Characterizing cognition in ADHD: beyond executive dysfunction

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The hypothesis that Attention-Deficit/Hyperactivity Disorder (ADHD) reflects a primary inhibitory executive function deficit has spurred a substantial literature. However, empirical findings and methodological issues challenge the etiologic primacy of inhibitory and executive deficits in ADHD. Based on accumulating evidence of increased intra-individual variability in ADHD, we reconsider executive dysfunction in light of distinctions between ‘hot’ and ‘cool’ executive function measures. We propose an integrative model that incorporates new neuroanatomical findings and emphasizes the interactions between parallel processing pathways as potential loci for dysfunction. Such a reconceptualization provides a means to transcend the limits of current models of executive dysfunction in ADHD and suggests a plan for future research on cognition grounded in neurophysiological and developmental considerations.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by pervasive behavioral symptoms of hyperactivity, impulsivity and inattention, beginning in childhood [1]. Despite its high prevalence and associated lifelong impairment [2], ADHD remains controversial because of the use of psychostimulants for treatment of a ‘behavioral condition’ that is diagnosed subjectively [3]. The heritability of ADHD is, however, both substantial and solidly established. Although major risk genes have yet to be identified, several genes related to monoaminergic neuromodulation are confirmed as minor contributors to the overall phenotypic variance [4]. Moreover, there is robust evidence of structural, functional and neurochemical brain differences in ADHD, in regions that support vital cognitive functions [5]. Thus, a coherent and comprehensive model of the cognitive substrates of ADHD would be a highly desirable means of linking genetic, neurobiological and phenotypic levels of analysis, with the objective of improving diagnostic approaches and therapeutic options.

Such a model should eventually encompass ADHD throughout the lifespan. However, the ADHD literature is preponderantly based on children of elementary school age. As neuropsychological differences are most detectable at this age [6], this brief review will generally exclude studies on preschool-age children or adults, despite remarkable consistency between cognitive deficits across these wide age ranges. We defer attempts to synthesize initial efforts at linking cognitive and neuronal phenotypes to current candidate genes, all of which have minor effects at best [4]. Similarly, active areas of potentially related research, such as psychopharmacology [7] or neuroimaging [8,9], which have been recently reviewed elsewhere, are not covered, but will certainly contribute to fully integrated models. Our purposes here are to reassess currently dominant cognitive models of ADHD in light of empirical and conceptual challenges and to highlight an integrative model that incorporates emerging neuroanatomical perspectives. We believe that this approach will provide a more robust framework for the translational multidisciplinary efforts that are already underway in laboratories throughout the world.

Evolving cognitive models of ADHD

The explicit criteria for ADHD that were first codified in 1980 (see historical review in [10]) emphasized inattention as much as hyperactivity, based on robust objective evidence of behavioral inattention and performance deficits on a laboratory measure of attention, the continuous performance task [11]. However, when specific attentional processes were targeted (i.e. divided, selective, sustained), investigators failed to observe specific diagnostic deficits [12]. Based on parallels between ADHD symptoms and presumed cognitive deficits and those of patients with frontal lobe disorders, researchers expanded the scope of inquiry to higher-order cognitive processes thought to be sub-served by the frontal lobes such as inhibitory control, attentional regulation and working memory – constructs grouped under the rubric of executive function (EF) [13] (see Box 1). In 1997, Barkley proposed a comprehensive theory of ADHD with deficient inhibitory control as the core deficit that secondarily disrupts other EF processes [14]. The explicit testable prediction that inhibitory deficits and broad EF dysfunction should be observable in all children with ADHD, taking into account measurement error, established the EF deficit model as the dominant paradigm over the past.
decade and catalyzed a burgeoning literature [15–19], much of it focused on inhibition as the core deficit in ADHD.

Testing inhibition as the primary executive deficit in ADHD

Of several types of inhibitory processes, only executive motor inhibition has clear replicated evidence in ADHD [24]. The bulk of support derives from Go/No-Go tasks [25] and particularly, the Stop task [26] (see Box 2). Converging lesion and imaging studies pinpoint the right inferior prefrontal cortex as a crucial region for effective Stop task performance [27,28]. Additionally, evidence of familiality [29–31] suggests that the Stop task could be a useful intermediate phenotype (endophenotype) for delineating risk genes corresponding to a neuropsychologically distinct subtype of ADHD.

The usefulness of the Stop task is also apparently supported by a meta-analysis of 15 studies (nearly 1200 children) reporting significant longer Stop Signal reaction times (SSRT) in ADHD (Cohen’s effect size, d = 0.58) [18]. However, several potential confounds complicate the interpretation of this difference. First, children with ADHD also exhibit significantly slower RTs to Go stimuli (d = 0.52) which may disproportionately influence the calculation of the SSRT. Second, they demonstrate even greater Go stimulus RT variability (d = 0.72) which challenges the Stop task’s assumption of SSRT invariance and undermines the feasibility of using a tracking procedure to establish appropriate interval between Stop and Go signals to produce equal proportions of successful and failed inhibitions [18]. More generally, the Stop task imposes subtle but continuous demands on stimulus anticipation, response preparation, speed of stimulus processing, and the ability to hold task instructions online [27] and children with ADHD may be impaired in each of these processes [19,32,33]. The alternative of examining motor inhibition with the simpler Go/No-Go task may also be problematic. Electrophysiological studies of Go/No-Go tasks in ADHD, which allow a more precise dissection of effects, find nonspecific deficits that are not limited to No-Go trials [34–37]. Also casting doubt on the centrality of inhibitory deficits is the largest study of stimulant naïve boys (n = 75) with severe pervasive ADHD (Hyperkinetic Disorder) and matched controls (n = 70) which found strikingly similar rates of No-Go errors and mean Go RT on a computerized Go/No-Go task [38]. Thus, these counterfactuals fail to support the strong hypothesis of deficient inhibition as the primary cognitive deficit in ADHD.

Is executive dysfunction intrinsic to ADHD?

When meta-analyses are extended to the broader domain of executive function, a similar pattern of significant albeit moderate associations emerges. A meta-analysis comprising 83 studies and over 6700 subjects found associations between ADHD and executive dysfunction across all domains tested (i.e. planning, vigilance, set shifting, and verbal and spatial working memory) ranging in effect from d = 0.4–0.7 [19]. A meta-analysis focused on working memory examined a somewhat different subset of studies and detected stronger effects (d = 0.85–1.14) when spatial working memory manipulation was distinguished from simple storage [33]. Thus, manipulation of spatial working memory appears to offer the strongest evidence in ADHD, but direct comparison studies have not yet been conducted. As in the case of response inhibition, EF effects are difficult to interpret because most executive function tasks fail to control for potential confounds ascribable to more ‘primitive’ cognitive or physiologic processes [39]. Two recent studies highlight the seriousness of this issue by demonstrating that when non-executive abilities are accounted for by using appropriate control tasks, little evidence of executive dysfunction remains [38,40].

The modest pattern of associations between a range of EF deficits and ADHD is frequently interpreted as providing evidence for a broader/weaker variant of the Barkley EF hypothesis. This is the result of a failure to understand the prediction of pervasive deficits, which has not been adequately tested until recently. An
approximation of such a test was performed by pooling data from three different sites [41]. EF impairment was defined in terms of performance exceeding the 90th percentile cutoff (based on the control samples) on five EF measures. On any individual measure, between 16% and 51% of children with ADHD were classified as impaired. When multiple deficits were compared, only 31% of children with ADHD, versus 9% of controls, displayed pervasive impairment (deficits on 3 or more measures) [41]. Only 10% of ADHD children showed deficits across all five domains. By contrast, 21% of children with ADHD (and 55% of controls) were unimpaired on all five measures. This combined analysis recapitulates the conclusion that ‘EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD’ ([19], p. 1336). Although not yet examined in meta-analyses, growing evidence links EF deficits to the inattention dimension of ADHD, rather than to hyperactivity/impulsivity [42,43]. Clearly the strong predictions of the EF deficit hypothesis of ADHD are not supported.

Cognitive heterogeneity of ADHD: multiple pathway models
The cognitive literature is thus incompatible with the assumption of pathophysiological homogeneity – of a single core deficit. Researchers have responded by building models that accept heterogeneity [41,44,45] – in which ADHD is regarded as an umbrella construct with clinical value that subsumes multiple potentially dissociable but overlapping cognitive profiles. So far, too few studies include measures from different functional domains (EF, reinforcement/motivational, sensory/perceptual and motoric), so heterogeneity is largely inferred from independent studies each working within a particular functional domain.

One notable exception, designed by proponents of both camps, contrasted EF and motivational models using a Stop task and a Choice Delay task in which children chose between small immediate and large delayed rewards [46]. This collaborative study produced two crucial findings: first, choices of the small immediate reward (Delay Aversive) were uncorrelated with SSRT – suggesting that inhibitory deficits and Delay Aversion in ADHD were dissociable processes. Second, performance on either task was only moderately associated with ADHD but together correctly classified nearly 90% of children with ADHD. Similar results were found in preschool children with ADHD [47] and in a study of the mediating pathways between hydrocephalus and hyperactivity [48], highlighting that neither EF nor Delay Aversion models are individually sufficient to account for neuropsychological findings in ADHD.

Towards an integration of multiple pathway models
‘Hot’ and ‘cool’ executive functions
In considering potential synthetic linkages between EF and processes related to motivation such as underlie Delay Aversion, a line of work on the development of EF is particularly pertinent. Noting the functional differentiations within frontal cortices, Zelazo and Muller distinguish between more purely cognitive aspects of EF associated with dorsolateral prefrontal cortex (DLPFC) which are characterized as ‘cool’ as contrasted with relatively ‘hot’ affective aspects of EF associated with orbital and medial prefrontal cortex (OMPFC) [49,50]. In this schema, ‘cool’ EF is elicited by relatively abstract, decontextualized problems, such as most of the EF tasks tested so far in ADHD (e.g. [15,16,19,24,33]), including Stroop, flanker, Go/No-Go, Stop, continuous performance and working memory tasks, which focus on the ability to suppress automatic processes or prepotent responses and/or maintain task instructions or representations in working memory. ‘Hot’ EF ‘is required for problems that are characterized by high affective involvement or demand flexible appraisals of the affective significance of stimuli’ ([49], p. 455). Based on the inarguable association of moderately impaired performance on ‘cool’ EF tasks and ADHD [19], Zelazo and Muller proposed that ADHD should be considered a disorder of ‘cool’ EF [49]. We believe this may be premature, reflecting the preponderance of studies which have used just such a conclusion as a starting point. Rather, we propose that inattention symptoms may be associated with deficits in ‘cool’ EF, whereas hyperactivity/impulsivity symptoms will be found to reflect ‘hot’ EF deficits. This gives rise to the possibility that some individuals with ADHD will manifest primarily ‘hot’ EF dysfunction, whereas others will show mainly ‘cool’ EF deficits and others will have both types. For example, risky decision making in the Iowa gambling task – an index of ‘hot’ EF – was associated with hyperactivity/impulsivity symptoms but not symptoms of inattention, or ‘cool’ EF measures such as working memory or IQ [51].

The increasing literature on the impact of reinforcement contingencies on ADHD comprising 22 studies with nearly 1200 children was recently reviewed [52]. Although the range of approaches used in these studies is too disparate to allow quantitative meta-analyses, the authors highlight clear evidence of delay aversion, and some support for greater behavioral and lower psychophysiological sensitivity to reinforcements in ADHD [52]. Abnormalities or inconsistencies in maintaining instructional set (‘cool’) or motivational state (‘hot’) may also account for the substantial variability in responding that emerges in many cognitive tasks and in behavioral descriptions of ADHD [39] (see Box 3). In summary, whereas the literature surrounding executive dysfunction in ADHD has mostly focused on ‘cool’ EF with modest success, the presence of impairments in incentive, motivational and reward-related processing suggests that both ‘hot’ and ‘cool’ EF deficits should be assessed, with particular attention to developmental aspects and symptom subtypes [53–55].

Spiraling cortico-striato-thalamo-cortical circuits
A recent synthesis highlights the neuroanatomical substrates for interactions between motivational and cognitive processes as potential loci of dysfunction in various forms of psychopathology, including ADHD [56] (see Figure 1). Dysfunction of distributed cortico-striato-thalamo-cortical loops is implicated in all neurophysiological models of psychopathology. However, models of parallel reciprocal
Box 3. Intra-individual variability and ADHD

Ironically, one of the most consistent manifestations of ADHD is the high prevalence of ‘moment-to-moment variability and inconsistency in performance. Such response variability is the one ubiquitous finding in ADHD research across a variety of speeded-reaction-time (RT) tasks, laboratories and cultures’ ([45], p. 624). Such variability can be quantified by decomposing RT responses into the sum of a normally distributed random variable, \( \mu \) (Figure la), and an independent exponentially distributed variable, \( \tau \) (Figure lb), which accounts for the positive skew of ‘ex-Gaussian’ RT distributions (Figure lc). Children with ADHD who had almost identical \( \mu \) values to those of controls differed markedly from controls in the skew of the RT distributions and in the derived values of \( \tau \) (Figure ld), yielding a remarkable diagnostic efficiency of 96% [60].

The implication that children with ADHD exhibit two distinct response modes, one of which is indistinguishable from normal responses, affects the interpretation of all speeded cognitive tasks. For example, although subjects with ADHD are deficient in time-discrimination and/or time-reproduction tasks, most timing findings in ADHD are confounded with significantly greater variability, particularly on time-reproduction tasks [61–67]. In some cases, the increased variability is striking (e.g. F ratio of variances >300 for reproduction of 2 s intervals in one report [62]), supporting the conclusion that putative deficits in temporal processing cannot be evaluated straightforwardly without first accounting for increased variability. Intra-individual variability of Go-RT exhibits moderate heritability in ADHD [88]. Increased variability or inconsistency is encountered as a correlate of superior and dorsolateral prefrontal brain lesions in adults, but interestingly is not associated with inferior medial prefrontal lesions [89]. These regionally specific findings have been confirmed in healthy adult subjects performing a Go/No-Go task using event-related functional imaging [70].

Returning to boys with ADHD, fluctuations in RT at very low frequencies (between 0.02–0.07 Hz) that parallel oscillations in basal ganglia neuronal firing rates are significantly more prominent compared with controls [39]. Each of these pioneering studies requires replication, but they independently validate the notion that intra-individual variability in ADHD needs to be examined in more detail [39,69]. In some paradigms, intra-individual variability may have greater explanatory power than the hypothesized alternatives, such as inhibition or timing deficits. Alternatively, accounting for the quantitative effects of between-group differences in variability should provide greater statistical power in head-to-head tests of competing cognitive models.

loops have failed to address ‘how information can be transformed across functional regions to help implement the learning and adaptability that is necessary in the development of goal-directed behaviors’ ([50], p. 322). The delineation of complex non-reciprocal pathways consisting of striato-nigral- striatal and thalamo-cortico-thalamic networks provides the anatomic basis through which emotion/motivation related OMPFC pathways influence ‘cool’ EF DLPFC pathways, which, in turn, influence motor pathways [50]. The unidirectional nature of information flow through
the non-reciprocal components of these spiraling circuits suggests a hierarchy of emotion/motivation affecting cognitive processing which can regulate motor outputs and which appears to be particularly applicable to ADHD and related disorders. However, as Haber points out, ‘parallel circuits and integrative circuits must work together, so that the coordinated behaviors are maintained and focused (via parallel networks), but also can be modified and changed according to appropriate external and internal stimuli (via integrative networks). Indeed, both the inability to maintain and to focus in the execution of specific behaviors, as well as the inability to adapt appropriately to external and internal cues, are key deficits in basal ganglia diseases which affect these aspects of motor control, cognition and motivation’ ([50], p. 325). In contemplating Haber’s spiraling circuits through the cortico-striato-thalamo-cortical loops, we acknowledge the temptation to converge again on a single model, albeit one that links motivational, cognitive and motoric domains. Such an interpretation would be inconsistent with the existing data [46]. It would also miss the point that the Haber model highlights likely loci of neuronal vulnerability that are hypothetically linkable to dissociable cognitive profiles. For example, we hypothesize that OMPFC and ventral striatal differences will be implicated in Delay Aversion and abnormalities in sensitivity to performance incentives and environmental factors [52]. We expect that pervasive ‘cool’ EF deficits, which are present in a minority of children with ADHD [41], will be more closely linked to DLPFC, dorsal anterior cingulate and anterior striatal dysfunction. Developmental Coordination Disorder, which occurs in up to half of children with ADHD [57], should reflect abnormalities in premotor prefrontal cortex, dorsal striatum and cerebellum.

**Conclusion**

The EF/inhibition model of ADHD set the stage for an impending paradigm shift in the neuropsychology of ADHD. ADHD is undeniably associated with ‘cool’ EF deficits at a group level of analysis, but the predicted central role of inhibitory and executive deficits is not supported for a substantial proportion of children with ADHD. ‘Hot’ EF deficits have been examined less frequently and yet may be more relevant from the perspective of functional outcomes and real-world decision making. Additionally, the neuroanatomical substrates of cortico-striato-thalamo-cortical circuitry are now revealed to include spirals of one-directional information flow from ‘hot’ ventro-medial/orbitalfrontal/ventral striatal regions to even ‘cooler’ premotor and motor circuits. This neuroanatomical circuitry provides a framework within which to embed continuing exploration of functional differences in ADHD through behavioral, cognitive and neuroimaging approaches. Such analyses will be more effective if they take into account the potential effects of intra-individual variability in the interpretation of task results. Additionally, the analysis of such variability in ADHD is worthy of further study in its own right.

**Future directions**

In response to the incontrovertible heterogeneity of the disorder and its presumed multiple underlying psychopathological signatures, various multiple pathway causal models are being proposed [44,58]. However, before being able to distinguish between competing models with sufficient statistical power, the following tasks will need to be accomplished:

(i) Convergence on subsets of key psychometrically validated dimensional measures that encompass both ‘hot’ and ‘cool’ EF. In the absence of ideal measures, the cognitive batteries adopted by the NIH-funded MRI Study
of Normal Brain Development and the NIMH-funded International Multi-Center ADHD Genetics (IMAGE) Project are likely to serve as de facto standards over the next decade: the multidimensional datasets (high-resolution brain anatomy and high-resolution genotyping, respectively, plus cognitive datasets in both studies) will be made available to the wider scientific community starting around 2008.

(ii) The dissemination of standardized computerized batteries used by publicly funded consortiums should be made a priority for the respective funding agencies, as this would facilitate convergence on common methods and approaches. The resulting loose networks of investigators should function more as 'confederations' than as contracting-regulated bodies. Encouraging such developments will maximize flexibility in rapidly advancing fields, and have benefits of increased statistical power at relatively low costs.

(iii) As many investigators will continue to work independently, we will need to decompose candidate cognitive measures into their most fundamental component processes, with particular attention to the potential contributions of non-executive components by using appropriate control tasks when assessing executive function [38].

(iv) The largest effect in ADHD appears to be associated with tasks that require manipulation of spatial working memory [33]. The extensive knowledge of the neuronal substrates of spatial working memory in humans and animals, and the possibility of minimizing verbal confounds, make this construct close to ideal for integrative examination [45]. Individual studies in numerous centers examining genetic effects, neuroimaging correlates, symptom subtypes, and diagnostic co-morbidity patterns of working memory are either underway or have been recently completed. The next stage in cognitive and functional neuroimaging studies will need to contrast working memory, inhibition, decision-making and motor coordination in 'cool' and well as 'hot' contexts, as a means of constructing neurobiological dimensional profiles of ADHD and related disorders that would improve on current symptom-based distinctions.

(v) Accounting for the potential effects of differences in intra-individual trial-by-trial variability [39,59] on executive and non-executive tasks, including tasks of inhibition, timing performance, perceptual, physiological and motor processes requires a paradigm shift from focusing on point estimates of means and variability to attending to time-series analyses. This approach is unfamiliar outside the field of functional imaging, but it could provide a closer link to neurophysiological processes than traditional neuropsychological measures, at the same time as improving our estimates of the variance associated with such traditional constructs.

Iteratively and collaboratively developing such measures, techniques and approaches will accelerate the momentum towards a fuller understanding of the cognitive neuroscience of ADHD, its relation to molecular genetic markers, and how these play out in the brain as reflected by the next generation of neuroimaging studies.

Acknowledgements

The authors appreciate the assistance of Daniel Margulies in preparing the manuscript, Suzanne Haber for providing the figure, and Phil Zelazo for helpful comments on an earlier version. Supported by grants to F.X.C. from NIMH (MH066398), The Stavros S. Niarchos Foundation, NARSAD, and the Leon Lowenstein Foundation, Inc.

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