Recent Developments in Neuropsychological Models of Childhood Psychiatric Disorders

Erik G. Willcutta · Edmund J.S. Sonuga-Barkeb-e · Joel T. Niggf · Joseph A. Sergeantg

aDepartment of Psychology, Institute for Behavioral Genetics, and Center for Neuroscience, University of Colorado, Boulder, Colo., USA; bInstitute for Disorders of Impulse and Attention, University of Southampton, Southampton, UK; cChild Study Center, New York University, New York, N.Y., USA; dSocial, Genetic, Developmental Psychiatry Centre, Institute of Psychiatry, London, UK; eDepartment of Experimental and Clinical Psychology, University of Ghent, Ghent, Belgium; fDepartment of Psychology, Michigan State University, East Lansing, Mich., USA; gClinical Neuropsychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

Abstract
The number of studies on the neuropsychology of childhood disorders has increased exponentially over the past decade. We report the results of an initial meta-analysis of key neuropsychological constructs included in studies of nine of the most prevalent childhood disorders. Results indicated that the neuropsychological etiologies of each of these disorders is complex and multifactorial. No single deficit is necessary or sufficient to explain all cases of any disorder, but preliminary evidence suggests that disorders may be distinguished by profiles across multiple neuropsychological processes. Slow processing speed and increased response variability are ubiquitous across disorders, but somewhat distinct profiles emerge on different aspects of executive functions. Attention deficit/hyperactivity disorder and Tourette's disorder are most strongly associated with inhibitory difficulties, whereas difficulties with cognitive flexibility are most pronounced in groups with autism spectrum disorders and childhood-onset schizophrenia. Working memory difficulties are significant in most groups, but these weaknesses are largest in groups with learning disorders and childhood-onset schizophrenia. Future research is needed to clarify further the relations among these heterogeneous diagnostic phenotypes and complex neuropsychological processes to facilitate studies that link these weaknesses to specific etiological risk factors.

Introduction and Overview
The study of the neuropsychology of childhood disorders is at a fascinating point in its development. During the latter half of the 20th century, conceptual models were
Guided by the classical disease formulation set out in diagnostic manuals, or on neurological lesion models of neuropsychology influence. These approaches built on a unitary concept of the neuropsychology of psychiatric disorders, which implicated single core deficits and simple linear models of the pathways from originating cause to symptom expression and associated impairment. Consequently the search for common and shared core deficits has defined the paradigm and various unitary core deficit models have vied for supremacy in models of attention deficit/hyperactivity disorder (ADHD) [1], autism [2, 3], conduct disorder (CD) [4], and reading disorder (RD) [5].

More recently, there has been a major shift in research strategy and a new paradigm for the neuropsychology of childhood disorders is emerging. This is based on the growing realization that the disorders defined in diagnostic manuals are by and large not neuropsychologically homogeneous entities as suggested by the unitary models set out above. At a clinical level children with a common diagnosis by definition share important commonalities of symptoms and impairment. In contrast, at a neuropsychological level they may display quite varying profiles of weakness.

In this chapter we summarize results from a meta-analytic review of neuropsychological studies of nine of the most common childhood disorders. After reviewing evidence regarding the associations between each individual disorder and neuropsychological construct, the second half of the chapter focuses on questions regarding diagnostic and neuropsychological heterogeneity. The final section of the chapter then summarizes the implications of these results for future neuropsychological models of childhood disorders and highlights several important directions for future research.

Why Study the Neuropsychology of Psychopathology?

Virtually all mental disorders are necessarily defined based on observable or reportable behaviors. From a clinical perspective, the validity of a diagnosis hinges on a straightforward question: do the behavioral symptoms of the disorder impair an individual’s functioning sufficiently that the risks of not treating outweigh the risks of treating? Previous studies have demonstrated that each of the disorders described in this chapter is valid in this sense [for a description of studies of the validity of ADHD see, 6].

Whereas a significant association with functional impairment is sufficient to demonstrate the validity of a disorder for clinical purposes, the validity of a behaviorally defined disorder will always be constrained by potential rater biases and other difficulties inherent in the measurement of behavior. The long-term objective of research on psychopathology is to understand all disorders at each of the four levels of analysis described by Pennington [7]: (1) behavior; (2) neuropsychology/cognitive processes; (3) brain development, and (4) etiology. Although the field is not yet at the
point at which etiological or neuropsychological markers can be identified that reflect
the diagnostic categories in the DSM-IV, neuropsychological assessment and its find-
ings have already inspired new literature suggesting intervention for children with
particular neuropsychological profiles [8, 9]. Thus, clinical practice is already moving
outside the behavioral classifications of the DSM-IV to recognize neuropsychological
profiles as useful clinical tools in some instances. Yet there is considerably more
potential here. Neuropsychological research has the potential to facilitate important
advancements in these areas by helping to pinpoint the specific neural systems and
processes which are compromised in childhood disorders, enabling more effective
applications of interventions.

Neuropsychological methods may also be helpful to understand the pervasive
diagnostic heterogeneity that characterizes many of the disorders and overarching
behavioral categories defined in the fourth edition of the Diagnostic and Statistical
Manual of Mental Disorders, Text Revision (DSM-IV-TR) [10]. Here we focus on
neuropsychological studies of diagnostic subtypes and comorbidity between different
disorders, but a similar approach could be used to assess the impact of heterogeneity
as a function of age, sex, socioeconomic status, or other variables of interest.

A Meta-Analytic Review of Neuropsychological Studies of Childhood Disorders

Overview
Over 400 studies have examined the neuropsychology and neurophysiology of
ADHD alone, and hundreds of additional studies have tested the neuropsychological
functioning of individuals with other developmental disorders. The sheer volume of
the extant literature precludes a comprehensive review of all of these measures and
constructs in anything less than a book length account [for overviews see, 11, 12].
Therefore, we focus here on five constructs that are important components of the
most prominent theoretical models of ADHD and other childhood disorders. These
constructs are executive functions (EFs), delay aversion, modulation of behavior in
response to reward and punishment cues, response variability, and overall cognitive
processing speed. To synthesize the extensive literature on the relations between these
constructs and ADHD, our group and several others have completed meta-analytic
reviews of published studies that administered measures of at least one of the con-
structs to groups with and without ADHD [13–21]. For this chapter we updated pre-
vious meta-analyses of ADHD by adding studies published since the initial reviews
were completed and measures that were excluded from the initial reviews.

In addition to updating the ADHD meta-analysis, we also review studies of these
five neuropsychological constructs in eight clusters of disorders with a modal age of
onset during childhood or adolescence. These disorders include other disruptive
behavior disorders such as oppositional defiant disorder (ODD) and CD, anxiety dis-
orders, autism spectrum disorders, childhood-onset schizophrenia (COS) and other
psychoses, juvenile bipolar disorder, major depressive disorder (MDD), learning disorders (LD), and Tourette’s syndrome (TS)/tic disorders. Due to space constraints we do not include a comprehensive review of other neuropsychological constructs that are important for childhood disorders, such as motor skills, basic learning and memory processes, and speech and language abilities, but we describe the key results for these domains in the text.

In the initial section of the chapter we briefly describe the theoretical and empirical foundation of each of the five neuropsychological constructs, then summarize the results of studies of each disorder that included measures relevant to the construct (fig. 1; table 1). All of the results in figure 1 and nearly all of the results in table 1 are from studies of children or adolescents. If neuropsychological studies of children had not been completed for a specific construct, effects from adult samples were included and this was noted in table 1 (e.g., planning weaknesses in individuals with MDD). Studies of response to reward and punishment are not included in table 1 because these studies have used a wide range of tasks and experimental designs that are difficult
## Table 1. Meta-analysis of neuropsychological studies of childhood disorders: Effect size (d)\textsuperscript{a} of the mean difference between groups with and without each disorder\textsuperscript{b}

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Intelligence</th>
<th>Executive functions</th>
<th>Other cognitive processes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>response inhibition</td>
<td>working memory</td>
<td>set shifting</td>
</tr>
<tr>
<td>ADHD\textsuperscript{c}</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Anxiety</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Autism</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Bipolar</td>
<td>++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>MDD</td>
<td>++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>LD/RD</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>ODD/CD</td>
<td>++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>COS</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Tics/TS</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Symbols indicate the estimated mean effect size (d) \cite{159} for comparisons between groups with the disorder and comparison groups without a diagnosis. \textbf{0} = Null result with an effect size of \(<0.1\); \textbf{+} = small effect (d = 0.1–0.3); \textbf{++} = medium effect (d = 0.4–0.6); \textbf{+++} = large effect (d = 0.7–0.9); \textbf{++++} = very large effect size (d = 1.0–1.5); \textbf{+++++} = extremely large effect size (d = 1.6+).

\textsuperscript{b}The reference numbers below each estimated effect size indicate a representative subset of all studies which included that specific comparison. The full list of studies and effect sizes used to compute the estimates in the table is available from the first author upon request.

\textsuperscript{c}ADHD effect sizes are based on the studies summarized in figure 1.

\textsuperscript{d}Study of adults included because studies of children and adolescents have not been completed.
to combine for a pooled analysis [for a comprehensive review see, 16], and delay aversion is not included in table 1 because only two studies have included childhood disorders other than ADHD. Studies of these constructs are summarized in the text.

The studies included in table 1 are a comprehensive list if a construct has been included in a small number of studies (e.g., response inhibition in children with anxiety disorders). In contrast, for many measures it was not feasible to list all studies due to space constraints (e.g., inhibition and set-shifting in groups with autism spectrum disorders and processing speed in groups with LDs). In those cases the estimated effect size is based on all available published studies, and a representative subset of all publications are listed in the footnote (please contact the first author for the full list of studies, measures, and effect sizes used to calculate the overall effects listed in table 1).

Executive Functions
For the past decade, prominent cognitive theories have suggested that symptoms of ADHD, autism, schizophrenia, and other childhood disorders arise in part due to a weakness in EFs, cognitive processes that serve to maintain an appropriate problem-solving set to attain a future goal [1, 22–24]. In a simplified model of cognitive control and decision-making processes, EFs represent ‘top-down’ cognitive inputs that facilitate decision making by suppressing irrelevant information and thus maintaining information about possible choices in working memory, then integrating this knowledge with information about reinforcement probabilities in guiding action. Although executive control processes involve several distributed brain networks, studies of primates and neuropsychological, neuroimaging, and lesion studies of humans suggest that the primary neural circuit includes the thalamus, basal ganglia, and dorsolateral and ventrolateral regions prefrontal cortex [7, 25].

Many theoretical models of ADHD have invoked the notion of ‘executive control’ as a single unified construct that encompasses many potentially separable cognitive functions [24]. However, exploratory and confirmatory factor analyses of EF tasks and results of a recent functional MRI study suggest that EFs may be more accurately characterized as a collection of related but separable abilities [26–30]. All of these studies suggest that EF tasks can be subdivided into measures of response inhibition, working memory/updating, and set-shifting, and several studies also found evidence of separable dimensions of vigilance, planning, and interference control, depending on which measures were included in the factor analyses. As a result, some theories of ADHD have posited a more focal weakness in a specific aspect of executive control such as response inhibition [1].

EF and ADHD
A significant difference was observed between groups with and without ADHD in 64% of the 215 comparisons in the 97 studies included in the meta-analysis (fig. 1). The weighted mean effect size across all EF measures fell in the range considered a medium effect ($d = 0.54$, $95\%$ CI = 0.51–0.5), with the most consistent group
differences and largest effect sizes observed on measures of motor response inhibition (or response suppression), working memory, vigilance, and planning (weighted mean $d = 0.53–0.62$). Similarly, correlations between ADHD symptoms and dimensional EF measures are typically significant but small to medium in magnitude ($r = 0.15–0.44$) [29–32], and appear to be stronger for inattention symptoms than hyperactivity-impulsivity symptoms [30, 33, 34]. Taken together, these results clearly demonstrate that EF weaknesses are associated with ADHD in general, and inattention symptoms more specifically, but also indicate that the majority of the variance in ADHD symptoms is not explained by individual differences in EF.

EF and Other Childhood Disorders

Table 1 summarizes studies that administered EF tasks to groups with other disorders. Groups with each disorder exhibit significant weaknesses on measures of multiple EF domains, with corresponding effect sizes that are similar to those reported in the studies of ADHD. The most pervasive and severe EF weaknesses are exhibited by individuals with autism spectrum disorders and COS. Groups with high-functioning autism (HFA) perform worse than a comparison group on all EF measures, with the largest deficits on measures of planning and cognitive flexibility (set shifting). Groups with COS also exhibit pronounced weaknesses on measures of set-shifting, along with significant impairments in working memory and vigilance. In contrast, individuals with COS exhibit a much milder weakness on measures of motor response inhibition such as commission errors on a continuous performance test [35].

In contrast to the results for HFA, COS, and ADHD, EF weaknesses are milder and less consistent in groups with juvenile bipolar disorder, ODD/CD, and TS or other tic disorders. Moreover, in many studies the moderate EF weaknesses in these groups are due to comorbidity with ADHD, an issue that we discuss in more detail later in the chapter.

Studies of adults suggest that MDD may be associated with significant weaknesses in several EF domains, and one published study found that children with MDD exhibited weaknesses in vigilance, fluency, and interference control [36]. In contrast, initial studies suggest that anxiety disorders are not associated with EF weaknesses in most domains, with the possible exception of difficulty shifting cognitive set. These initial results are intriguing and fit well with theoretical models of internalizing disorders, but all require replication in additional samples of children and adolescents.

One of the most surprising findings from the past 5 years has emerged in studies of EF tasks in samples with RD [29, 30, 37]. The phonological deficit theory of RD is arguably the most compelling single-deficit theory for a childhood disorder. The phonological model suggests that reading difficulties occur due to a weakness in the ability to recognize and manipulate phonemes, the units of sound that are combined to form words [5, 7]. Individual differences on measures of phonological processing often account for over 50% of the variance in reading ability [38], and the effect size of the difference between groups with and without RD is large ($d = 1.5–2.5$) [30].
Phonological skills strongly predict early growth in single-word decoding abilities and a wide range of long-term academic outcomes [39], and the best validated treatments for RD improve reading ability by providing focused instruction and practice to improve phonological processing skills [40].

Against this historical background, initial studies that reported EF weaknesses in groups with RD suggested that these effects might be a secondary consequence of the linguistic impairments that characterize groups with RD [29]. Contrary to this hypothesis, however, more recent studies have consistently found that groups with RD exhibit weaknesses on a range of EF measures, including spatial working memory tasks that are specifically designed to minimize the extent to which they can be verbally encoded ($d = 0.7–1.1$) [30, 41, 42]. Therefore, these unexpected but consistent results across several studies suggest that RD is associated with significant EF weaknesses that are not simply a secondary consequence of a deficit in another domain.

In summary, these studies suggest that weak executive control is a ubiquitous correlate of nearly all childhood disorders. In contrast, EF weaknesses are neither necessary or sufficient to cause any of the disorders included in this review, and are instead one important component of the complex neuropsychology of childhood disorders.

Motivational Dysfunction

There has recently been renewed interest in the role of motivational dysfunction in ADHD and other childhood disorders [43]. Studies that manipulated reward and punishment contingencies have reported mixed results for ADHD and ODD/CD [for a comprehensive review of studies of ADHD see, 16]. Some studies found that response contingencies improved or normalized task performance in individuals with ADHD [44, 45], whereas several others found a main effect of reinforcement or response cost on the task performance of all groups, but no differential effect on individuals with ADHD or ODD/CD [46]. A third line of research found that when both reward and punishment were possible outcomes (i.e., one possible response received a reward and one response resulted in a penalty), individuals with elevations in ADHD or CD symptoms exhibited higher rates of impulsive behavior, whereas no group differences were detected in the condition with response-cost alone [47, 48]. Finally, several studies found that children with ODD or CD were more likely to continue to pursue a reward even when task probabilities indicated that punishment was becoming increasingly likely, consistent with the hypothesis that individuals with CD may be oversensitive to reward cues [49–51].

Taken together, these studies tentatively suggest that in contrast to children without ADHD or ODD/CD, individuals with ODD/CD may be differentially sensitive to reward and punishment cues in the environment. These studies do not rule out the possibility that ADHD may arise from motivational dysfunction, but the mixed results provide little conclusive support for this association with the possible exception described in the subsequent section.
Delay Aversion

An intriguing variant of the motivational hypotheses is the delay aversion model which suggests that children with ADHD have a motivational style that leads them to find delay extremely aversive [52, 53]. The model suggests that this style leads individuals with ADHD to make choices that will minimize delay even when presented with other options that take longer to complete but maximize long-term gains. Furthermore, if there is no choice except to tolerate the delay (for example, during a boring classroom session of a fixed duration), delay aversion may then be expressed as increased activity or inattention.

The delay aversion theory is grounded in the neurocircuitry of catecholamine-modulated brain reward circuits [54, 55]. These circuits are functionally segregated from the executive circuits described above and link the ventral striatum (in particular the nucleus accumbens) to frontal regions (especially the anterior cingulate and orbito-frontal cortex), reciprocated via the ventral pallidum and related structures through the thalamus. The amygdala is also implicated in this system, possibly playing a role in defining the motivational significance of incentives [56], and dopamine is a key neuromodulator [57]. This circuit is specifically implicated in signaling rewards, coding incentive value and regulating other behavioral processes involved in the maintenance of responding under conditions of delayed rewards [54]. The delay aversion model suggests that children with ADHD have fundamental impairments in the neural signaling of delayed rewards that lead to steeper discounting of the value of delayed rewards, leading the child to choose smaller reinforcers that will be delivered soon rather than larger rewards that will be delivered after a delay ([for a rat model relevant to the discounting of delayed rewards see, 58]).

Ten studies have tested the delay aversion theory by assessing how often children with and without ADHD select a small immediate reward rather than a larger delayed reward on simple laboratory choice tasks (fig. 1) [for a description of the meta-analysis of delay aversion see, 59]. The effect sizes for the two delay aversion measures (mean $d = 0.57$ and 0.71) are similar to the most discriminating EF tasks described in the previous section, albeit on a much smaller number of studies to date. Thus, although the magnitude of these effects suggests that delay aversion is also neither a necessary nor sufficient cause of all cases of ADHD, delay aversion and EF may contribute to a comprehensive model of ADHD and its cognitive heterogeneity.

Few studies have examined delay aversion in groups with disorders other than ADHD. One recent study of HFA and ADHD found that the group with ADHD was more likely to make the choice to minimize delay than the group with HFA and the control group, whereas the group with HFA did not differ from the comparison group [60]. Moreover, studies of several different disorders in adults have examined individual differences in delay discounting, a measure of the extent to which the subjective value of a future reward is reduced as a function of the delay before it will be received [61]. One study found that adults with schizophrenia had a significantly steeper
delay-discounting function than a control group without each disorder [62], indicating that the group with schizophrenia devalued future rewards more than individuals without the disorder. Similar results have been reported in studies of adults with substance abuse disorders and undergraduate students with significant social anxiety [63–65].

In summary, delay aversion appears to be an important component of the pathophysiology of ADHD, and a similar construct has shown promise in studies of adults with a range of disorders. In contrast, children with autism do not exhibit significant delay aversion, providing important support for the discriminant validity of the construct. Future research is needed to compare groups with ADHD to other groups that might be predicted to find delay especially aversive, such as ODD/CD and bipolar disorder.

Response Variability
Perhaps the most ubiquitous result in neuropsychological studies of childhood disorders is the finding that the reaction times (RTs) of individuals with a disorder tend to be slower and more variable than those of individuals from a comparison group [66–70]. Most previous studies have quantified response variability as the standard deviation or standard error of an individual’s RT across all trials on a task, whereas more recently several authors have suggested that one of several more sophisticated analytic procedures may be optimal for the analysis of the complex temporal patterns present in RT data collected over hundreds of trials [66, 71, 72].

Differences between groups with and without ADHD replicate consistently even when the primary dependent measure is a relatively coarse measure such as standard deviation of RT [for review of 33 of 39 studies see, 67], and the mean effect size in these studies is comparable to or larger than the effects observed for EF tasks (weighted mean d = 0.71; fig. 1). Although fewer studies have examined response variability in other disorders, the results of the current meta-analysis suggest that all childhood disorders included in this review are associated with increased response variability with moderate to large estimates of effect sizes (table 1).

Until recently, interpretation of increased response variability was complicated by the absence of an explanatory theoretical model [43, 73]. An initial parsimonious hypothesis suggested that RT variability might simply be an inevitable consequence of slower overall response speed, and many studies have confirmed that measures of intra-subject variability are typically correlated with mean RT [67]. However, a closer analysis of individual trials revealed that increased response variability is due to a relatively small number of long RTs, a finding that is consistent with the possibility that these trials reflect momentary attentional lapses rather than slow RTs on most trials [66, 71]. Further support for this hypothesis is provided by studies that found that mean RT did not explain the relation between response variability and important external measures such as symptoms of psychopathology and performance on other cognitive measures [67, 74].
Taken together, these findings underscore the need for improved models of the pathophysiology of response variability. Recent theoretical models have proposed that increased response variability may be due to momentary attentional lapses that result from weak executive control [74] or interference from a ‘default-mode’ network that produces low frequency neuronal oscillations when the brain is in a resting state [66, 73]. Other models have suggested that increased variability may reflect chronic under-arousal or inconsistent regulation of arousal [75, 76], deficient extinction processes [58], or dysfunction in short-duration timing mechanisms [77, 78]. Finally, one of the most elaborated models incorporated neuropsychological data, psychopharmacological manipulations, and neurocomputational models to support the hypothesis that weaknesses in executive control may reflect reduced striatal dopamine, whereas increased response variability may be due to an independent process that is attributable to noradrenaline dysfunction [79].

The existing literature conclusively shows that response variability is associated with nearly all childhood disorders, and the initial success of new approaches suggests that additional research will be of considerable interest. Of particular importance will be studies that also measure constructs such as EF, delay aversion, and response to motivational contingencies, providing a direct test of whether response variability is independent of these other processes, interacts with weaknesses in one or more of these domains, or is simply a secondary consequence of another dysfunctional process.

**Cognitive Processing Speed and Alerting**

Along with increased response variability, groups with each childhood disorder included in this review exhibit general slow processing speed in situations in which responding quickly is important. Effect sizes are large for most disorders, with somewhat smaller effects for ODD/CD and anxiety disorders.

No theoretical model of a childhood disorder explicitly posits processing speed as a single core weakness that is a necessary or sufficient cause, although lowered cortical arousal is the most parsimonious neuropsychological explanation. Consistent with a low arousal hypothesis is the vigilance weakness on the continuous performance test that is present in nearly all groups (table 1), as well as consistent findings of increased slow wave activity on brain electrical recordings in individuals with ADHD [80]. Alternatively, slow response time could be attributed to poor response activation, a distinct process linked to left lateralized processing [81]. In either case, the magnitude and consistency of these effects indicates that a comprehensive model of the neuropsychology of ADHD must explain slowed processing. Future research is needed to test whether slow processing speed is related specifically to other measures of arousal, vigilance, activation or alerting, and then whether those domains account for findings in the realm of executive control, aversion to delay, or response variability.
Initial Conclusions from Neuropsychological Studies of Childhood Disorders

The results summarized in this section confirm that groups with childhood disorders differ from groups without a diagnosis in multiple neuropsychological domains, with average effect sizes that are medium to large (d = 0.30–0.80). These effect sizes are sufficiently large to be important for etiological theories of the disorders, but are not large enough to identify DSM-IV categories of children with adequate sensitivity and specificity.

Similar to studies of adult disorders [82], the nine childhood disorders included in this review are characterized by a generalized neuropsychological weakness across a range of cognitive processes, including intellectual ability, multiple aspects of executive control, processing speed, and response variability. In addition, the results of the meta-analysis provide tentative support for distinct neuropsychological profiles across disorders. For example, the largest effects for ADHD and Tourette’s disorder were reported on measures of response inhibition, response variability, and processing speed, whereas cognitive flexibility appears to be relatively spared in these groups [83]. In contrast, groups with HFA and COS exhibited pronounced weaknesses on measures of cognitive flexibility and planning, but were less impaired on measures of response inhibition. Individuals with LD/RD were most impaired on measures that involved retention and rapid processing and manipulation of information, and groups with mood disorders and ODD/CD exhibited moderate nonspecific weaknesses on most tasks.

We discuss the implications of the similarities and differences in the neuropsychological profiles of the disorders in more detail later in the chapter. First, we briefly review studies of the impact of comorbidity, the co-occurrence of two or more distinct diagnoses in the same individual, on the neuropsychological profile of each disorder. These results help to clarify which neuropsychological weaknesses are independently associated with each disorder, providing important information regarding the interpretation of clinical heterogeneity in theoretical models of childhood disorders.

Comorbidity

Comorbidity is clearly the rule rather than the exception for DSM-IV-TR disorders in childhood and across the lifespan. For example, 70–90% of individuals with DSM-IV-TR ADHD meet criteria for at least one comorbid diagnosis [84, 85]. Disorders comorbid with ADHD include other disruptive behavior disorders (ODD 30–60%; CD 20–50%), LDs (20–40%), anxiety disorders (15–30%), and depression (15–30%) [84–88]. Rates of comorbidity are even higher when ADHD is assessed in groups that were first identified due to a diagnosis of Tourette’s disorder (40–60%) [89, 90], COS (>80%) [91], or bipolar disorder (50–90%) [92].
These striking results clearly indicate that in addition to explaining the symptoms of a specific disorder of interest, neuropsychological models of childhood disorders must also account for the high rates of comorbidity with other disorders. However, surprisingly few neuropsychological studies of childhood disorders have controlled for comorbidity or tested its impact. Therefore, in the remainder of this section we present new data and review previous studies that tested the implications of comorbidity. Because space constraints do not permit a comprehensive summary of results for all possible pairs of comorbid disorders, the review is restricted to studies that examined comorbidity between ADHD and the other eight disorders.

The results summarized in tables 2 and 3 address two main questions that arise if a disorder is associated with a neuropsychological weakness when examined in isolation. The first question asks if a disorder is independently associated with the neuropsychological weakness after any significant comorbidity is controlled. If the effect is restricted to the comorbid group, it can be described more parsimoniously as a correlate of the comorbid disorder rather than as a neuropsychological weakness of the initial disorder per se. The columns on the left side of tables 2 and 3 summarize results from studies that addressed this first question for the neuropsychological constructs included in the meta-analysis.

Even if the initial disorder is associated with significant neuropsychological weakness when the comorbid disorder is controlled, the other disorder may still moderate this association. The columns on the right side of tables 2 and 3 summarize results of studies that tested if the relation between the primary disorder and neuropsychological performance was significantly stronger or weaker in the subset of individuals with the comorbid disorder.

Neuropsychology of ADHD after Controlling for Comorbidity

Because relatively few studies have systematically tested if the profile of neuropsychological functioning differs in groups with ADHD with and without comorbidity, we conducted analyses to test this question in the Colorado Learning Disabilities Research Center (CLDRC) twin sample, an ongoing study of the etiology of reading difficulties and ADHD [30]. Consistent with other community samples [93, 94], the majority of participants in our sample met criteria for the inattentive type (n = 214) or combined type (n = 95), and a much smaller proportion met criteria for the hyperactive-impulsive type (n = 39). Because results from our sample and others suggest that the hyperactive-impulsive type is not consistently associated with the neuropsychological weaknesses that characterize the inattentive and combined types [33, 95], the hyperactive group was excluded from these analyses. In addition, because the pattern of results was extremely similar for the inattentive and combined subtypes, these groups were combined to create a single ADHD group to simplify interpretation.

In our sample, the group with ADHD without RD exhibited weaknesses on nearly all neuropsychological measures in comparison to the control group (fig. 2a), indicating
Table 2. The effects of comorbidity on the neuropsychological functioning of individuals with ADHD

<table>
<thead>
<tr>
<th>Comorbid disorder</th>
<th>Studies that reported a significant ADHD effect when the comorbid disorder was excluded or controlleda (representative studies)</th>
<th>Studies that compared neuropsychological functioning in groups with ADHD with and without each comorbid disorderb (representative studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>All tested measuresc,d</td>
<td>The group with ADHD + anxiety was less impaired than the group with ADHD without anxiety on measures of response inhibition [130]</td>
</tr>
<tr>
<td>LD/RD</td>
<td>All measuresa [29, 30, 32, 37, 41, 151, 159]</td>
<td>The group with ADHD + LD/RD was more impaired than the group with ADHD without LD/RD on measures of verbal fluency (fig. 2a), response inhibition [29, 142], processing speed [151] (fig. 2a), response variability [37, 159], vigilance [142], and working memory [30, 159]</td>
</tr>
<tr>
<td>Bipolar</td>
<td>Speed, working memoryf [145]</td>
<td>After controlling for comorbid bipolar disorder, the ADHD effect was no longer significant on measures of processing speed [129], response variability [145], vigilance [145], and working memory [129]</td>
</tr>
<tr>
<td>ODD/CD</td>
<td>All measuresc [32, 60, 72, 121, 127, 136]</td>
<td>The group with ADHD + ODD/CD was more impaired than the group with ADHD without ODD/CD on measures of response inhibition [158] The group with ADHD + ODD/CD was less impaired than the group with ADHD without ODD/CD on measures of response inhibition [147], planning [136], and vigilance [121]</td>
</tr>
<tr>
<td>MDD</td>
<td>All tested measuresd</td>
<td>The group with ADHD + MDD was more impaired than the group with ADHD alone on measures of verbal fluency, response inhibition, processing speed, and working memory (fig. 2b)</td>
</tr>
<tr>
<td>Tics/TS</td>
<td>All tested measuresg [144, 152]</td>
<td>The ADHD effect remained significant in all studies [144, 152]</td>
</tr>
</tbody>
</table>

aAlthough no studies have directly tested for mediator or moderator effects of autism spectrum disorders or childhood-onset schizophrenia in groups with ADHD, multiple studies have shown that ADHD is independently associated with deficits on all of the measures that were significant in table 1 and figure 1 when individuals with autism or schizophrenia spectrum disorders were excluded.

bThe eight dimensions included in the table are fluency, planning, processing speed, response inhibition, response variability, set shifting, vigilance, and working memory. Delay aversion was not included in the table because few previous studies have examined the relation between ADHD and delay aversion while controlling other psychopathology. Interference control is not included because the initial main effect of ADHD was not significant in most studies.

c Results described in this chapter.

d No studies included a measure of planning.

f Results are summarized in figure 2.

g No studies included measures of delay aversion, fluency, or planning.

h Fluency and planning were not included in any study of tics/TS.
Table 3. Summary of studies that tested if the neuropsychological performance of other disorders differed as a function of comorbid ADHD

<table>
<thead>
<tr>
<th>Primary disorder</th>
<th>Studies that reported a significant effect of the primary disorder when ADHD was excluded or controlleda (representative studies)</th>
<th>Studies that compared neuropsychological functioning in groups with the primary disorder with and without ADHDb (representative studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Nonec [130, 134, 135]</td>
<td>The group with LD/RD + ADHD was more impaired than the group with LD/RD without ADHD on measures of response inhibition [29, 142], response variability [142, 159], vigilance [37, 142], and working memory [37]</td>
</tr>
<tr>
<td>LD/RD</td>
<td>All measures [29, 30, 41, 139, 142, 159]</td>
<td>The group with LD/RD + ADHD was more impaired than the group with LD/RD without ADHD on measures of response inhibition [29, 142], response variability [142, 159], vigilance [37, 142], and working memory [37]</td>
</tr>
<tr>
<td>Autism</td>
<td>Fluency, shifting, working memoryd [70]</td>
<td>After controlling for ADHD symptoms, the autism main effect was no longer significant on a measure of response variability [70]</td>
</tr>
<tr>
<td>Bipolar</td>
<td>All tested measurese [117, 124, 138, 145]</td>
<td>The group with bipolar disorder + ADHD was more impaired than the group with bipolar disorder without ADHD on measures of set shifting [138] and vigilance [138] After controlling for ADHD symptoms, the bipolar main effect was no longer significant on measures of set shiftinge [133], processing speede [145], response variability [145], or vigilanced [145]</td>
</tr>
<tr>
<td>ODD/CD</td>
<td>Variability, planningf, shiftingg, vigilance, working memory [46, 150, 156]</td>
<td>After controlling for ADHD symptoms, the main effect of ODD/CD was no longer significant on measures of processing speed [132], planningf [132, 133], response inhibition [121], or set shiftingf [51, 133]</td>
</tr>
<tr>
<td>Tics/TS</td>
<td>Inhibitiong [120]</td>
<td>After controlling for ADHD symptoms, the main effect of Tourette’s disorder was no longer significant on measures of verbal fluency [158], processing speed [144], response inhibitiong [97, 152], response variability [97], vigilance [152], or working memory [144, 158]</td>
</tr>
</tbody>
</table>

aNo studies have tested the effect of comorbid ADHD on the neuropsychological functioning of groups with COS or MDD.
bThe eight dimensions included in the table are fluency, planning, processing speed, response inhibition, response variability, set shifting, vigilance, and working memory. Delay aversion was not included because few previous studies have examined the relation between ADHD and delay aversion while controlling other psychopathology. Interference control is not included because the initial main effect of ADHD was not significant in most studies.
cNo simple main effect of anxiety was observed on measures of inhibition, planning, or processing speed. Measures of fluency, planning, and shifting were not included in any study of anxiety disorder that controlled for ADHD.
dPlanning, speed, and vigilance were not included in any studies that controlled for ADHD.
eNo studies included a measure of planning. In some studies the group with bipolar disorder without ADHD differed from controls on measures of processing speed, set shifting, and vigilance [112, 138], whereas in other studies these effects were explained by comorbid ADHD [133, 145].
fIn some studies the group with ODD/CD without ADHD differed from controls on measures of planning and set shifting [156], but these effects were explained by comorbid ADHD in other studies [51].
gThe main effect of TS on inhibition measures remained significant when ADHD was controlled in some studies [120] but not in others [97, 152].
that ADHD is associated with neuropsychological weaknesses that are independent of the influence of comorbid RD. On the other hand, the group with ADHD and comorbid RD performed more poorly than the group with ADHD without RD on nearly all neuropsychological measures in our battery. Similarly, several of the studies...
summarized in table 2 found that the group with comorbid RD scored lower than the group without RD on measures of response inhibition, vigilance, working memory, and naming speed (table 2). These converging results suggest that comorbid RD may be a marker for a subset of individuals with ADHD with more severe neuropsychological difficulties.

To our knowledge no published studies have examined the influence of comorbid mood disorders on the neuropsychological correlates of ADHD. Analyses conducted for this chapter indicated that the group with ADHD with comorbid MDD or dysthymia was more impaired than the group with ADHD alone on measures of response inhibition, working memory, and processing speed (fig. 2b). Although we did not predict this pattern of results when we initiated the study, it is consistent with studies that reported weaknesses in executive control in children and adults with MDD (table 1). This pattern is also similar to the pattern reported in studies of ADHD with and without bipolar disorder, the other major mood disorder included in the review (table 2).

In contrast to the results for MDD and RD, comorbidity with CD or anxiety did not significantly change the ADHD main effect on any of the neuropsychological composites in our sample (d between groups with ADHD with and without the comorbid disorder = 0.0–0.2). Most previous studies also reported no significant differences between groups with ADHD with and without anxiety or ODD/CD, and those that did report a significant difference usually found that the group with a comorbid anxiety or disruptive disorder performed better than the group with ADHD alone (table 2). Similarly, available studies suggest that comorbidity with Tourette's disorder does not influence the neuropsychological performance of groups with ADHD (table 2), and a number of studies have demonstrated that ADHD is associated with a range of neuropsychological weaknesses when individuals with autism or COS are excluded a priori at the beginning of the study.

These studies indicate that no single comorbid disorder can account for the neuropsychological weaknesses associated with ADHD. However, the possibility still exists that the neurocognitive correlates of ADHD might be explained by a combination of multiple comorbid disorders rather than by ADHD per se. We tested this hypothesis by analyzing data from the CLDRC twin sample [30, 96]. All participants with ADHD who met criteria for RD, CD, generalized anxiety disorder, separation anxiety disorder, MDD, or dysthymia were excluded from analyses (approximately 70% of the initial sample met criteria for at least one of these disorders). After excluding this extensive list of comorbid disorders the remaining participants had slightly less severe ADHD symptoms and neuropsychological impairment, but still differed significantly from the control group without ADHD on all of the neuropsychological measures listed in figure 2 (mean d across all neuropsychological tasks = 0.6–1.1 in the group with comorbidity and 0.4–0.6 in the group without comorbidity).
Impact of Comorbidity with ADHD on Neuropsychological Functioning of Other Disorders

Table 3 summarizes studies that tested whether the presence of comorbid ADHD affected the neuropsychological performance of groups with other disorders. Groups with RD/LD, bipolar disorder, and ODD/CD exhibited neuropsychological weaknesses that are independent of ADHD (table 3, left column), but several studies also found that children in the comorbid group exhibited greater impairment than the group without ADHD (table 3, right column). The most striking results were reported in studies of Tourette’s disorder, which consistently found that the neuropsychological weaknesses in groups with Tourette’s disorder were almost entirely restricted to the subset of individuals who also met criteria for ADHD [97].

Conclusions Regarding Comorbidity
ADHD is associated with a range of neuropsychological weaknesses that remain significant when comorbid disorders are excluded or controlled. Similarly, groups with RD, ODD/CD, and bipolar disorder exhibit neuropsychological weaknesses that are independent of ADHD, although the presence of ADHD is often associated with more severe impairment. In contrast, neuropsychological weaknesses in groups with Tourette’s disorder appear to be better explained by comorbid ADHD. Additional studies are needed to clarify the influence of comorbidity on the relation between ADHD and delay aversion, response variability, and response to reinforcement contingencies, and to test the influence of comorbidity between other pairs of disorders that do not include ADHD.

Conclusions and Implications for Theoretical Models of Childhood Disorders

Similar to findings for adult disorders [82], the nine childhood disorders included in this review are characterized by a range of neuropsychological weaknesses on measures of intellectual functioning, EFs, processing speed, and response variability, along with significant aversion to delay in groups with ADHD. Mean effect sizes are medium or large for most disorders (d = 0.4–0.8), indicating that each of these weaknesses is an important component of the overall neuropsychology of the disorder. On the other hand, the magnitude of these effect sizes and data from other previous studies [98] suggest that no single neuropsychological weakness is likely to be necessary or sufficient to cause all cases of any childhood disorder.

A comparison of results across different disorders revealed an issue with similar implications. Results of both the meta-analysis and individual studies that directly compared different combinations of comorbid diagnoses indicate that each neuropsychological weakness is associated with multiple childhood disorders. Taken together, these results argue against single-deficit theories that propose that all cases of a disorder are due to a single neuropsychological weakness that is unique to that disorder. Instead, it is likely that there is simply not going to be a 1:1 mapping of any
neuropsychological domains to all individuals with the specific behavioral disorders defined currently in DSM-IV.

Does the absence of a single necessary and sufficient core deficit for each disorder mean that the neuropsychological approach is not useful? On the contrary, several lines of evidence suggest that these complex neuropsychological results are simply a reflection of reality that was predictable based on the previous literature. Studies of ADHD have shown that individuals with childhood disorders may exhibit weaknesses in multiple neuropsychological domains, and the specific profile of neuropsychological weaknesses may differ among individuals who all meet diagnostic criteria for the same disorder [20, 98–100]. On the other hand, the ubiquitous comorbidity between nearly all pairs of disorders suggests that at least a subset of risk factors may be shared by multiple disorders. However, both of these findings could potentially be explained by weaknesses in diagnostic criteria rather than heterogeneity within and shared risk factors between valid diagnostic categories. Therefore, it will be important in future work to design studies in such a way that the natural boundaries of neuropsychological dysfunction can be mapped backwards onto behavior, rather than assuming that the behavioral categories are always valid in their current form. Support for that conclusion and for the neuropsychological findings described here is provided by studies of the genetic and environmental etiology of childhood disorders.

Although most childhood disorders are highly heritable (50–80%) [101–103], this does not imply that they result from a single major gene. In fact, molecular genetic data increasingly suggest that each of the disorders included in this review has a complex etiology that is likely to include many genetic and environmental risk factors that each increase susceptibility to the disorder a relatively small amount [104–106]. Moreover, multivariate twin studies suggest that at least a subset of genetic and environmental risk factors increase risk for two or more different disorders [101–103].

Though it is possible that each disorder could be due to a unique set of multiple risk factors that all influence a single neuropsychological weakness that is specific to that disorder, it is more likely that at least some of these risk factors may affect more than one disorder. Some may influence general risk factors that play a role in most childhood disorders, possibly by contributing to a weakness in a broadly distributed neural network that affects numerous other cognitive functions. Other more specific risk factors may increase risk for a cluster of related disorders by altering the function of a more specific neural network, such as the frontal-striatal network implicated in EF. It is likely that a third subset of risk factors will indeed be uniquely associated with each disorder, but rather than single core deficits, these unique risk factors will comprise one important component of a more complex multifactorial etiology.

**Neuropsychological Profiles**

A closer examination of the results of the meta-analysis illustrates how analysis of neuropsychological functioning in different domains may help to explain the similarities and differences across childhood disorders. Slow processing speed and increased
response variability appear to be general risk factors for most disorders, whereas weaknesses in different aspects of executive control may distinguish between disorders. Although all groups exhibited mild weaknesses on measures of inhibitory control and working memory, the effect size for response inhibition was largest in the groups with ADHD and Tourette’s disorder, and the groups with a LD or COS exhibited a larger weakness in working memory than groups with other disorders. In contrast, groups with ADHD, LD, and Tourette’s disorder exhibited minimal and inconsistent weaknesses on measures of set shifting and cognitive flexibility [83], whereas these were the most pronounced difficulties in the groups with autism (mean $d = \text{approximately 1.1}$ for measures of set shifting and planning) and COS (mean $d = \text{approximately 1.0}$).

Groups with anxiety disorders, mood disorders, or ODD/CD exhibited moderate weaknesses across many of the tasks. In contrast to the other disorders, however, the neuropsychological profile of these groups was relatively nonspecific. This pattern of results may be due to the fact that previous studies have focused primarily on cognitive aspects of executive control and processing speed, whereas these clusters of disorders might show larger effects on measures that more directly tap motivational circuits and processes involved in regulation of emotion.

Though much more work remains to be done, the current findings illustrate how neuropsychological methods have helped to constrain and refine overarching theories of childhood disorders. Given that neuropsychological deficits do not map cleanly onto current diagnostic categories, the neuropsychological level of analysis is likely to help to identify neuropsychologically distinct subgroups within disorders, as well as groups of individuals across disorders who exhibit similar neuropsychological difficulties. Both of these approaches may inform future remapping of diagnostic boundaries, and may provide a useful way to parse behavioral syndromes for targeted interventions and studies of genetic and environmental risk factors. Results of these studies will facilitate the development and refinement of complex multiple-deficit models of childhood disorders. We briefly describe two specific examples of such models below.

### Multiple Deficit Models

The theoretical models that best fit existing data from neuropsychological and etiological studies explicitly hypothesize that each disorder is neuropsychologically heterogeneous. For example, a satisfactory theoretical model of ADHD must explain how multiple genetic and environmental risk factors lead to weaknesses in multiple EF domains, significant aversion to delay and possibly differential sensitivity to other motivational contingencies, and slower and more variable responses on both individual task trials and across entire measures. In addition, these models must account for the significant neuropsychological heterogeneity at the level of the individual child. Several multiple-deficit models have now been articulated by us and others [12, 53, 77, 107]. In the remainder of this section we describe just two examples of these models to illustrate ways that these models could be conceptualized.
Independent pathway models suggest that disruption in any one of two or more pathophysiological substrates can independently lead to the same final behavioral manifestation of a disorder. Therefore, independent pathway models propose neuropsychological subtypes. For example, Sonuga-Barke [99] proposed a dual-pathway model in which some individuals exhibit ADHD symptoms due to significant aversion to delay, whereas others have ADHD due to weak inhibitory control. In parallel using a temperament perspective, Nigg et al. [107] suggested that some cases of ADHD are due to an excessive approach system (appetitive), and others due to failures in cognitive control (executive system).

In contrast to independent pathway models, multifactorial models suggest that the symptoms of complex childhood disorders arise due to the additive and interactive combination of multiple dysfunctional processes. Because no specific weakness is a necessary or sufficient cause of the disorder, the exact cluster of weaknesses may differ among individuals, leading to neuropsychological and clinical heterogeneity. For example, individuals with weaknesses in executive control and processing speed may be most likely to meet criteria for ADHD, LD, or MDD, whereas the same EF weaknesses couple with aversion to delay or disruption in other motivational processes might increase susceptibility to hyperactive-impulsive behaviors, disruptive behavior disorders, or substance abuse.

In one of the first direct tests of these models, Sonuga-Barke et al. [59] re-analyzed the dataset from the ADHD multimodal treatment study [100] to test the relations between delay aversion, response inhibition, and the DSM-IV-TR combined type. A cutoff score at the 10th percentile of a control group without ADHD was used to identify the number of children who exhibited deficient response inhibition, significant delay aversion, or significant dysfunction in both domains. A subset of the group with ADHD exhibited weak inhibitory control but not delay aversion (23%), and another group exhibited significant delay aversion only (15%), providing support for the dual-pathway model described by Sonuga-Barke [99]. In contrast, a higher proportion of the sample than would be expected by chance (23%) exhibited both delay aversion and weak inhibitory control, consistent with the predictions of the multifactorial model. Finally, 39% of the sample did not exhibit either significant aversion to delay or inhibitory difficulties, indicating that additional cognitive dysfunctions not captured by delay aversion or response inhibition represent either additional alternative pathways to ADHD or additional components in a multifactorial etiology. A similar pattern of results was obtained in parallel analyses of response variability and EF in three large independent samples [98], suggesting that this pattern is not specific to delay aversion and inhibition (18–27% of the group with ADHD exhibited no deficits, whereas 28–36% exhibited weaknesses on three or more measures).

In summary, the multiple-pathway and multifactorial models agree with earlier neuropsychological models that a comprehensive neurocognitive model of ADHD is almost certain to include dysfunction in multiple separable neural networks, but differ in not giving primacy to a single core deficit that drives the others. The reason for
not giving primacy is the modeling of heterogeneity into the conceptual framework. Additional research is needed to test if dysfunction in these different networks leads to distinct neuropsychological subtypes within each disorder, or if multiple dysfunctional processes act in combination to increase susceptibility to different disorders. Perhaps the most likely scenario is that both of these models may be partially correct, such that some cases of each disorder are attributable to a primary deficit in a relatively specific neurocognitive function, whereas other cases are caused by the combined effects of dysfunctions in multiple neural substrates.

Key Remaining Issues and Directions for Future Research

The transition from models positing a single primary deficit to multiple-deficit models represents a paradigm shift in the way that the neuropsychology of childhood disorders is conceptualized [99]. In this final section we summarize several key remaining issues for the field, then highlight future directions for studies of the neuropsychology of ADHD within a multiple-deficit framework.

Clinical Heterogeneity

The results of the current review indicate that additional research is sorely needed to clarify the meaning of the nearly ubiquitous comorbidity in childhood disorders. One approach that has been used frequently in previous studies is to apply stringent exclusion criteria at the beginning of a study to maximize the homogeneity of the sample. For example, many studies of different disorders have excluded participants who also met criteria for ADHD, LD/RD, ODD/CD, TS, mood disorders, pervasive developmental disorder, and mental retardation [for a detailed summary of these exclusion criteria in previous studies see, 70]. However, the a priori exclusion of a subset of individuals makes strong assumptions about the meaning of heterogeneity that are not easily justified based on existing knowledge, and may even be counterproductive. For example, whereas few would argue that children with mental retardation should be excluded from studies of the neuropsychological correlates of disorders in which most children have cognitive ability in the normal range, the justification for exclusion criteria based on other comorbidities is less clear. When we selected children with ADHD without any comorbidity for the analysis described earlier in this chapter, the neuropsychological effect sizes were less than half the size of the effects in the entire sample who met criteria for ADHD. Therefore, if we had made an a priori decision to exclude children with any comorbid disorder at the beginning of the study we would have excluded the subset of individuals with the greatest neuropsychological impairment and symptom severity – arguably the cases most in need of intervention and study and those with the most clear-cut case of ADHD.

The exclusion approach may be optimal if resource limitations or the study design mean that the final sample will be small. For example, neuroimaging studies are
required to carefully select which subset of participants to include due to the cost required to run each individual. In contrast, for most purposes the optimal approach is to include all individuals with a disorder for the initial sample, then to assess carefully putative diagnostic subtypes, comorbid disorders, and any other potential markers of heterogeneity. These markers can then be controlled statistically or used as exclusion criteria for specific analyses, facilitating a direct test of the impact of these variables on the neuropsychology of the disorder.

**Direct Tests of Competing Neuropsychological Models**

Most previous studies have examined the neuropsychological correlates of childhood disorders from a single theoretical perspective or with only one or two measures, making it difficult or impossible to test competing theories in the same study. Although effect sizes from multiple studies can be used to conduct preliminary comparisons between theories, interpretation of such comparisons is inevitably complicated by differences in study design and sampling procedures. Therefore, studies are needed that test multiple competing theoretical models in the same sample, such as the study by Rucklidge and Tannock [37] that showed that reading difficulties were predicted independently by letter naming speed and verbal working memory and studies that found that delay aversion and EFs independently predicted ADHD [100, 108].

**New Methodological Techniques**

Finally, perhaps the most exciting future direction for neuropsychological studies of childhood disorders is the increasing opportunity to incorporate new methodological approaches and multiple levels of analysis in a single study. In this section we briefly describe how neuropsychological studies might interface with five methods that show promise as tools for future research on the pathophysiology of childhood disorders.

**Statistical Methods**

The neuropsychological measures used in previous studies are complex tasks that involve multiple cognitive processes, making it difficult to determine which component of the task is responsible for a difference between groups. Moreover, the predictive power of many of these tasks is constrained by their relatively modest reliability in children. Both of these concerns may be mitigated in future studies by administering multiple measures of key constructs to facilitate the creation of latent trait or factor scores. These scores are based on the shared variance across multiple measures of a construct, separate from the variance associated with measurement error or other processes that are idiosyncratic to a particular measure. The potential utility of this approach is illustrated by results from the Colorado Longitudinal Twin Study that showed that the relation between inhibition and attention problems was stronger when inhibition was measured with a latent trait ($r = 0.44$) versus any individual inhibition measure ($r = 0.20–0.34$) [31].
Etiologically Informative Designs
Although individual differences in delay aversion appear to be primarily attributable to environmental influences [109], estimates of familiality and heritability are moderate to high for most measures of EF, processing speed, and response variability [109–111], and multivariate twin analyses suggest that common genetic influences account for most of the phenotypic covariance between these neuropsychological weaknesses and ADHD symptoms, reading difficulties, and symptoms of other disruptive disorders [96, 109]. Based on these results, studies have recently begun to test whether neuropsychological measures are useful as intermediate phenotypes (often called 'endophenotypes') that mediate or moderate the relation between specific genetic and environmental risk factors and the symptoms of childhood disorders [83, 112, 113]. Although this line of research is still early in its development, the endophenotype approach is likely to provide an important tool for the continued refinement of causal models of childhood disorders.

Neurocomputational Modeling
Sophisticated neurocomputational modeling techniques are likely to provide an extraordinary tool to understand the pathophysiology of complex disorders. Theoretical models of the neurophysiology of a disorder can be instantiated in computational models, then used to derive and constrain predictions to be tested using neuropsychological tasks. The neuropsychological results will then provide new data that the theoretical and computational models must explain, leading to further refinements to the models that can again be tested with revised neuropsychological tasks. The potential utility of this iterative approach is demonstrated in a recent paper that used a neurocomputational model and psychopharmacological manipulation to begin to tease apart the differential influence of dopamine and noradrenaline on different aspects of neuropsychological dysfunction in ADHD [79].

Brain Imaging
Similar to neurocomputational modeling, the collection of neuroimaging and neuropsychological measures in the same sample will allow these methods to inform and constrain one another. Theoretical models make specific predictions regarding the brain regions and neurotransmitter systems that are likely to be implicated in childhood disorders. Neuropsychological measures can then be developed that should recruit these specific regions of the brain to test these predictions using structural and functional MRI, event-related potentials, or other measures of neurophysiology [114, 115].

Treatment Response
The overarching goal of all neuropsychological research is to inform and improve clinical diagnostic procedures and subsequent interventions for childhood disorders. By including measures of neuropsychological functioning in treatment studies
along with other potential markers of clinical heterogeneity, it may eventually be possible to begin to predict the treatment that is most likely to be helpful for a specific individual.

Conclusions

A meta-analysis of nine of the most common childhood disorders indicated that the neuropsychological etiologies of most childhood disorders are complex and multifactorial. Comprehensive neuropsychological models of most disorders must incorporate increased response variability on single trials of cognitive tasks, slower overall processing speed across entire measures, and weaknesses in at least some aspects of executive control. No single deficit is necessary or sufficient to explain all cases of any disorder, but preliminary evidence suggests that disorders may be distinguished by profiles across multiple neuropsychological processes. Slow processing speed and increased response variability are ubiquitous across disorders, but somewhat distinct profiles are apparent on different measures of EFs. ADHD and Tourette’s disorder are most strongly associated with inhibitory difficulties, whereas difficulties with cognitive flexibility are most pronounced in groups with autism spectrum disorders and COS. Working memory difficulties are significant in most groups, but these weaknesses are largest in groups with LDs and COS. Future research is needed to clarify further the relations among these heterogeneous diagnostic phenotypes and complex neuropsychological processes to facilitate studies that link these weaknesses to specific etiological risk factors.

Conflicts of Interest

Dr. Willcutt currently receives grant support from the National Institutes of Health, the Ackerman Foundation, and the Australian Research Council.
Dr. Sonuga-Barke: UCB – consultancy, project support, advisory board, speaker; Shire – advisory board; Janssen Cilag – grant support, speaker; QBTech – grant support.
Dr. Nigg receives grant support from the National Institutes of Health.
Dr. Sergeant: Shire – advisory board; Lilly – advisory board, grant; Pfizer – advisory board.

Acknowledgements

The authors were supported in part during the preparation of this manuscript by National Institutes of Health grants R01 MH 62120, R01 MH 63941, R01 HD 47264 (E.G.W.) and P50 HD 27802 (Center Director: Richard K. Olson). The authors thank Bruce F. Pennington, John C. DeFries, and Richard K. Olson for sharing a portion of the data presented here, and Nomita Chhabildas for her helpful comments on an earlier version of the manuscript.
References


Neuropsychology of Childhood Disorders


91 Ross RG, Heinlein S, Tregellas H: High rates of comorbidity are found in childhood-onset schizophrenia. Schizophr Res 2006;88:90–95.


111 Bidwell LG, Willcutt EG, Pennington BF: Executive functions in twins discordant for ADHD. Biol Psychiatry, in press.


