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Neuroanatomic and Cognitive Abnormalities in Attention-Deficit/Hyperactivity Disorder in the Era of “High Definition” Neuroimaging

Argelinda Baroni, M.D¹ and F. Xavier Castellanos, M.D^{1,2}

¹The Child Study Center at NYU Langone Medical Center, New York, NY, USA

²Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

Abstract

The ongoing release of the Human Connectome Project (HCP) data is a watershed event in clinical neuroscience. By attaining a quantum leap in spatial and temporal resolution within the framework of a twin/sibling design, this open science resource provides the basis for delineating brain-behavior relationships across the neuropsychiatric landscape. Here we focus on attention-deficit/hyperactivity disorder (ADHD), which is at least partly continuous across the population, highlighting constructs that have been proposed for ADHD and which are included in the HCP phenotypic battery. We review constructs implicated in ADHD (reward-related processing, inhibition, vigilant attention, reaction time variability, timing and emotional lability) which can be examined in the HCP data and in future “high definition” clinical datasets.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most investigated, prevalent [1] and controversial conditions included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2]. ADHD is characterized by impairing and developmentally inappropriate levels of hyperactivity/impulsivity or inattention, or both. Like all psychiatric disorders, ADHD is highly heterogeneous, but its validity as a clinical entity is well supported [3] and the test-retest reliability of the DSM-5 criteria was found to be “very good” [4]. Nevertheless, in the absence of biomarkers, the diagnosis relies exclusively on subjective judgments which permit wide variations in prevalence [5;6]. Multiple psychological and neuroanatomic models of ADHD have been proposed but most studies in the field have been underpowered [7], which, combined with the limited spatial and temporal resolution of imaging approaches, have only allowed “approximate

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Correspondence to: F. Xavier Castellanos, MD, Center for Neurodevelopmental Disorders, The Child Study Center at NYU Langone Medical Center, One Park Avenue, 7th Floor, New York, NY, 10016 Francisco.Castellanos@nyumc.org.

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replications” [8]. Consequently, established facts regarding the neurobiology of ADHD are lacking.

Fortunately, psychiatric neuroscience is entering the era of “high-definition” magnetic resonance imaging (MRI) as heralded by the launch of the Human Connectome Project (HCP). The design of the HCP and its optimized methods set the stage for discovery of brain-behavior relationships in neurotypical young adults with remarkable anatomic fidelity. We assert that the full prospective sharing of the HCP data can provide templates to achieve more defined insights into the pathophysiology of clinical syndromes such as ADHD. Here, we highlight HCP features that support our optimism and briefly review clues to the neurobiology of ADHD and related conditions that we believe are currently most salient, while identifying some of the opportunities and gaps that remain.

The Human Connectome Project (HCP)

In 2010, the US National Institutes of Health awarded HCP grants to two consortia, one led by Washington University, University of Minnesota, and Oxford University (the “WU-Minn” HCP consortium) and the other by Harvard/MGH and UCLA (now USC) [9]. The MGH-USC consortium is exploiting a prototype 3.0 Tesla scanner with unprecedented gradient strength (300 mT/m) which is particularly beneficial for diffusion imaging [10]. As of July 22, 2014, data for 45 healthy controls scanned with these novel methods were available for download [<http://www.humanconnectomeproject.org/data/>].

The WU-Minn consortium was also provided with a prototype 3.0 Tesla scanner (with 100 mT/m gradient set) which has been dedicated to scanning 1200 individuals, ages 22-35, composed of 300 pairs of monozygotic or dizygotic twin pairs and their full siblings. The sample was designed to be broadly inclusive, with exclusions largely limited to severe psychiatric, neurological, endocrine or cardiovascular disease. Participants undergo two full days of assessment including four hours of scanning at 3 Tesla; they provide a broad array of phenotypic measures, as shown in Table 1. Wu-Minn HCP data are being made available to the scientific community on a quarterly basis; the 500 subject dataset was released in June 2014.

The HCP has attained multiple incremental advances in imaging resolution, quality and preprocessing that taken together represent a quantum leap in spatial and temporal resolution [9], as illustrated in Figure 1. Beyond providing spectacular resolution, HCP measures overlap substantially with the constructs delineated by the NIMH Research Domain Criteria Project (RDoC) <http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml> [11]. The explicit rationale for RDoC is to identify specific neural circuitry underlying typical and atypical behaviors and symptoms, with the goal of directing the search for treatment targets in multiple domains [11]. As shown in Table 1, HCP measures also incorporate many public domain NIH Toolbox instruments [12] and additional measures. The HCP provides an opportunity to perform unbiased data mining for detecting brain-behavior correlates in syndromes such as ADHD which can approximate a full “dimensionome” [13], the complete set of all dimensions relevant to ADHD symptoms. This utility is not limited to ADHD, but ADHD is well-suited to such a whole-brain dimensional approach because its syndromic

dimensions extend beyond the diagnostic category of ADHD, and because many of its underlying characteristics appear to represent quantitative traits in the general population [14].

Current Clues to the Neurobiology of ADHD

Magnetic resonance imaging has allowed investigators to relate traditional neurocognitive variables to variations in brain structure and function at the group level. The next generation of studies needs to address brain-behavior relationships at the level of the individual [e.g., 14] to attain clinical utility. Some of the traits that are eventually validated may be included in “the usual suspects,” i.e., constructs included in current models. However, the substantial heterogeneity found at every level of analysis and the lack of strong findings to date suggest that dimensions not currently under consideration will also turn out to be relevant. We anticipate that such surprises will emerge from analyses harnessing the survey of potentially relevant traits included in the HCP phenotypic battery [15].

The most studied models of pathophysiology of ADHD involve frontal-striatal-cerebellar circuits, associated with top-down, executive control deficits, and ventral striatal-limbic circuits, associated with bottom-up, reward-related and motivation deficit theories. These models have only partly been supported by structural and functional brain abnormalities in individuals with ADHD but reviewing this voluminous literature is beyond our scope. Instead, we highlight recent research directions, mostly validated by meta-analyses, which hold the greatest promise to support evolving models of pathophysiology. None of the results in the field are currently definitive, so all can benefit from more precisely defined anatomic specification, which can be gleaned from HCP-based methods, combined with statistically well-powered study designs [7].

Inhibition and Attention

Deficits in inhibiting motor responses and in vigilant attention have long been observed in patients with ADHD and have been linked to the symptom dimensions of hyperactivity/impulsivity and inattention, respectively. An imaging meta-analysis found distinct functional abnormalities in ADHD in these two domains [16]. For motor inhibition tasks, the most prominent hypoactivations in ADHD were found in right inferior frontal cortex (IFC) extending into the anterior insula, supplementary motor area, anterior cingulate cortex (ACC), caudate and thalamus [16]. By contrast, a range of attentional tasks highlighted ADHD hypoactivation in right dorsolateral prefrontal cortex, putamen, posterior thalamus, caudate tail, and parietal lobe [16]. At least for inhibition tasks, the clinical effects of stimulant medication are also likely mediated by actions on right IFC and anterior insula [17]. These areas are key hubs of the right-lateralized ventral attention network and are also key components of the fronto-parietal central executive network. As reviewed elsewhere [18], the patterns of interplay among these networks are candidate neural substrates for suboptimal behavioral and cognitive functioning in ADHD and related conditions. Improved resolution will provide greater individual subject delineation of these networks and more precisely formulated testable hypotheses. For example, a large community sample of siblings revealed that motor inhibition on the stop task is coheritable with dimensional ratings of ADHD [19]. Determining the heritability of the structural and functional

connectivity of the right IFC and anterior insula in the HCP sample would set the stage for future studies of affected probands and siblings in ADHD.

Structurally, decreased volume in globus pallidus, putamen, caudate and ACC in ADHD has been confirmed meta-analytically [20], consistent with the dominant model of fronto-striatal dysfunction [18]. Although all studies examined were cross-sectional, putamen/pallidal differences were found in children and ACC differences in adults, suggesting the possibility of developmental effects. Hand-traced group differences in caudate volume were more prominent in studies with greater proportions of untreated patients, suggesting the possibility that stimulant medication may have a normalizing effect [20]. However, a longitudinal examination of basal ganglia surface morphology in ADHD comprising ages 4 to 19 years in 270 patients and 270 age-matched controls failed to find any evidence of stimulant treatment on developmental trajectories [21]. Instead, Shaw and colleagues found the greatest differences in surface area of the ventral striatum. The typically developing controls exhibited continued expansion during the study period, whereas children and adolescents with ADHD showed steady contraction [21]. These results extend the only previous volumetric analysis of the ventral striatum in ADHD, which reported ~25% smaller volume in 42 children and adolescents with ADHD compared to 42 controls with a large effect size, albeit in mostly previously treated patients [22].

Reward-related Processing

Morphometric abnormalities in the ventral striatum square well with findings from functional imaging studies of reward anticipation. Abnormal reward sensitivity is considered a core element in ADHD pathophysiology [23] and ventral striatum underlies reward processing in animals and humans. A recent meta-analysis found ventral striatal hypo-responsiveness during reward anticipation in individuals with ADHD, in contrast to the response of neurotypical individuals, questioning the concept of ADHD as a simple extreme of a continuum of normal variability [24]. Showing a similar discontinuity, an fMRI study of neurotypical young adults showed activation in the right ventral and left dorsal striatum during reward anticipation in a classical conditioning paradigm, but no significant effects in the ADHD group. Conversely, upon receipt of rewards, never-medicated adults with ADHD demonstrated significantly greater responses in the ventral striatum bilaterally and in left dorsal striatum relative to controls [25]. Recently emerging resting-state functional MRI (fMRI) methods [26] have also been used to examine ventral striatal functional connectivity. A comparison of 64 neurotypical children and 35 children with ADHD found significantly increased functional connectivity of the ventral striatum and ventromedial prefrontal cortex in the ADHD sample [27], which correlated significantly with a measure of temporal discounting [28], an index of impulsivity [27]. In an aggregated multi-center open science sample of 247 children with ADHD and 304 controls (“the ADHD-200 sample” [29]), Tomasi and Volkow also detected abnormally increased functional connectivity of the ventral striatum and orbitofrontal cortex [30]. Future investigation of ventral striatal and related circuitry should reference HCP data on temporal discounting [15], while keeping in mind the complex nature of intertemporal choices [31;32].

In searching for mechanistic explanations of striatal dysfunction, radioligand-based studies have quantified dopamine transporter density in striatum, where it terminates the synaptic effects of dopamine. While patients with ADHD have, on average, higher striatal dopamine transporter density than healthy comparisons [33], the major determinant appears to be prior stimulant treatment. Drug naïve patients with ADHD have been found to have significantly lower dopamine transporter density, while the opposite holds in previously treated patients [33]. Increased striatal dopamine transporter density following stimulant treatment has been confirmed [34]. It increased 25% in 18 never-medicated adults with ADHD who were scanned before and after stimulant treatment for one year, in contrast to no change in 11 healthy controls who were rescanned without medication [34]. These data call into question the assumption that long-term efficacy of stimulants is primarily or exclusively mediated by striatal dopaminergic effects. We believe that neurochemical models of ADHD have been biased towards dopaminergic hypotheses because of investigators' ability to quantify multiple aspect of the striatal dopaminergic system. This "light under the lamppost" bias has persisted despite accumulating evidence implicating the noradrenergic system in modulating prefrontal cortical function [35]. While extending beyond the bounds of the HCP, we anticipate that novel ligands quantifying noradrenergic markers [e.g., 36] will play an increasing role in delineating the neurochemistry of ADHD in adults in the near future. Such approaches are unlikely to be used in children or adolescents, because of ethical protections. Those limitations support an initial focus on young adults with ADHD for studies that will link HCP methods to multimodal MRI combined with positron emission tomography [37].

Vigilant Attention and Reaction Time Variability

The most frequently used neuropsychological test in ADHD has been the continuous performance test (CPT) which targets deficits in vigilant attention [38;39]. A meta-analysis of vigilant attention studies implicated mainly right-lateralized circuits including dorsomedial, mid- and ventrolateral prefrontal cortex, anterior insula, and parietal areas [40]. As noted above, these areas are frequently linked to ADHD, but CPT fMRI studies in ADHD have been insufficient to support a specific imaging meta-analysis [16]. A meta-analysis of CPT neuropsychological studies found the largest effect sizes for children with ADHD vs. controls in omission errors, a traditional index of deficient vigilance, and reaction time variability (RTV) [41]. The suggestion that RTV should be studied in ADHD [23;42] resonated in the field, as confirmed by a recent meta-analysis of 319 studies in ADHD [43]. This impressive accumulation reported conclusively that both children and adults with ADHD exhibit increased RTV relative to healthy controls, but also found that increased RTV is present in other clinical conditions. Despite the lack of diagnostic specificity, RTV was found to be a stable feature of ADHD and other conditions which is robust to tasks and methods [43]. Increased RTV has become a major focus of recent research [44-51]. For example, building on the known heritability of both ADHD and of RTV, a twin study demonstrated that both ADHD and RTV are genetically related to theta-band phase variability [46]. This illustrates how prioritizing constructs based on their heritability may serve as a filter to accelerate the search for mechanistic clues.

Evidence of increased RTV in ADHD led to the formulation of a mechanistic hypothesis of default network interference [52]. Sonuga-Barke and Castellanos posited that deficient

regulation of the default network by cognitive control and attention networks underlies intrusions in their interplay that manifest as phasic lapses of attention or in impulsive behaviors. Abnormalities involving the default network in ADHD have been reported repeatedly [e.g., 29;53;54] but this hypothesis needs to be specified with greater resolution, spatially, temporally (i.e., network interactions are dynamic), and by specifying which component processes are expressions of which neural events. The broad range of fMRI tasks and extensive task-free (resting-state) scans in the HCP combined with an even more extensive battery of measures obtained outside the magnet will help delineate the structure and function of the default network and its large-scale partner networks.

Timing

Converging lines of evidence suggest that multiple aspects of timing-related dysfunction are involved in ADHD [55;56]. Individuals with ADHD present with impairments in motor timing, perceptual timing and temporal foresight, encompassing time intervals from hundreds of milliseconds to tens of seconds, up to years for deficient temporal foresight [55]. The most consistent deficits are found in sensorimotor synchronization, duration discrimination, reproduction, and delay discounting [55]. These deficits are accompanied by functional hypoactivation of areas typically associated with time processing, IFC, dorsolateral prefrontal cortex, supplementary motor area, ACC, basal ganglia, parietal regions and cerebellum [55;56]. Stimulants appear to improve some timing deficits and to normalize hypofunctioning of fronto-striato-cerebellar networks [55;56]. Unfortunately, the HCP phenotyping battery only includes one timing related measure, hypothetical temporal discounting [32].

Emotional Dysregulation

Emotional dysregulation is not considered a core criterion for ADHD, although it is reemerging as an important contributor to functional outcomes [51;57-64]. This fits with the notion that overlapping circuits underlie both attentional and emotional regulation [39;60]. The HCP is explicitly not a psychiatric sample, but its phenotypic battery includes multiple measures that can tap dimensional variation in mood, psychiatric symptoms, personality traits, social relatedness, psychological well-being, and perceived stress. All such measures could be fruitfully obtained from patients with ADHD-related symptomatology in future HCP-based studies.

Arousal, Sleep and Primary Functions

For the construct of arousal, both hypo- and hyper-arousal have been proposed and observed in ADHD, but whether the two poles of the arousal spectrum identify alternative neurobiological subtypes, or alternative manifestations of dysfunction in a single regulatory process, remains unknown. Arousal and vigilant attention are closely linked to disorders of sleep, which is related to ADHD in a complex manner [65]. Also worthy of closer reexamination are primary motor and sensory cortical systems which have been largely ignored in ADHD in behavioral studies but which emerge in neuroimaging studies [18].

Conclusions

ADHD is not likely to be determined by any single construct or a fixed combination of the constructs we have enumerated. We have argued that the HCP provides brain-behavior templates that can be applied to dimensional constructs, many of which are likely to be appropriate for ADHD and related conditions. Novel clustering algorithms have documented cognitive heterogeneity in both patients with ADHD *and* healthy controls [66;67]. Awareness of the extent of phenotypic variation among typically developing individuals further calls into question the traditional approach of contrasting patients and highly-screened healthy controls [68] and confirms the value of documenting the extent of such variation in non-clinical samples such as the HCP.

The twin/sibling design is particularly appropriate for revealing heritabilities of brain-behavior relationships. Heritable relationships can be prioritized in data-driven analyses, as they are likely to reflect neurobiological processes. Studies of unaffected siblings can also reveal intermediate results that validate dimensional findings in patients while avoiding confounds from treatment history or chronicity of illness. From the perspective of ADHD research, the launching of a Human Pediatric Connectome Project is urgently needed. In the meantime, application of the advances attained by the HCP to young adults with ADHD represents the next best step forward.

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Highlights

- ADHD is well characterized clinically but its neurobiology remains unclear
- The Human Connectome Project can provide high-definition brain-behavior templates
- Dimensions provided by HCP map well to current neurobiological hypotheses in ADHD
- Application of HD imaging methods to young adults with ADHD holds great promise

Figure 1.

The improvement in spatial resolution of the Human Connectome Project (HCP) data is illustrated for two separate individuals scanned at conventional “high resolution” (2 mm isotropic voxels) on the left and HCP “high definition” (1.25 mm isotropic voxels) on the right. Reproduced from Van Essen et al. [9] by permission.

Table 1
Cross-linkage between Research Domains Criteria Project (RDoC) and Human Connectome Project (HCP) measures

RDoC Domains	RDoC Constructs	HCP fMRI tasks overlapping with RDoC	Additional HCP measures related to RDoC Constructs
Cognitive Systems	Attention	Posner task variant	NT List Sorting *
	Working memory	N-back task	NT Dimensional Change Card Sort NT Flanker Task
	Cognitive (effortful) control	Category specific representation task Relations between features vs. matching	Penn Word Memory Test NT Picture Sequence Memory
	Declarative memory	Episodic retrieval task	NT Picture Vocabulary NT Oral Reading Recognition
	Language behavior	Sentence presentation; story presentation tasks	Visual measures Variable Short Penn Line Orientation Test NT Words in Noise (Audition) NT Odor Identification Task (Olfaction) NT Taste Intensity Test (Taste) NT Pain Intensity and Interference Surveys
	Perception	Retinotopic mapping	
Positive Valence Systems	Expectancy/Reward processing		Delay Discounting Fagerstrom Test for Nicotine Dependence Brethalyzer, urine drug screen, self-report of drug use
	Action selection	Gambling decision making task	
Negative Valence Systems		Valence judgments (IAPS pictures) task	
Arousal and Regulatory Systems	Arousal		NT Negative Affect Scales Short Penn Continuous Performance Test Pittsburgh Sleep Questionnaire
Systems for Social Processes	Circadian rhythms Sleep and wakefulness		
	Affiliation and attachment Social communication Perception and understanding of self		NT Psychological Well-being Scales NT Perceived Stress & Self-efficacy Scales
	Perception and understanding of others	Biological motion task	NT Social Relationship Scales
		Frith-Happe animations task Motor systems	Penn Emotion Recognition Test Motor systems

RDoC Domains	RDoC Constructs	HCP fMRI tasks overlapping with RDoC	Additional HCP measures related to RDoC Constructs
		Finger responses Motor strip mapping	NT Pattern Completion Processing Speed NT 9-hole Pegboard NT 2-min Walk Test of endurance NT 4-meter Walk Test of locomotion NT Grip Strength Dynamometry
			Personality Five factor model
			Intelligence Penn Progressive Matrices
			Psychiatric Symptoms and Life Function Achenbach Adult Self Report Semi-structured Assessment for the Genetics of Alcoholism
			Physical Function Hematocrit levels Menstrual cycle and hormonal status Thyroid stimulating hormone levels Hemoglobin A1C

Extracted from [15] and <http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml> [11].

* NT = NIH Toolbox measure