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Corpus Callosum in Attention Deficit Hyperactivity Disorder

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Graham Dupont and R. Shane Tubbs

39.1 Introduction

Attention deficit hyperactivity disorder (ADHD) is a complex neurobehavioral disorder featuring impulsivity, emotionality, varying degrees of inattention, issues with psychosocial adjustment and social cohesion, and hyperactivity. Many children with ADHD have issues with focusing on and completing tasks, causing learning issues in early education [1]. The focus of this chapter is the abnormal anatomy and physiology of the corpus callosum (CC) in ADHD. Further, this chapter aims to discuss the neurobiological causes of behavioral changes in children and adults diagnosed with ADHD; the alterations in brain development, structure, and executive function of the brain; and the neurophysiological differences in children diagnosed with ADHD versus a control group, as these topics pertain to the CC; lastly, the chapter aims to discuss changes in the CC following current treatments with dopamine transporter blockers and amphetamines.

G. Dupont (✉)
Department of Cellular and Structural Biology, Tulane School of Medicine, New Orleans, LA, USA
e-mail: gdupont4@tulane.edu

R. S. Tubbs
Department of Neurosurgery, Tulane School of Medicine, New Orleans, LA, USA
e-mail: rtubbs@tulane.edu

39.2 ADHD-Related Changes in Corpus Callosum Neurophysiology

Historically ADHD has been a controversial diagnosis due to its epidemic rise in rates of diagnosis in the last two decades in the United States, a hot topic in the media, to the point where some may argue it is an American disease that has led to the "medicalization of American childhood"—the cost of ADHD in the United States per year has been estimated to be $42.5 billion per year [2–4]. Certainly, there are genetic and sociocultural elements of ADHD, notably being that boys are diagnosed and medicated for ADHD in higher proportion and display more of the inattentive, peer-directed aggressive-type features of the disorder, compared to girls [5]. Neuroimaging studies have shown consistently that there is abnormal brain structure, function, functional co-processing and connectivity, and white matter growth [6]. Advanced MRI techniques have pointed to the dysfunction of prefrontal and striatal regions of the brain [7]. Of these brain regions, abnormal formation of the CC seems to have a strong effect on social behavior and cohesion amongst peers, as CC malformation can result in a wide array of neurodevelopmental issues such as bipolar disorder, dyslexia, Tourette syndrome, and autism spectrum disorders [8–11]. ADHD is highly heritable (70%), and there is current research that aims to understand the genetic factors of ADHD, via susceptibility genes [2].

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The textbook neuroanatomy of the CC has it split into wedges based on the parent brain region it serves. From rostral to caudal, there are the prefrontal, premotor and supplementary motor, motor, sensory, parietal, temporal, and occipital regions. The rostral-most region of the CC contains the highest population of unmyelinated axons and smaller-diameter fibers, which will increase in diameter as the CC continues caudally. Functionally these diameter changes allow integration of higher-order prefrontal cortical functions in the rostral CC and higher conduction velocities in the mid-CC [12]. There is a varied consensus in ADHD-related CC abnormalities, as several studies report reduction in CC mass rostrally, with others reporting caudal reduction [8, 10, 12, 13]. The degree of brain lateralization, brain asymmetry, and CC size has been implicated in the development of ADHD.

Neurophysiological changes have been demonstrated by various authors; in particular a study on developmental trajectories of the subregions of the CC (I, prefrontal; II, premotor/supplementary motor; III, motor; IV, sensory; V, parietal, temporal, and occipital) by Gilliam et al. focused on the growth rates of these regions in right-handed children diagnosed with ADHD versus typically developing participants [12]. In right-handed children diagnosed with ADHD, region I (prefrontal) demonstrated the highest percent change per year (0.92%) compared to typical development (0.32%) [12]. There were no reported differences in CC surface area. Interestingly, there were no growth velocity differences found for growth rates in left-handed nor ambidextrous participants. These atypical CC growth patterns in ADHD can result in atypical cerebral lateralization in the prefrontal region of the brain, as evidenced by changes in EEG coherence, cerebral blood flow, and activation during cognitive tasks [14, 15]. Growth rates in regions II–V, however, were lower in the ADHD group, with a large difference in region IV compared with typical CC development [12]. In children, increases in the degree of impulsivity and hyperactivity are correlated with loss of rostral size in the CC [13].

39.3 ADHD, Lateralization, and Executive Function

Cerebral asymmetry and abnormal lateralization play an important role in the severity of ADHD, as mixed-handed individuals have a higher risk for developing ADHD and dyslexia. Further, non-right-handed individuals are far more likely to develop ADHD and to be considered “weaker students” [16]. Dysfunction in the right hemisphere and right striatal-parietal regions have been suggested to affect left motor function and spatial attention to the left visual field. In addition, children diagnosed with ADHD do poorly on tests involving maintaining attention and executive function, as well as tests designed to target interhemispheric processing [16]. Neuroimaging studies have suggested dysfunction in the anterior cingulate, dorsolateral prefrontal, and ventrolateral prefrontal cortices, in addition to the striatal-parietal and cerebellar regions of the brain [17].

39.4 Brain Mapping Patients with ADHD Versus Control

Dickstein et al. summarized activation patterns obtained from various neuroimaging techniques (PET, fMRI, EEG) in the brains of children, adolescents, and adults diagnosed with ADHD and control groups using an analytical technique called activation likelihood estimation (ALE), which detects the above-chance convergence of activation probabilities across multiple neuroimaging studies, of which a total of 134 foci of activation were studied in the ADHD group and 180 for the control group [17]. As a baseline, the control group demonstrated elevated probabilities of activation for frontal and posterior (anterior cingulate cortex, left dorsolateral prefrontal cortices, bilateral inferior prefrontal cortices) regions of the brain, as well as the thalamus, claustrum, insula, striatum, and parietal lobe. Patients with ADHD demonstrated increased probability of activation patterns in the middle frontal gyrus, frontal lobe, and left ventral prefrontal cortex (bilateral in controls), bilateral thalamus, and

right putamen and globus pallidus [17]. When comparing the ADHD and control groups, the results were consistent with the consensus on ADHD, that being hypofrontality; control groups had higher probabilities of activation in the frontal and parietal lobes compared to those diagnosed with ADHD. Patients diagnosed with ADHD demonstrated higher probability of activation in the insular cortex, middle frontal gyrus, and left thalamus [17].

Current research is consistent with functional hypoactivation of the frontal and cingulate areas, as well as morphological and structural differences in the CC. In addition to hypoactivation, patients with ADHD display reduction in total cerebral volume, as well as the parietal lobe, basal nuclei in right caudate, putamen, and CC, respectively [18]. Fractional anisotropy (loss of white matter density, diameter, myelination) reduction in the CC is also seen in patients diagnosed with ADHD [19]. The CC is certainly implicated in ADHD; yet, it is one small piece of the puzzle, and currently researchers are adapting a multi-neurophysiological network model of ADHD that encompasses the dopaminergic and fronto-striato-cerebellar system which corresponds to cognitive tasks and executive function, the limbic system which corresponds to emotionality associated with ADHD, and the cortico-striato-thalamic-cortical circuit that regulates sensorimotor, cognitive, and limbic processes [18]. Reduction in inhibitory control is a hallmark of ADHD, and due to abnormal growth in striato-frontal-cingulate areas [20, 21].

39.5 Default Mode Network and the Corpus Callosum

The default mode network (DMN) in the brain is a resting process that governs basic consciousness, cognition, and behavior and is contained within the medial prefrontal cortex, posterior cingulate cortex/precuneus, and the medial, lateral, and inferior parietal regions [22]. The DMN is more active during rest, and activity decreases during focused cognition [23]. There is not yet a direct connection between the DMN, the CC, and the ADHD; however dysfunction of the DMN and diagnosis of ADHD are highly intertangled and have had a wide body of support grow in the last two decades [24–26]. DMN dysfunction in children with ADHD can result in brain maturational delay and result in difficulties in learning, completing tasks, and social cohesion. It has been suggested that children with ADHD may in fact not struggle with tasks due to DMN dysfunction during rest but that the DMN fails to attenuate when changing from rest- to task-oriented brain programs [27]. Interestingly, Mitaki et al. reported a case of a 29-year-old man with a reversible lesion spanning the entire CC that demonstrated disturbances in consciousness during the resting state and reduced functional connectivity between the posterior cingulate cortex/precuneus within the DMN, without resolution after disappearance of the lesion [28]. The CC appears to be a principal connecting point for the DMN, as demonstrated by Van Den Heuvel et al. and Greicius et al. [29, 30].

39.6 Methylphenidate Treatment and CC Reorganization

Methylphenidate (brand name: Ritalin) is a brain stimulant and a dopamine reuptake inhibitor, which increases the value of reward in children and adults diagnosed with ADHD and was found to enhance the neurophysiological value of reward, increase the levels of extra-cellular dopamine, and cause attenuation in the DMN [24]. Methylphenidate has an extreme therapeutic effect, as typically developing children are indistinguishable from those diagnosed with ADHD and being treated with methylphenidate [24]. Further, methylphenidate has been shown to increase fractional anisotropy in the CC, restoring and restructuring white matter in the brain [31]. A clinical study by Bouziane et al. demonstrated an age-based modulation of white matter in the CC, showing that children are more neuroplastic than adults receiving the same treatment with methylphenidate [31]. One of the hallmark studies by Castellanos et al. demonstrated an 8.9% increase in white matter volume in children

on a medication regiment for ADHD [32]. Across the board, studies have demonstrated that children without treatment have smaller cerebral and cerebellar volumes; therefore treatment with methylphenidate or other first-line brain stimulants is indicated in order to reclaim the white matter loss and disorganization [12–14, 24, 32]. Methylphenidate works by initiating a dopamine transporter blockade, which in turn increases synaptic and extracellular dopamine, and allows for higher stored dopamine release and dopamine signal amplification in a dose-dependent fashion [33]. This effect differs slightly from current lines of treatment, amphetamines, which block dopamine reuptake but promote synthesis of dopamine [34]. Both methylphenidate and amphetamines are highly therapeutic for patients diagnosed with ADHD, as the pathways that have been demonstrated to have reduced activity (cortico-subcortical) are mediated by dopamine [34].

39.7 Conclusion

Connections between ADHD and subregions of the brain are still being researched, and while there is an undeniable therapeutic effect from first-line treatment, further therapies and research may be called for in order to develop more comprehensive models of treatment for medication-resistant types of ADHD. There are sociocultural predictors for ADHD diagnosis that can be alleviated with perspective and educational shifts on how children and young adults ought to conduct themselves in Western society. There are certainly more ways to learn than decades ago, when many of the epidemic-like ADHD diagnoses took place, and coincidentally, education was not as capable of adapting to children with different styles of learning or with learning deficits. The interactions between ADHD/neurobehavioral disorders and Western society are a convergence of psychiatry and sociocultural, and it is helpful for the clinician to be aware of these topics when developing treatment goals for the patient.

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