex, polygenic background; multiple genetic variants (many of them with small effects) that contribute to ADHD were identified in five genome-wide studies of the etiology of the disorder in most patients. Although a substantial fraction of ADHD etiology is due to genes, many environmental risk factors and potential gene–environment interactions (see the following) are also linked to an increased risk for ADHD that adds further to the disorder's complexity.

Among monozygotic cotwins with ASD, the probability of having a diagnosis of ADHD is 44%, compared with 15% for dizygotic cotwins (Rommelse et al., 2010). Ronald et al. (2008) reported correlations between autistic and ADHD traits in the general population (54% for parent reported data, 51% for teacher data). In bivariate models, all genetic correlations were >50%, indicating a moderate degree of overlap in genetic influences on autistic and ADHD traits, both throughout the general population and at the quantitative extreme. Substantial overlap in suspected cases (41% of children who met criteria for ASD had suspected ADHD; 22% with suspected ADHD met criteria for ASD). These results suggest there are some common genetic influences operating across autistic traits and ADHD behaviors throughout normal variation and at the extreme. They also support clinical observations noted above for the overlap of ADHD with other psychiatric disorders.

The genes most often identified are part of the DAergic system including the dopamine transporter (DAT) and DA4 and DA5 receptors (Cook Jr et al., 1995; Klein et al., 2017). Although effect size is often small and complex and only explains a small fraction of the assigned risk, the DA system is one of the most likely targets of ADHD genetic defects and treatment given the effectiveness of methylphenidate. Hasler et al. (2015) assessed a number of DA receptor alleles and found novel alleles of the *DAT1* and *DRD4* and *DAT1* associated with impulsiveness and trait anger and these alleles were surprisingly protective in ADHD.

The noradrenergic (NE) system is also engaged in ADHD. Amiri et al. (2018) evaluated peripheral blood samples with polymerase chain reaction in a study of the polymorphism position rs5320 and allele and genotype frequency of the DBH gene. The results suggest that DBH polymorphism, position rs5320, plays a role in the pathogenicity of ADHD.

Catechol-*O*-methyl-transferase (COMT) has been localized to the gray and white matter of the cerebral cortex and subcortex (encoded by the COMT gene, located at 22q11.21). It is involved in the degradation of the catecholamines DA and NE and is highly expressed in the frontal lobe where it is responsible for regulation of DA levels (Hong et al., 1998). Recently, Basay et al. (2016; Fig. 16.1F) reported on children with ADHD who were homozygous for the valine allele; they used diffusion tensor imaging (DTI) to show reduced fractional anisotropy and increased radial diffusivity values in the cingulum bundle, particularly in MCC. This indicates that demyelination may affect white matter connections between cingulate cortex and prefrontal cortex (PFC), premotor regions, cortical association areas, thalamus, and hippocampus and may contribute to MCC hypofunctionality.

Seeman and Madras (2002) proposed that stimulants, such as methylphenidate, reduce hyperactivity in children and adults and these drugs, which raise extracellular DA, result in psychomotor slowing of hyperactive children, when DA is known to enhance motor activity. The hypothesis for the antihyperactivity effects of the stimulants is as follows: during normal activity, extracellular DA transiently rises 60-fold. At low therapeutic doses (0.2–0.5 mg/kg) to treat ADHD, methylphenidate reduces locomotion and raises resting extracellular DA several-fold but reduces the extent to which DA is released with presynaptic activity. This relatively reduced amplitude of impulse-associated DA results in less activation of postsynaptic DAR, which drives psychomotor activity. At higher doses, stimulants produce generalized stimulation of the nervous system, as a result of the very high concentrations of extracellular DA at rest, and the markedly increased release of presynaptic DA. These high levels of resting and pulsatile DA cause widespread stimulation of postsynaptic DAR, overcoming any concomitant presynaptic inhibition of DA release.

Fig. 16.2 shows the outcome of a study by Bush et al. (2008; Fig. 16.2A) who used the Multisource Interference Task (MSIT; scan 1 at baseline and scan 2 at 6 weeks) to assess the role of methylphenidate on MSIT responses. Group-averaged, random effects, repeated measures, and general linear model analyses were used to compare daMCC and whole-brain fMRI activity during the MSIT. Performance and baseline fMRI measures in the daMCC and other a priori regions did not differ between groups. However, group comparisons showed a group by scan interaction and confirmation of higher activation in the daMCC at 6 weeks in the methylphenidate group than in the placebo group. Individual daMCC volume-of-interest analyses confirmed group-averaged findings and suggested that daMCC activity might be related to the clinical response. Thus, methylphenidate increased daMCC activation during the MSIT and may act, in part, by normalizing daMCC hypofunction in ADHD. An interesting additional observation from Fig. 16.1A is that this effect was mainly in the rostral cingulate premotor area (rCPMA; Fig. 16.1A) as shown, with the arrow further emphasizing its localized action in rCPMA. This latter finding may account for the positive effects of methylphenidate on hyperactivity.

In another study, Schulz et al. (2012; Fig. 16.4I) contrasted changes in brain activation related to symptomatic improvement with methylphenidate vs the nonstimulant atomoxetine; in fMRI before and after 6–8 weeks of treatment with the other drug 36 youths with ADHD showed changes in brain activation during a Go/No-go test of response inhibition and investigator-completed ratings on the ADHD Rating Scale-IV-Parent Version. Treatments of the ligands were associated with comparable improvements in response inhibition on the Go/No-go test. Ratings of ADHD symptom improvement were associated with common reductions in motor cortex activation for both treatments and were differentially related to gains in task-related activation for atomoxetine and reductions in activation for methylphenidate in the ACC and PCC, among other areas. Thus, treatment with methylphenidate and atomoxetine produce symptomatic improvement via both common and divergent neurophysiologic actions in frontoparietal cortex that have been implicated in the pathophysiology of ADHD. Of interest is the fact that aMCC was not identified as a target of methylphenidate in this latter study.

Fig. 16.2 shows the distribution of dopamine (DA) in monkey with dopamine-β hydroxylase (DBH; Miller et al., 2009; Fig. 16.2B). The highest level of DBH activity is in aMCC including the rCPMA, and this binding could predispose the aMCC as a site of methylphenidate

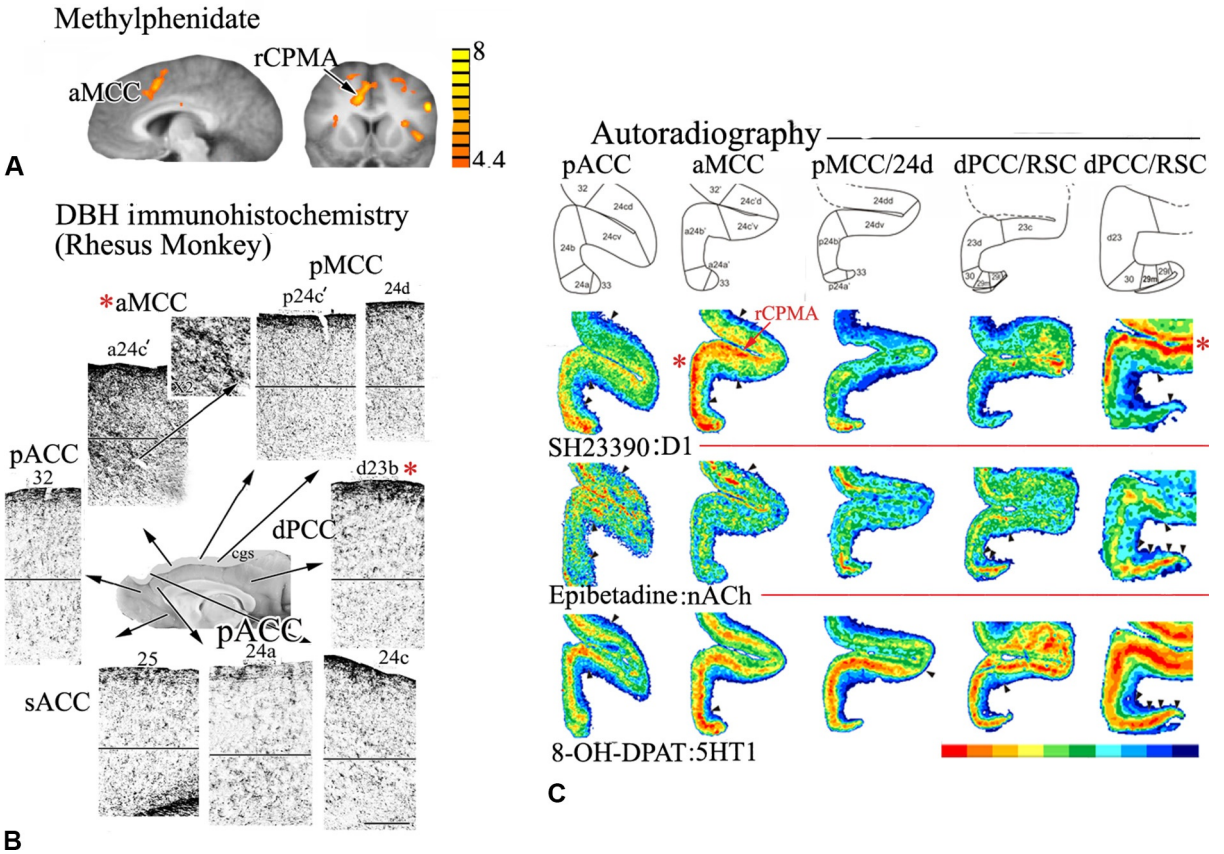

Fig. 16.2. (A) Methylphenidate from Bush et al. (2008); (B) DBH immunohistochemistry from Miller et al. (2009); and (C) autoradiography from Palomero-Gallagher and Zilles (2009). The color scale is pseudocolored for receptor binding.

actions, shown in Fig. 16.2A. Finally, this figure shows the pattern of D1 receptors (D2R were not available in this study) of normal healthy individuals from Palomero-Gallagher and Zilles (2009; Fig. 16.2C). Nevertheless, binding of SH23390 was highest in aMCC, as is DBH, including the rCPMA. Similar plots are required in ADHD with D2R ligands to determine the effects of methylphenidate on the distribution and density of D2R.

The serotonin system has also been implicated in ADHD. In controls, the ligand 8-OH-DPAT has a rostrocaudal increase in density with the highest binding in dPCC (Fig. 16.1C). This cingulate subregion should be a specific site-of-interest for studies of ADHD, as it is involved in stress responses and sensory orientation functions (see Chapter 1). The serotonin transporter gene known as SLC6A4 is implicated in ADHD. This gene contains a variable number of tandem repeat polymorphisms in its promoter region (5-HTTLPR), consisting of a 14-repeat short variant (S-allele) and a 16-repeat long variant (L-allele) and both 5-HTTLPR genotypes (Lesch et al., 1996). Stress exposure has been characterized in ADHD by a delay in brain development, which showed that the 5-HTTLPR genotype moderates the effect of stress on regions involved in social cognition and cognitive control. This gene–environment interaction is related to ADHD severity. An MRI study by van der Meer et al. (2015; Fig. 16.4F) showed the serotonin transporter 5-HTTLPR genotype moderates the effect of stress on severity in ADHD, with stronger effects of stress in carriers of the short allele than in individuals homozygous for the long allele, using the effect of stress on brain gray matter volume with structural MRI. The 5-HTTLPR genotype and a stress exposure questionnaire was used for patients with ADHD: 78 with subthreshold ADHD and 332 healthy controls with an average age of 17 years. ADHD symptom count was determined through multiinformant questionnaires and whole-brain VBM combined with mediation analysis. Stress exposure was associated with less gray matter volume in the dPCC, among other areas in S-allele carriers, as compared with participants homozygous for the L-allele. The association of this gene–environment interaction with ADHD symptom count was mediated by gray matter volume in ACC and dPCC. Thus the 5-HTTLPR genotype moderates the effect of stress on brain regions involved in social cognitive processing and cognitive control.

Park et al. (2015; Fig. 16.4G) proposed that genetic and environmental adversities contribute to

the occurrence and severity of ADHD via DNA methylation. This was explored with the serotonin transporter gene (SLC6A4) methylation patterns and their association with clinical characteristics and regional cortical thickness in children with ADHD (ages 6–15). Higher methylation status of the SLC6A4 promoter was associated with worse clinical presentations (more hyperactive–impulsive symptoms and more commission errors). Additionally, a negative correlation was observed between SLC6A4 methylation and cortical thickness in the occipitotemporal regions. However, as shown in Fig. 16.4G, there is at least a trend toward significance in the MCC that was not noted. Thus SLC6A4 methylation status may be associated with behavioral disinhibition in ADHD and related brain changes, including MCC.

ENVIRONMENTAL RISKS

ADHD links to environmental factors have been demonstrated as a number of risk factors. For example, all children born to mothers who bore their first child early in their reproductive lives are at increased risk of ADHD. The association has been mainly explained by genetic factors transmitted from mothers to their offspring that contribute to both age at childbirth and ADHD in offspring (Chang et al., 2014). Also, prenatal smoking enhances the risk for ADHD (Han et al., 2015; Gard et al., 2016). The latter study predicted hyperactivity/impulsiveness during adolescence and young adulthood across multiple informants, but not inattention. A review by Storebø et al. (2016) showed that parental attachment problems and environmental mediating factors were associated with childhood ADHD. Adults with ADHD had a much higher incidence of insecure attachment styles than is found in the general population. Saez et al. (2018) found that clusters of ADHD could be related to some environmental variables, such as exposure to pesticides, organochlorine compounds, and air pollutants due to traffic.

Kofler et al. (2016) proposed that hyperactive behavior reflects, to a large extent, purposeful behavior to cope with environmental demands and to interact with underlying vulnerabilities. This review evaluated the ubiquity and environmental modifiability of hyperactivity in ADHD in a metaanalysis of children, adolescents, and adults with ADHD relative to typically developing groups. They confirmed elevated gross motor activity in ADHD; surprisingly, neither participant age (child vs adult) or the proportion of each ADHD sample diagnosed with the inattentive subtype presentation moderated this effect. In contrast, activity assessed during high cognitive load in general and high executive functioning demands in particular revealed higher effect sizes than activity level during low cognitive load and in-class school work. Low stimulation environments, more rigorous diagnostic practices, actigraph measurement of movement frequency and intensity, and ADHD samples were also associated with larger effects. Overall, the results are inconsistent with DSM-V and ADHD models that (a) describe hyperactivity as ubiquitous behavior, (b) predict a developmental decline in hyperactivity, or (c) differentiate subtypes/presentations according to perceived differences in hyperactive behavior. Instead, their results suggest that the presence and magnitude of hyperactive behavior in ADHD may be influenced to a considerable extent by environmental factors in general, and cognitive/executive functioning demands in particular.

Generally speaking, children's reward responsivity and sensitivity to punishment are positively associated with child ADHD symptoms (Li, 2018). However, children with high reward responsivity had more symptoms of ADHD, but only under conditions of low negative parenting (self-reported and observed) and high self-reported positive parenting compared to children with low reward responsivity. Children with high sensitivity to punishment had more ADHD symptoms relative to children with low sensitivity to punishment, but only under conditions in which observed praise was infrequent. These results provide evidence that individual differences in sensitivity to reward/punishment may be an important marker of risk for ADHD, but they also highlight how children's responses to positive and negative parenting behavior may vary by children's sensitivities.

Environmental risks can be high in childhood, including stressful and challenging jobs and education, and this may impair functioning. Lasky et al. (2016) suggested that changing environmental contexts could play a positive role in the decline of ADHD symptoms in adults. As adults, these patients have more latitude to control their day-to-day environments and this may alter their experience, including occupational or educational contexts in which young adults report functioning better than others. These investigators examined 125 young adults originally diagnosed with ADHD as children. Regarding their work and postsecondary educational environments, many subjects described their symptoms as context dependent with some contexts resulting in feeling better able to focus; in others, their symptoms, such as high ADHD energy, becomes a strength rather than a liability. Thus, differential environmental influences can reduce some of the symptoms of ADHD in adults.

CHOLINERGIC SYSTEM

The cholinergic system has been frequently related to ADHD in terms of genetics, environmental influences,

and the potential for drug therapeutics. Potter and Newhouse (2008) showed that acute nicotine in young adults with ADHDC affected cognition, including behavioral inhibition, delay aversion, and recognition memory. Cognitive tasks included the stop signal reaction time (SSRT) task, the choice delay task, and the high–low imagery task (a verbal recognition memory task). A significant positive effect of nicotine on the SSRT was observed. The SSRT was improved without changes in Go reaction time or accuracy. Thus nonsmoking young adults with ADHDC showed improvements in cognitive performance following nicotine administration in several domains that are central to ADHD, supporting the hypothesis that cholinergic system activity may be important in the cognitive deficits of ADHD and may be a useful therapeutic target.

Attempts to uncover the effect of prenatal exposure to nicotine on inhibitory control may be of clinical importance. To clarify the influence of maternal smoking during pregnancy on response inhibition and its association with related behavioral phenotypes in ADHD and novelty seeking in the mother's offspring, Holz et al. (2014; Fig. 16.4H) performed fMRI on the offspring at 25 years of age during a modified Eriksen flanker/No-go task, and used VBM to study volume differences of the offspring. Prenatal smoking and lifetime ADHD symptoms were determined using parent interviews at the offspring's age of 3 months and over 13 years. Novelty seeking was assessed at 19 years. The researchers analyzed a total of 178 young adults (73 males) without current psychopathology followed since birth. Participants prenatally exposed to nicotine exhibited a weaker response in the aMCC, among other areas, during the processing of the No-go compared to neutral stimuli, while presenting a decreased volume in the right inferior frontal gyrus. There was an inverse relationship between inferior frontal gyrus activity and ADHD symptoms and between aMCC activity and novelty seeking. Thus there is a functional involvement of prenatal exposure to tobacco smoke in neural alterations similar to ADHD, which underlines the importance of smoking prevention treatments.

The distribution and density of nAChR as measured with epibetadine (Palomero-Gallagher and Zilles, 2009; Fig. 16.2C) in controls show the highest relative levels in the pACC sulcal region, dPCC, and RSC. As noted later, a major site of action of nAChR may be in subcortical sites, where they regulate DA release. Genetic studies show that nicotinic receptor mutations are present in the alpha 3 receptor (Polina et al., 2014), the alpha 4 receptor (Guan et al., 2009), and the alpha 7 receptor (Williams et al., 2012). Exposure of the fetus to maternal smoking has a profound effect on the development of ADHD. It is associated with hyperactivity and impulsiveness (Gard et al., 2016) and adolescent girls with the inattentive form of severe ADHD are at higher risk to start smoking early and escalate their smoking, in comparison to males, as shown in Elkins et al. (2018). To the extent that smoking in inattentive ADHD, but not hyperactive ADHD, is a causal factor, it suggests these patients are self-medicating their symptoms via nicotinic receptor mechanisms. Thus, nicotinic agonists may serve as a treatment for cognitive impairments in ADHD.

Jucaite et al. (2014) employed AZD1446, a selective α4β2 nAChR agonist, in a clinical trial. While this was only a 2-week trial and the clinical deficits in ADHD were not resolved, there was improvement on executive function as measured with the Groton Maze Learning task, possibly reflecting the higher level of nAChR binding in dPCC and RSC, which are engaged in spatial orientation (see Chapter 1). A longer duration trial is necessary to adequately test this and similar compounds.

Behavioral inhibition, recognition memory, and delay aversion were assessed at different doses of mecamylamine, a noncompetitive nicotinic agonist by Potter et al. (2009). The 0.5-mg dose of mecamylamine significantly improved cognitive memory and reduced tolerance for delay. Mecamylamine increased participant-rated irritability and investigator-rated restlessness. There were no effects on vital signs or physical side effects. Thus, while measurable effects of ultralow doses of mecamylamine did not improve core ADHD cognitive symptoms, they significantly improved recognition memory. These effects may represent mixed receptor activity (activation and blockade) at the doses tested. The finding of beneficial effects on memory processes has important clinical implications and further exploration of this effect is warranted.

There is emerging evidence that cholinergic neurotransmission, particularly in children involving nAChRs, may play a role in adolescent pathophysiology of ADHD. In a review by Wilens and Decker (2007), it was hypothesized that DA and NE are particularly important and ABT-089 was used to evaluate ADHD. In a small proof-of-concept treatment of adult ADHD, nicotine has demonstrated procognitive effects and cognitive deficits. Although adverse effects associated with nicotine preclude its therapeutic development, a number of novel nAChR agonists with improved safety/tolerability profiles have been discovered. Of these, ABT-418 and ABT-089 have a demonstrated efficacy in adults with ADHD. Notably, tolerability issues that might be expected of a nAChR agonist, such as nausea and emesis, were not observed at efficacious doses of ABT-089.

While most studies of ADHD emphasize cortical and striatal deficits, there are a number of small nuclei with cholinergic neurons in the brainstem that project to thalamic nuclei that in turn project to cingulate cortex; i.e., not all systemic cholinergic drug responses arise from cortical sites. The dorsal tegmental, laterodorsal

tegmental nuclei, and the cuneiform nucleus project to nuclei with thalamocingulate projections. The DAergic system is under tight control by the cholinergic system and these systems cannot be viewed as independent. Dong et al. (2013) showed that firing of DA neurons in the VTA, which projects to ACC and MCC (Porrino and Goldman-Rakic, 1982), and the release of DA by the projections of these neurons in the nucleus accumbens (NAc), are under tight control by nAChR. The capacity for cholinergic signaling is dictated by the availability and activity of the presynaptic, high-affinity, choline transporter (ChT, SLC5A7), which acquires choline in an activity-dependent manner for ACh synthesis. A transporter constitutive loss of ChT expression, mediated by genetic elimination of one copy of the Slc5a7 gene in mice (ChT+/−), leads to a reduction in basal extracellular DA levels in the NAc. Moreover, ChT heterozygosity results in blunted DA elevations following systemic nicotine administration. This reinforces a critical role of ACh signaling in both tonic and drug-modulated DA signaling and argues that genetically imposed reductions in ChT that lead to diminished DA signaling may lead to poor responses to reinforcing stimuli, possibly contributing to disorders linked to perturbed cholinergic signaling, including ADHD.

Grady et al. (1992) assessed the actions of DA release in mouse from striatal synaptosomes. The response was blocked by a number of nAChR antagonists. Marshall et al. (1997) extended this issue using microdialysis probes in three terminal DA regions (striatum, nucleus accumbens [NAc], frontal cortex) of behaving rats. Prior administration of mecamylamine abolished DA release, emphasizing these are presynaptic, nAChR-mediated responses.

Mereu et al. (1987) studied the effect of nicotine on the single unit activity of midbrain DA neurons in rats. Nicotine (50–500 mg/kg) produced a dose-related 25% increase in the firing rate of nigral pars compacta DA cells and the same doses were more than three times as effective on VTA DA cells in rats. All of these effects were reversed and prevented by mecamylamine. Moreover, after nicotine-induced stimulation, low doses of apomorphine inhibited the firing rate similar to controls, indicating that DAR are not directly involved in nicotinic action.

ADHD DEVELOPMENTAL DELAY

Although maturation progresses in a similar manner regionally in children with and without ADHD, with primary sensory areas attaining peak cortical thickness before polymodal, high-order association areas including cingulate cortex, Shaw et al. (2007) reported there was a marked delay in ADHD in attaining peak thickness throughout most of the cerebrum. The median age by which 50% of the cortical points attained peak thickness for this group was 10.5 years, which was later than the median age of 7.5 years for typically developing controls. The delay was most prominent in prefrontal regions (including aMCC and ACC) important for control of cognition for attention and motor planning. Thus there is neuroanatomic documentation of a delay in regional cortical maturation in ADHD, including that in cingulate cortex. However, Montes et al. (2012) argued that using longitudinal MRI showed reduced cortical thickness in ADHD, but this disappears with age, suggesting a developmental delay. Differences revealed that location, number, and magnitude of cortical thickness differences were different between males and females in each age group. Thus, these data support the hypothesis that anatomic abnormalities in ADHD represent abnormal development rather than developmental delay. In fact, neither of these findings are mutually exclusive. They both point to a developmental disorder with some cortical changes resolving as the patient group ages.

A CORE ADHD DEFICIT IN URGE CONTROL AND IMPULSIVITY

A common feature of ADHD and many of its comorbid syndromes (OCD, Tourette syndrome) appear to be reflected in deficits in urge control organized in MCC. As noted in Chapter 1, the concept of "attention-for-action" proposed by Posner et al. (2014) put the MCC premotor concept in a broader context. This designation underscores its role in mismatch detection/conflict resolution (Carter et al., 1998, 2000), selecting among cognitive options that do not require movement (Corbetta et al., 1991), anticipation of cognitive processing (Murtha et al., 1996), or working memory (Petit et al., 1998). All of these dimensions of cognitive processing may be impaired in ADHD.

Hsieh et al. (1994) first reported in a positron-emission tomography study that the urge to scratch activated pMCC. Fig. 16.3 shows some images from studies evaluating urge. Athwal et al. (2001; Fig. 16.3A) made the interesting observation that the urge to micturate could be distinguished from bladder filling. The former was linearly related to the urge-to-void and associated with inactivations in aMCC, while the latter were associated with pMCC activations. Andrew and Nathan (1965) explored patients with voiding deficits who were treated with surgical removal of aneurisms and tumors. They concluded that cortical areas, including MCC, control the septal and hypothalamic nuclei to integrate micturition and defecation into normal daily activities within the environment. This is to say, MCC likely selects the social and environmental conditions under which micturition and defecation can be deployed.

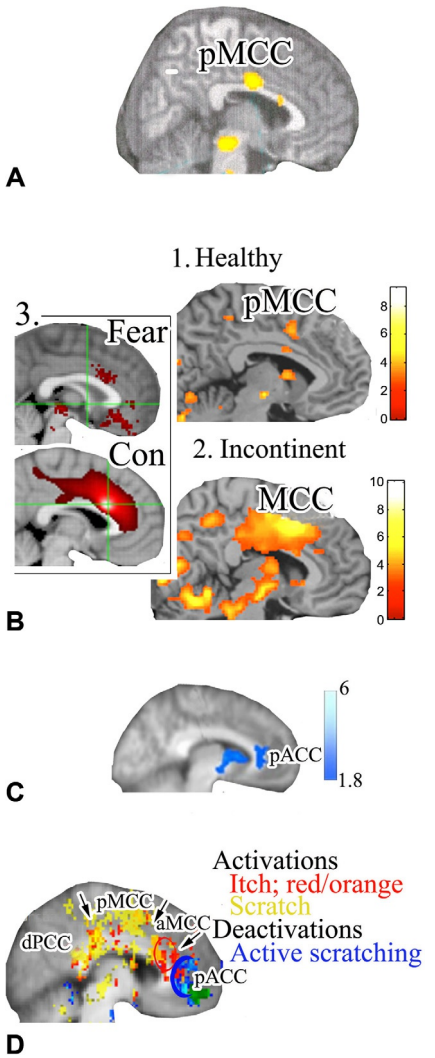

Fig. 16.3. Urge control including incontinence is mediated by aMCC as demonstrated by these images. Urge control is likely an important deficit in ADHD suggesting why activity in aMCC is frequently impaired. (A) Athwal et al. (2001), (B) (inset 3) fear and connections (Con) derived from Neurosynth (Griffiths et al., 2007), (C) Leknes et al. (2007), and (D) Papoiu et al. (2013) shows active itch site with a red oval in aMCC and the itch activation site with a blue oval in aMCC. Active scratching is in yellow in pMCC and dPCC as noted in the original publication and deactivations for both forms of scratching are shown with blue oval in pACC.

Griffiths et al. (2007; Fig. 16.3B) showed a small level of activity in the rostral part of pMCC during bladder filling, continuing the theme that pMCC has a role in micturition; however, the response of their incontinent patients engaged the entire MCC (Fig. 16.3B, 2). In order to explain this large response, one should consider the role of fear for an accidental emission. Fig. 16.3B, 1–3 (inset) is from Neurosynth and localizes both the predominant fear site in aMCC and its connections (Con) throughout the cingulate gyrus that engage the CPMA in the cingulate sulcus. Thus lack of control of micturition and its urges in incontinent patients may evoke fear and a high level of MCC activity.

Leknes et al. (2007; Fig. 16.3C) used histamine to evoke itch and pACC was activated, which they attributed to the urge for relief. This may be interpreted in terms of the emotional component of itch, given that pACC has a prominent role in emotional activity (Vogt, 2005). Papoiu et al. (2013; Fig. 16.3D) observed that active scratching evoked inactivation of pACC, as did Leknes et al., suggesting that scratching may be a way to relieve the negative affect associated with itch. The latter study also showed itch evoked activity in aMCC (rostral oval) and dPCC (caudal oval). Finally, scratching evoked activity in most of pMCC including cortex in the cingulate sulcus that contains the cCPMA and is assumed to be associated with the urge to scratch, as demonstrated in other studies noted earlier.

The concept of urges and their localization to MCC was further discussed by Jackson et al. (2011) under the concept of "urge-to-action," similar to the "attention-to-action" proposed by Posner and Raichle (1998). The former authors suggested that micturition and its relation to clinical disorders in which the urge-to-action is considered pathologic interfere with activities of daily living, as in ADHD, and concluded that urges are chiefly associated with actions that cannot be realized immediately and must be held in check until an appropriate time when they might be released. When we become aware of having a full bladder, we experience an "urge-to-void," because we do not simply void our bladder, but employ a coordinated set of central, autonomic, and peripheral mechanisms to withhold micturition until in an appropriate context. Their activation likelihood estimation assessment showed a pMCC site. Taken together, these findings support the view that pMCC is involved in many urges (although voiding the bladder and scratch are stressed here). One postulate about ADHD is that deficits in urge control are associated with impulsiveness in its psychopathology. Lack of impulse control in OCD patients and controls (Fitzgerald et al., 2005) demonstrated aMCC activation during errors of commission. However, OCD patients exhibit greater error-related activation of the sACC than controls. Activity in this region was positively correlated with symptom severity in patients. Thus error-processing abnormalities within the sACC occur in the absence of symptom expression in OCD.

CINGULATE CONNECTIVITY PATTERNS IN ADHD

The final connectivity map will only be completed when there are anatomic methods that provide information on

the specific neuronal origin by layer and laminar axonal termination sites. DTI, for example, provides some information but not the direction of information flow or the exact origin and termination of a projection system. Nevertheless, with current methods applied to ADHD, interesting structure/dysfunction relationships can be determined.

Griffiths et al. (2016; Fig. 16.4A) used quantified anatomic organization in children and adolescents with ADHD and they generated anatomic networks based on covariance of gray matter volumes from 92 regions in the brain. Metrics were computed that characterized the global organization of networks (interconnectivity; clustering), integration (path length), and balance of global integration and localized segregation (small-worldness). In their local nodal measures (participation degree) and interaction (betweenness within a network) relative to controls, ADHD participants exhibited altered

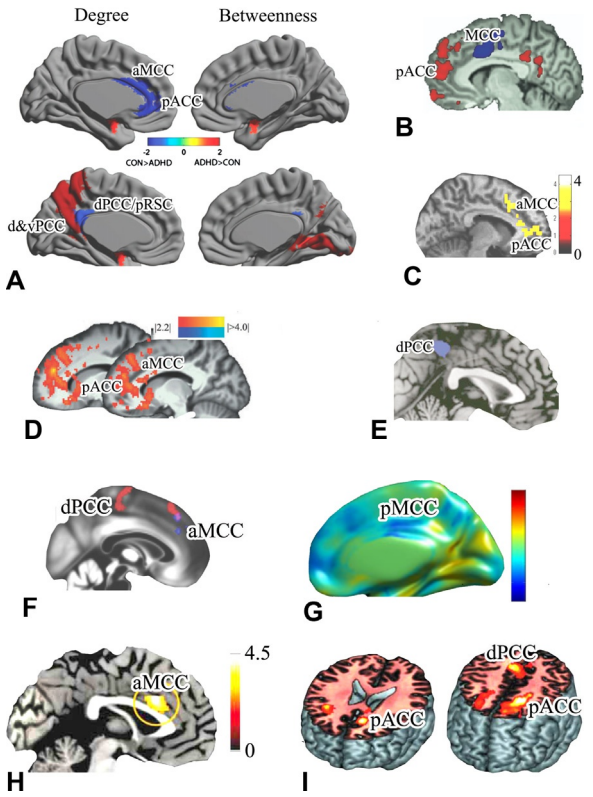

Fig. 16.4. Depending on the testing strategy used to evaluate cingulate cortex, other subregions than aMCC have been implicated in ADHD including pACC, pMCC and dPCC/vPCC. (A) Griffiths et al. (2016), (B) Castellanos et al. (2008), (C) Takeuchi et al. (2017), (D) Mattfeld et al. (2014) shows greater remitting over persistent ADHD symptoms with sites mainly in pACC and aMCC, (E) Bédard et al. (2014); note the blue site in precuneus/dPCC, (F) van der Meer et al. (2015), (G) Park et al. (2015), (H) Holz et al. (2014), and (I) Schulz et al. (2012).

global organization reflected in more clustering or network segregation. Locally, nodal degree and betweenness were increased in the amygdalae in ADHD, but reduced in cortical nodes in the ACC, PCC, midtemporal pole, and rolandic operculum. In ADHD, anatomic networks were disrupted, reflecting an emphasis on subcortical local connections centered around the amygdala, at the expense of cortical organization. Brains of children and adolescents with ADHD may be anatomically configured to respond impulsively to the automatic significance of stimulus input without having the cortical organization to regulate and inhibit amygdalar responses.

Resting-state fMRI scans were obtained by Castellanos et al. (2008; Fig. 16.4B). Control subjects verified the presence of a negative relationship between activity in aMCC and in default mode network (DMN). Group analyses revealed ADHD-related compromises in this relationship, with decreases in the functional connectivity between ACC and precuneus/PCC. Secondary analyses revealed an extensive pattern of ADHD-related decreases in connectivity between precuneus and other DMN components, including portions of PCC. Thus together with prior unbiased evidence of posterior volumetric abnormalities, findings suggest that the long-range connections linking aMCC to PC/precuneus are candidates for dysfunction in ADHD.

Working memory training (WMT) induces changes in cognitive function and various neural systems. Takeuchi et al. (2017; Fig. 16.4C) investigated changes in resting-state fMRI of global information processing (degree of the cortical hub), which may have a central role in information integration in the brain, and also in degree centrality (DC). The magnitude of intrinsic brain activity (fractional amplitude of low-frequency fluctuation; fALFF) and local connectivity (regional homogeneity) in young adults who either underwent WMT or received no intervention for 4 weeks was determined. Compared with no intervention, WMT increased DC in the cluster including pACC to the medial prefrontal cortex (mPFC). Furthermore, WMT increased fALFF in the cluster including the mPFC. WMT increased regional homogeneity in the cluster in the precuneus and PCC. These results suggest that WMT-induced plasticity in spontaneous brain activity and global and local information processing occurs in areas of the major networks during rest. WMT may help resolve some of the cognitive deficits observed in ADHD.

Correlation studies are also helpful in determining potential connectivity and links to ADHD organization. Mattfeld et al. (2014; Fig. 16.4D) characterized the differences and similarities of persistence and remittance with resting-state fMRI in individuals who had been longitudinally and uniformly characterized as having or not having ADHD in childhood and again in adulthood

(16 years after baseline assessment). Intrinsic functional organization was measured in patients who had a persistent diagnosis in childhood and adulthood and in patients who met diagnosis in childhood but not adulthood, and in controls who never had ADHD. A positive functional correlation between PCC and medial prefrontal cortices, major components of the DMN, was reduced only in patients whose diagnosis persisted into adulthood. A negative functional correlation between medial and dorsolateral prefrontal cortices was reduced in both persistent and remitted patients. This dissociation between the persistence and remittance of ADHD may provide a framework for the relation between the clinical diagnosis, which indicates the need for treatment, and additional deficits that are common, such as executive dysfunctions.

Visuospatial working memory impairments have been implicated in the pathophysiology of ADHD. However, most ADHD research focuses on the neural correlates of nonspatial mnemonic processes. A study by Bédard et al. (2014; Fig. 16.4E) examined brain activation and functional connectivity for visuospatial working memory in youths with and without ADHD. Patients and controls were scanned with fMRI while performing an *N*-back test of working memory for spatial position. Block-design analyses contrasted activation and functional connectivity separately for high (2-back) and low (1-back) working memory load conditions vs the control condition (0-back). The two groups performed comparably on the task and demonstrated similar patterns of frontoparietal activation with no differences in linear gains in activation as working memory load increased. However, youths with ADHD showed greater activation in the dorsolateral prefrontal cortex (DLPFC) and PCC (blue in the figure), greater functional connectivity between the DLPFC and intraparietal sulcus, and reduced DLPFC connectivity with MCC and PCC for the high load contrast compared to controls. A more conservative statistical approach yielded group differences in PCC activation and DLPFC-MCC connectivity. Thus youths with ADHD show decreased efficiency of DLPFC for high load visuospatial working memory and greater reliance on posterior spatial attention circuits to store and update spatial position than healthy controls.

SUMMARY AND CONCLUSIONS

There is a growing body of work linking subregions of cingulate cortex with ADHD symptomatology and connections. Most of the imaging of ADHD, however, is based on volumetric changes, yet their source is not known: dendrite and/or neuron hypertrophy, or more often hypotrophy. ADHD is one of the most frequent neurodevelopmental disorders and there is evidence for a developmental delay. The median age by which 50% of the cortical points attained peak thickness was 10.5 years for ADHD, later than the median age of 7.5 years for typically developing controls. The delay was most prominent in prefrontal regions, including aMCC and ACC.

In terms of diagnosis and syndrome overlap, the A-TAC for ages 9–12 is often used. The ASSQ and ADHD Rating Scale-IV show that patients with strictly diagnosed ADHD have many PDD-related symptoms, and patients with PDD have many ADHD-related symptoms. In one study of ADHD in children and adolescents with ASD, criteria for ADHD in the DSM-IV were met by 78%, and ADHD-impulsive scores were substantial in ASD. Thus ADHD symptoms are pervasive in clinically referred children/adolescents with ASD. A brief rating scale that performs well is also available. Another study of children/adolescents with ASD showed 72% have at least one comorbid disorder with anxiety (41%) with ADHD (31%) being most prevalent. Apart from the core symptoms of ASD, the prevalence of ADHD symptoms and attention deficits and impulsivity have long been noted in ASD. Among monozygotic cotwins with ASD, the probability of having ADHD is 44%, compared with 15% for dizygotic cotwins. There is also substantial overlap in suspected cases (41% of children who met criteria for ASD had suspected ADHD; 22% with suspected ADHD met criteria for ASD). These results suggest common genetic influences across autistic traits and ADHD behaviors.

ADHD has a complex, polygenic background, with multiple variants. Genes that are most often identified are part of the DAergic system and include the DAT and DA4 and DA5 receptors. Novel alleles of *DAT1* and *DRD4* and *DAT1* are associated with impulsiveness and trait anger and these alleles are surprisingly protective in ADHD. Thus, a balance between damaging and protective genes is operable in ADHD. A reduced volume of aMCC in adults with ADHD is mainly in the rostral cingulate premotor area, which has links to high DAR density. Drugs that raise extracellular DA result in psychomotor slowing of hyperactive children. The MSIT performance and baseline fMRI measures in the daMCC and other a priori regions did not differ between ADHD and controls. However, group comparisons show a group by scan interaction and confirmation of higher activation of daMCC at 6 weeks in patients treated with methylphenidate. Methylphenidate treatment is associated with comparable improvements in both response inhibition on the Go/No-go test and ratings of ADHD symptoms. Improvements in ADHD symptoms are associated with common reduction in bilateral motor cortex and symptomatic improvement differentially relates to

gains in task-related reductions in activation in the ACC and bilateral PCC, among other areas.

While structural and functional changes tend to be ameliorated in adults, both youths and adults share similar deficits in cingulate structure and function and cognition. These include restricted and repetitive behavior, social interaction, and communication problems; reading comprehension and decoding are uniquely associated with inattention through a shared genetic etiology; reduced volume of aMCC is present in adults and increases in ACC. The Stroop Color-Word test and WCST are impaired and VBM volumes correlate with deficits in executive dysfunction with reduced volumes in ACC and pMCC among other areas in ADHD, while volumes in pMCC are positively correlated with the WCST, and volumes in pMCC are negatively correlated with total and nonperseverative errors on the WCST; the Go/No-go task in patients shows more errors of both omission and commission than controls. The ADHD group showed marked abnormalities in activation during response inhibition, including hypoactivation of aMCC, suggesting that underactivation in frontal regions reflects a core deficit in response/task switching abilities; the counting Stroop shows that controls and ADHD patients have an interference effect but the ADHD group inactivated aMCC. Decoding and reading comprehension are correlated with ADHD dimensions. Activity during high cognitive load in general and high executive functioning demands in particular reveals higher effect sizes than during low cognitive load and in-class schoolwork.

The serotonin transporter gene (SLC6A4) has been implicated in ADHD. This gene contains a variable number of tandem repeat polymorphisms in its promoter region (5-HTTLPR), consisting of a 14-repeat short variant (S-allele) and a 16-repeat long variant (L-allele) and both 5-HTTLPR genotypes and stress exposure have been characterized in ADHD by a delay in brain development, showing that the 5-HTTLPR genotype moderates the effect of stress on regions involved in social cognition and cognitive control. This gene–environment interaction may be related to ADHD severity and the 5-HTTLPR genotype moderates the effect of stress on severity with stronger effects of stress in carriers of the short allele than those homozygous for the long allele. Stress exposure is associated with lower volume in the dPCC among other areas in S-allele carriers compared with those homozygous for the L-allele. The association of this gene–environment interaction with ADHD symptom count is mediated by volumes in the ACC and dPCC. Finally, DNA methylation patterns of SLC6A4 are associated with clinical characteristics and regional cortical thickness in children with ADHD. Of particular note is the higher methylation status of the SLC6A4 promoter, associated with worse clinical presentations (more hyperactive–impulsive symptoms and more commission errors) that may occur in pMCC.

Environmental risks have been identified and add another dimension of variability to ADHD. Some examples are: children born to mothers who bore their first child early, prenatal smoking enhances the risk for ADHD hyperactivity/impulsiveness during adolescence and young adulthood across multiple informants, but not inattention; parental attachment problems and environmental mediating factors are associated with childhood ADHD; adults with ADHD have a much higher incidence of insecure attachment styles than in the general population; exposure to pesticides, organochlorine compounds, and air pollutants due to farming and traffic. Also, children's reward responsivity and sensitivity to punishment are positively associated with child ADHD symptoms. Relationships between low negative parenting and high self-reported positive parenting compared to children with low reward responsivity have been shown. Children with high sensitivity to punishment have more ADHD symptoms relative to children with low sensitivity to punishment, but only under conditions in which praise is frequent. Changing environmental contexts may play a positive role in the decline of ADHD symptoms in adults, as they have more latitude to control their day-to-day environments and this alters their experience, including occupational or educational contexts. Many patients describe their symptoms as context dependent, with some contexts resulting in feeling better able to focus; in other contexts, their symptoms, such as high ADHD energy levels, become strengths rather than liabilities.

Genes most often identified in ADHD are part of the DAergic system and include the DAT and DA4 and DA5 receptors. Children with the 10–10 repeat allele of the DAT1 (vs a combined group of all other genotypes) exhibit less severe symptoms of hyperactivity and impulsivity and less severe language deficits. Teacher ratings indicated that social anxiety and tic symptoms were more severe for children with this genotype. Thus heterozygosity (9–10 repeat genotype) may be a risk protective factor. The DBH polymorphism at position rs5320 plays a role in the pathogenicity of ADHD, and atomoxetine (a selective NE reuptake inhibitor) is a treatment for ADHD that is effective and well tolerated. It is more effective than placebo and standard therapy and less effective than the extended-release methylphenidate. MSIT scans at baseline and 2 and 6 weeks later to assess the role of methylphenidate confirm higher activation in the daMCC at 6 weeks. Individual daMCC volume-of-interest confirmed group averages and suggests that daMCC activity might be related to clinical response. After 6–8 weeks of treatment with methylphenidate or atomoxetine in boys, improvement in activation was

shown during a Go/No-go test in both response inhibition on the Go/No-go test and ratings of ADHD symptoms. Improvement in ADHD symptoms was associated with reduced symptoms and was differentially related to gains in task-related activation for atomoxetine and reductions in activation for methylphenidate in the ACC and PCC.

The cholinergic system has been frequently related to ADHD in terms of genetics, environmental influences, and the potential for drug therapeutics. Acute nicotine in young adults with ADHDC affects cognitive domains, including behavioral inhibition, delay aversion, and recognition memory including the SSRT, choice delay task, and the high–low imagery task (a verbal recognition memory task). A positive effect of nicotine on the SSRT is observed, which improved without changes in Go reaction time or accuracy. Functional MRI on the offspring of ADHD parents at 25 years during a modified Eriksen flanker/Go/No-go task and VBM have been used to study volume differences of offspring. Prenatal smoking and lifetime ADHD symptoms were determined using parent interviews at the offspring's age of 3 months and over a period of 13 years. Novelty seeking was assessed at 19 years. Young adults without current psychopathology followed since birth participated to show that children prenatally exposed to nicotine exhibited a weaker response in aMCC, among other areas, showing that the NoGo compared to neutral stimuli presented a decreased volume in the inferior frontal gyrus. There was an inverse relationship between inferior frontal gyrus activity and ADHD symptoms and between aMCC activity and novelty seeking.

A major site of action of nAChR may be in subcortical sites, where they regulate DA release. Genetic studies show that nicotinic receptor mutations are in the alpha 3, 4, and 7 receptors. Exposure of the fetus to maternal smoking has a profound effect on the development of ADHD, which is associated with hyperactivity and impulsiveness. Moreover, adolescent girls with the inattentive form of severe ADHD are at higher risk to start smoking early and escalating it in comparison to males. To the extent that smoking in inattentive ADHD, but not hyperactive, is a causal factor, it suggests these patients are self-medicating their symptoms via nicotinic receptor mechanisms. AZD1446, a selective $\alpha 4\beta 2$ nAChR agonist, in a clinical trial showed improvement in executive function as measured with the Groton Maze Learning task, possibly reflecting the higher level of nAChR binding in dPCC and RSC that are engaged in spatial orientation. Behavioral inhibition, recognition memory, and delay aversion were assessed at different doses of mecamylamine, a noncompetitive nicotinic agonist. The low dose improved memory and reduced tolerance for delay. Mecamylamine increased participant-rated irritability and restlessness. ABT-089 was used to evaluate ADHD in a small trial of adult ADHD. Nicotine demonstrated procognitive effects. Although adverse effects associated with nicotine preclude its development as a therapeutic, a number of novel nAChR agonists with improved safety/tolerability profiles have been discovered. These include ABT-418 and ABT-089.

The DAergic system is under tight control by the cholinergic system and these systems cannot be viewed as independent. A transporter constitutive loss of ChT expression, mediated by genetic elimination of one copy of the Slc5a7 gene in mice (ChT+/−), leads to a reduction in basal extracellular DA in the NAc. Moreover, ChT heterozygosity results in blunted DA elevations following systemic nicotine. Prior administration of mecamylamine abolishes DA release, emphasizing these are presynaptic, nAChR-mediated responses. All of these effects were reversed and prevented by mecamylamine.

A common feature of ADHD and many of its comorbid syndromes appear to be reflected in deficits in urge control that is organized in MCC. Its role is in mismatch detection/conflict resolution, selecting among cognitive options and anticipation of cognitive processing. The urge-to-void is a relevant concept and is associated with inactivations in aMCC and activations in pMCC. The MCC integrates micturition and defecation into normal daily activities within the environment; MCC likely selects the social and environmental conditions under which micturition and defecation and other functions can be deployed. Incontinent patients engaged the entire MCC and likely a predominant fear site in aMCC and its connections throughout the cingulate gyrus. Thus lack of control of urges in incontinent patients may evoke fear and a high level of MCC activity. Scratching is another form of urge control, over itch. It evokes activity in aMCC and dPCC. Finally, scratching evokes activity in most of the pMCC, including cortex in the cingulate sulcus that contains the cCPMA. Urges are chiefly associated with actions that cannot be realized immediately and must be held in check until an appropriate time when they might be released. When patients become aware of having a full bladder, they experience an "urge-to-void," because they do not simply void the bladder, but employ coordinated mechanisms to withhold micturition until in an appropriate context. One postulate about ADHD is that deficits in urge control are associated with impulsivity and are a critical part of impulsiveness. This deficit appears to be an underlying feature of psychomotor syndromes including ADHD and likely contributes to cognitive/learning difficulties, hyperactivity, and social adjustment difficulties.

Connectivity patterns in cingulate cortex of patients have been studied with different methods. Networks based on covariance of gray matter volumes from 92 regions in ADHD exhibited altered global

organization reflected in more clustering or network segregation. Locally, nodal degree and betweenness were increased in the amygdalae in ADHD, but were reduced in cortical nodes in the ACC and PCC. In ADHD, networks reflect an emphasis on subcortical local connections centered around the amygdala at the expense of cortical organization, and children/adolescents with ADHD may be configured to respond impulsively to the automatic significance of a stimulus without having the cortical organization to regulate and inhibit amygdalar responses.

Resting-state fMRI in controls verified the presence of a negative relationship between activity in aMCC and in the DMN. ADHD-related compromises in this relationship occur with decreases in the functional connectivity between the ACC and precuneus/PCC. Changes in resting-state fMRI measures of global information processing (degree of the cortical hub) may have a central role in information integration along with DC. The magnitude of intrinsic activity (fALFF) and local connectivity (regional homogeneity) in young adults who underwent a WMT for 4 weeks showed increased DC in the cluster including pACC. Furthermore, the WMT increased fALFF in the cluster including the mPFC. The WMT also increased regional homogeneity in the cluster that included the precuneus and PCC among other areas. With resting-state fMRI in individuals who had been longitudinally and uniformly characterized with ADHD or not in childhood and again in adulthood (16 years after baseline assessment), intrinsic functional organization was measured in patients who had a persistent diagnosis in childhood and adulthood. In patients who met the diagnosis in childhood but not in adulthood, and in controls who never had ADHD, a positive functional correlation between PCC and medial prefrontal cortices was reduced only in patients whose diagnosis persisted into adulthood. Finally, most research focuses on the correlates of nonspatial mnemonic processes. Brain activation and functional connectivity for visuospatial working memory, however, in youths with and without ADHD, were performed with fMRI on an *N*-back test of working memory for spatial position. Those with ADHD showed greater activation in PCC and greater functional connectivity between the DLPFC and intraparietal sulcus and reduced prefrontal connectivity with MCC and PCC for the high load contrast.

Thus extensive ADHD research has implicated most parts of the cingulate cortex in multiple cognitive tasks and symptoms. Genetic and environmental associations are extensive and add to the complexity. The challenge will be to develop a multivariate analysis of variance model that integrates all of these findings and involves data reduction to identify the most important variables.

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