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By

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ABSTRACT

EXECUTIVE FUNCTION DEFICITS IN PSYCHOPATHOLOGY

By

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Purpose: Striking parallelism in the literature links deficits in executive functions (EF) with a wide range of seemingly different psychiatric disorders. Questions have been raised about how these diverse disorders can all be related to a similar cognitive and/or neural dysfunction. Previous literature has focused primarily on effects associated with individual, or few, disorders. As a result, the potentially significant role of comorbidity, as well as specificity of effects, is poorly understood. The present study was an attempt to understand the specificity of EF deficits to different types of psychopathology, taking into account the effect of comorbidity. Four models examining the relationship at different levels in the diagnostic hierarchy were tested as possible explanations for the frequent association of EF deficits to psychiatric disorders. **Methods:** Adults participants from two large, preexisting studies were combined (total $n = 641$). Diagnostic interviews and neuropsychological testing were completed for all participants. Disorders investigated were attention-deficit/hyperactivity disorder (ADHD), childhood externalizing disorders, antisocial personality disorder (ASPD), alcoholism, drug dependence, depression, and anxiety disorders. EF tests were the Stroop Color-Word Test (Stroop), Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT), and Stop Signal Test (Stop). Profile analysis, linear regression, analysis of variance, and structural equation modeling (SEM) were used to test the explanatory power of the following models and their associated hypotheses: (1) componential – individual disorders were

associated with deficits in different EF processes; (2) comorbidity-specific – only a few specific disorders accounted for the association between EF and psychopathology, with high rates of comorbidity making the relationship appear more widespread; (3) comorbidity-nonspecificity – number of comorbid disorders, rather than type, was related to EF impairment; and (4) dimension-specific – shared underlying dimensions of psychopathology (i.e., internalizing versus externalizing) were differentially related to EF deficits. **Results:** The comorbidity-nonspecificity hypothesis was not supported. There was support for comorbidity-specific and componential effects, as certain individual disorders (ADHD predominantly, as well as alcoholism and ASPD) were associated with poorer performance on measures from certain EF tests (TMT Residual Score, Stop Response Inhibition and Response Variability). Individual-disorder analyses were further elucidated by structural models testing dimension-specific effects. Externalizing disorders were associated with poorer performance on cognitive tests. Specificity was found for types of disorders associated with cognitive functioning, but not for cognitive effects, as externalizing disorders were related to poorer performance on both EF and processing speed tasks. Further, many EF effects disappeared after controlling for FSIQ (although not those associated with ADHD), while speed-related effects were more robust. **Conclusions:** Findings suggest that shared underlying effects associated with externalizing disorders contribute to cognitive deficits (or vice versa). Certain EF processes and tasks are particularly sensitive to psychopathology, but neurocognitive effects crossed cognitive domains in the present findings. Longitudinal and symptom-based studies are needed to better understand the role of neurocognitive deficits in the etiology and maintenance of psychological disorders.

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Executive Function Deficits in Psychopathology

Executive functions (EF) refer to cognitive abilities that are recruited in the pursuit of goal-directed activity. Deficits in this cognitive domain have been associated, at least conceptually, with risk for the emergence of a wide range of psychological disorders. These include, but are not limited to, attention-deficit hyperactivity disorder (ADHD), major depressive disorder (MDD), anxiety, obsessive-compulsive disorder (OCD), schizophrenia, antisocial personality disorder (ASPD), alcoholism, and drug use. To demonstrate interest in studying EF and psychopathology, each of these disorders were entered as keywords into a PsycINFO search for articles dating from 1995 through mid 2007, with the stem "executive function*" also appearing in the keyword field. The numbers of citations found for each disorder were: "schizophrenia" – 767; "depression" – 520; "ADHD" – 437; "anxiety" – 193; "drug abuse" – 134; "alcoholism" – 91; "antisocial" – 85; and "OCD" – 75. These numbers undoubtedly underestimate the actual number of studies in the field, given that different terms are often used for EF as well as the individual disorders. However, they illustrate the strong interest in understanding the involvement of EF across numerous psychiatric disorders. The specific results of these studies vary considerably, and as I will emphasize, the effects of comorbidity have been understudied and are poorly understood. Yet it is clear that the presence of some EF impairment has been suggested for each of these disorders.

The parallelism in the literature, with EF deficits being associated with such a wide range of disorders, is striking and not easily explained. How can claims regarding the involvement of EF deficits be made across so many diverse disorders? Moreover, going beyond simple associations, EF impairment has often been hypothesized to play a

causal role in the etiology of psychiatric disorders. However, if each of these hypotheses were correct, then how the same underlying cognitive deficit could lead to these very different symptom presentations is perplexing. This question of disorder-deficit specificity, or the *discriminant validity problem*, has been posed by Pennington & Ozonoff (1996): "How can symptomatically different complex behavior disorders all be due to the same cognitive and/or neural dysfunction?" (p. 57). Such queries have led to attempts to differentiate between EF as an etiologically specific deficit versus a nonspecific marker of dysfunction for individual psychiatric disorders.

In examining the discriminant validity problem, the goal of researchers was often to find the primary neurocognitive deficit for each disorder, with primary referring to a deficit that is universal, specific, necessary, and sufficient to cause the symptoms of the disorder (Pennington & Ozonoff, 1996). Several problems with searching for this so-called primary deficit have precluded clarity on the issue and suggest the need to reconceptualize.

The first problem is that without the use of longitudinal study designs and neuroimaging technology to test for localized changes in the structure and function of the brain (which may be beyond the scope of present technology), the discriminant validity problem cannot be solved at the level of brain mechanisms. Second, it is not realistic to expect to find a single cognitive deficit that is sufficient to cause all cases of what are now recognized to be multifactorial psychiatric disorders (Garber & Hollon, 1991). Finally, any search for a primary deficit assumes that the current classification system for differentiating disorders, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994) is accurate, which

would require placing greater faith in the present nosology than it may be due (Garber & Hollon, 1991). Given the problems with searching for a primary deficit, this line of reasoning cannot be strictly applied in an attempt to understand the relationship between EF deficits and psychiatric disorders. It may be more realistic to demonstrate "partial specificity" between psychopathology and EF deficits. Such a relationship may be suggested if EF deficits were one of several factors consistently implicated in the manifestation of certain disorders. As will be discussed, even this level of specificity has been difficult to support in the literature.

This study attempted to better understand the specificity of EF deficits to wide-ranging psychiatric disorders by examining the relationship at different levels in the diagnostic hierarchy. The DSM-IV is the currently accepted diagnostic classification system for individual disorders, but there may be other ways to conceptualize psychiatric disorders given their frequent comorbid presentations (Angold, Costello, & Erkanli, 1999; Kessler, Berglund, Demler, Jin, & Walters, 2005a; Kessler, Chiu, Demler, & Walters, 2005b; Kessler, McGonagle, Zhao, Nelson et al., 1994) and similar symptomatology and characteristics (Krueger, 1999). The focus of this study was to examine the relationship between EF deficits and exemplars of putative EF-related psychopathology using four "models" or hypotheses to explain their associations. Each hypothesis represented an alternative solution to the question of how EF deficits could be related to such a wide range of disorders. These four possible models incorporated different levels of abstraction in a diagnostic classification "hierarchy" – from individual disorders, to multiple or comorbid diagnoses, to shared underlying psychopathological processes. By using alternative conceptualizations of psychopathology, this study

attempted to understand both the cognitive levels and possible profile differences between these disorders without being constrained by only one definition of psychopathology. The goal was to examine possible distinctions in types and extent of EF deficits that are associated with the presence versus absence of putatively different kinds of psychopathology. The four main hypotheses are detailed as follows.

The first possibility, at the level of the individual disorders, was that different disorders are associated with different types of EF deficits. In other words a *Componential Model*, or profile analysis of EF deficits, may show that individual psychiatric disorders, as defined by the DSM-IV, are associated with deficits in different types of EF abilities so that several disorders may show some form of an EF deficit, but the affected component processes may vary between disorders.

Second, moving to the level of multiple disorders, two more possibilities are apparent. One (second overall) is that specificity of EF deficits is present for only one or very few disorders. In this case, the appearance of EF deficits with the other disorders may be due to comorbidity between disorders that are and are not associated with EF deficits. As mentioned, comorbidity is often uncontrolled in neuropsychological studies of mental disorders, and use of the appropriate controls (which, admittedly, are not easily arrived at – see subsequent discussion) may provide a clearer picture of the relationship between disorders and EF deficits. Therefore, examination of this *Specificity Model* may suggest that only a few disorders show EF deficits while others do not, once comorbidity is accounted for.

The other possibility at the level of multiple disorders (third overall) was that there is no specificity of EF deficits with the individual disorders, but that EF impairment

is related to the *number* of co-occurring disorders. That is, perhaps EF deficits are seen in relation to number, rather than form, of psychopathology (Kessler et al., 2005a). In this case, the number of disorders alone would be a marker for impaired EF, regardless of the particular disorder(s) that is (are) manifested. This *Nonspecificity Model* would suggest that number, not type, of disorder could account for the findings of EF deficits across multiple disorders.

Finally, at the level of symptom dimensions, EF deficits may be related to only certain psychopathological processes and not to others. Recent research has suggested that high levels of comorbidity amongst DSM-III-R (Kessler et al., 1994) and DSM-IV disorders (Kessler et al., 2005a) may result from shared underlying core psychopathological characteristics (Kessler, Crum, Warner, Nelson et al., 1997; Krueger, 1999, 2005). In a population-based prevalence study, Krueger (1999) found that two broad, superordinate factors accounted for the pattern of correlations among liabilities to have common mental disorders: an internalizing factor (that included two subfactors), and an externalizing factor (note that these are Krueger's (1999) labels for the factors). In other words, the individual disorders appear to cluster together according to shared underlying processes, with mood and anxiety disorders loading onto an "internalizing" factor, and ASPD and substance use disorders loading onto an "externalizing" factor (Krueger, 1999). This finding suggests that current nosology may be misleading to the extent that it relies on completely separating behavioral syndromes into discrete disorders (Krueger, 1999, 2005). Krueger (1999) recommended that research should focus on these core processes rather than the individual disorders. It is possible that one of these higher-order dimensions of psychopathology (i.e., internalizing versus externalizing

syndromes) may be related to EF deficits, while the other may not. Therefore, according to this *Dimension-Specific Model*, the findings of EF deficits across multiple disorders may be a result of shared underlying core processes that are related to EF deficits.

Because EF are potentially relevant to so many disorders, to constrain the scope of the study some decisions were made regarding which disorders to include. The following disorders were selected for inclusion: childhood externalizing disorders (i.e., ADHD, conduct disorder (CD), and oppositional defiant disorder (ODD)), ASPD, alcoholism, drug dependence, depression, and anxiety disorders. Theses disorders were included for three reasons.

First, these are among the most common disorders diagnosed in the general population and as such they are usually included in major prevalence studies (i.e., Kessler et al., 2005a; Kessler et al., 2005b; Kessler et al., 1994; Krueger, 1999). Disorders that were not included in this list, such as bipolar disorder, schizophrenia, and borderline personality disorder have also been associated with EF impairments (Antonova, Sharma, Morris, & Kumari, 2004; Henry & Crawford, 2005; Monarch, Saykin, & Flashman, 2004; Quraishi & Frangou, 2002), but their low base rates in community samples made it unlikely that they will be adequately represented in the present study (Ekselius, Tillfors, Furmark, & Fredrikson, 2001; Kessler et al., 2005a). Secondly, the disorders that have been selected for inclusion frequently co-occur with each other (Kessler et al., 2005b), such that teasing apart specific EF correlates has been difficult. Third, these disorders share similar surface characteristics, such as impulsivity (i.e., ADHD, drug dependence, ASPD), and withdrawal or lack of initiative (i.e., MDD and anxiety disorders), which splits them conceptually into those disorders that are typically associated with

externalizing versus internalizing behaviors, respectively (Achenbach, 1966; Krueger, 1999). By the same token, in order to address the dimension-specific model (Hypothesis 4, above), it was necessary to include both "externalizing" and "internalizing" disorders in the present study. Therefore, the selection of disorders for the present study was based upon their associations with EF deficits, prevalence in the population, high rates of comorbidity, and similarities in symptom profiles.

The hierarchical approach to analyzing the relationship between EF and psychopathology using the four proposed models (i.e., componential, comorbidity-specific, comorbidity-nonspecific, and dimension-specific) underscores the importance of looking at the broader concepts of behavior as well as their individual manifestations (Gorenstein & Newman, 1980). These hypothesized models to explain the relationship between EF deficits and psychopathology are not necessarily mutually exclusive; one may better explain the relationship than the others, or they may all contribute to our understanding. By examining individual as well as comorbid disorders from multiple perspectives, this study aimed to clarify the nature of EF deficits in these conditions. While a long-term goal for this research is to find clues regarding the etiology of these conditions, there are other more immediate benefits associated with this line of inquiry.

Why Study Psychopathology and Executive Functions?

It is understandable that researchers in so many areas of psychopathology have sought use the concept of EF. Confirming a link between EF and individual psychiatric diagnoses can provide objective support for classifying behavior as disordered. There is much debate about the validity of various psychological disorders (see: Clark, 1999; First, Spitzer, Gibbon, & Williams, 1997; Lilienfeld & Marino, 1995, 1999; Spitzer,

1999; Wakefield, 1999). For instance, the current diagnostic nosology, the DSM-IV (American Psychiatric Association, 1994), has been criticized for being over-inclusive in its criteria because it does not meet the dysfunction requirement in the "harmful dysfunction" conceptualization of a mental disorder (Wakefield, 1997). Wakefield (1992) indicated that while "harm" involves a societal value judgment, dysfunction should ideally be a scientific term referring to "the failure of an internal mechanism to perform a natural function for which it was designed" (p. 383). In this influential view, both harm and dysfunction are required to label behavior as a disorder. Dysfunction, if it can be accurately identified, has the potential to differentiate between the abnormal functioning of internal mechanisms and nondisordered reactions to external stressors to avoid pathologizing normal behavior (Wakefield, 1992). Although there have been criticisms of Wakefield's analysis (Clark, 1999; Lilienfeld & Marino, 1995, 1999), he provides a useful perspective from which to begin to refine the definition of disorder (Cosmides & Tooby, 1999; Spitzer, 1999). Being able to substantiate a connection between a disorder and EF deficit could provide an objective index of dysfunction, thus helping to validate behavior as disordered.

The potential gains that could result from studying the relationship between EF deficits and major disorders extend beyond this very general objective of being able to validate a disorder with regard to dysfunctional internal mechanisms in the mind or the brain. It may also provide insight into the validity of the specific criteria used to define and differentiate various conditions. This is particularly so, however, when considering more than one disorder at the same time. For instance, a problematic result of the current definitions for various disorders is that there is a high degree of comorbidity between

disorders. Recent research using DSM-IV criteria suggested that while almost half of the population had met criteria for a psychiatric disorder at some point in their lifetime, the prevalence of having two or more lifetime conditions was 27.7%, and the prevalence of having three or more disorders was 17.3% (Kessler et al., 2005a). Prevalence of comorbidity was similar for the previous classification system, the DSM-III-R, as well (Kessler et al., 1994). Therefore, the majority of lifetime disorders are comorbid conditions, which raises questions about the validity of our diagnostic criteria – or at least about the assumption of discrete conditions.

The high rates of comorbidity may partially result from problems with the nosology (i.e., overlapping symptomatology or the artificial separation of similar disorders; Angold et al., 1999; Krueger, 1999) that an understanding of the specificity of neuropsychological deficits to individual disorders may help to clarify and refine. In other words, being able to differentiate disorders based upon patterns of neuropsychological test performance could provide support for the validity of individual disorders and might help to determine whether comorbid conditions represent some "combination" of the individual disorders or a separate, third disorder (Angold et al., 1999). On the other hand, if the same deficits are seen for multiple individual disorders, this may provide support for the idea that common underlying pathological processes could lead to symptoms of several related conditions (Krueger, 1999). In short, an understanding of the neuropsychological deficits could guide the manner in which we specifically define and conceptualize disorders, with implications for their assessment and, potentially, treatment.

As mentioned, EF deficits have been associated with a wide range of disorders. Despite the problem of parallelism in the literature and the importance of clarifying it before meaningful conclusions can be drawn about individual disorders, most research has focused upon the EF deficits associated with individual conditions. Fewer studies have examined this issue with the intention being to understand the specificity versus generalizability of EF deficits to different psychological disorders. Those that have involved comparisons across disorders have dealt with only a small number of disorders (Airaksinen, Larsson, & Forsell, 2005; Boldrini, Del Pace, Placidi, Keilp, Ellis, Signori et al., 2005; Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Moritz, Birkner, Kloss, Jahn, Hand, Haasen et al., 2002; Selby & Azrin, 1998; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003; Weyandt, Rice, Linterman, Mitzlaff, & Emert, 1998), and/or examined a number of domains of cognitive abilities without a specific focus upon EF (Riordan, Flashman, Saykin, Frutiger, Carroll, & Huey, 1999). A small number of review papers have integrated the findings on the neuropsychological correlates across many individual disorders, and these have been helpful in highlighting the specificity of EF deficits in childhood (Pennington & Ozonoff, 1996; Sergeant, Geurts, & Oosterlaan, 2002). However, as several of those reviewers pointed out, comparing effects across different studies which used different methodology makes interpretation difficult, and this has slowed progress in the study of EF deficit specificity (Sergeant et al., 2002). An empirical study considering key, frequently comorbid disorders is needed and is, for the most part, unprecedented.

The present study was an attempt to address some of these issues to more clearly understand the relationship between psychopathology and EF deficits. The empirical

examination of multiple disorders within two large and well-defined samples of adults was guided by the following suggestions that were made by Sergeant et al. (2002) to improve research and enhance our knowledge on the specificity of EF deficits: (a) include multiple clinical group comparisons; (b) use EF tasks which show frontal lobe involvement and some process specificity; (c) use the exact same EF tasks and dependent variables across the different disorders/samples being studied; and (d) provide some form of statistical control for comorbid disorders to increase confidence that any observed deficits are related to the disorder in question and not to other co-occurring disorders.

Regarding this latter point, control of comorbidity is a conceptually complex issue. Therefore, comorbidity was controlled in some analyses, but it was also a focus of other analyses in order to understand how co-occurring disorders interacted to affect neuropsychological performance. One issue here was that it was possible that the overlap of symptoms and interactions between some disorders are necessary and core components of their psychopathology. Controlling their covariance could remove key aspects of the psychopathology that may be contributing to EF deficits. Including multiple levels of diagnostic analysis with the four models helped to address this issue. Before shifting the focus to review previous literature on EF and psychopathology, it is important to examine the EF construct and clarify how it was conceived in the present study.

Executive Functions

The concept of EF is poorly defined, often underspecified, and its definition tends to vary between studies. As a result, the very term 'executive functions' is becoming somewhat outdated, as there is (a) increased recognition of the need for more descriptive

terminology to better specify and capture the components of EF, and (b) a need to avoid the 'meta-cognitive' or hierarchical implications connoted by the use of the word 'executive' (for example, Denckla (1996) suggests "control processes", p. 264). Given that the term executive functions is well recognized by most neuropsychological researchers as referring to a group of cognitive processes involved in goal-directed activity, it was used herein despite its recognized meta-conceptual drawbacks. Nonetheless, a number of conceptual clarifications are necessary.

EF have often come to be synonymous with the brain's frontal lobes, and have at times been taken to be any process disrupted by damage to that region of the brain (Denckla, 1996; Hayes, Gifford, & Ruckstuhl, 1996). Such an interpretation dates to early descriptions of disorganized behavior, impulsivity, and lack of initiation following frontal lobe damage, such as references to the well-known frontal lobe patient Phineas Gage. This "frontal metaphor" (Pennington & Ozonoff, 1996), however, does not clarify any shared mechanism amongst EF processes, nor provide a functional understanding of the EF concept; instead, it explicitly avoids an operational definition of the concept (Barkley, 1996). Further, while the frontal cortex is important to EF, its role is not exclusive. Some patients with frontal lobe damage do not have any problems on EF tasks (Shallice & Burgess, 1991), and damage to other key brain areas may also cause EF impairment (Anderson, Damasio, Jones, & Tranel, 1991). The vast circuitry connecting the frontal lobes to other regions of the brain means that other forms of damage may affect EF (Lichter & Cummings, 2001). Therefore, a sole focus on frontal localization does not aid in understanding the EF concept or the related, more current concepts, such as cognitive control.

Many different cognitive abilities have been subsumed under the heading "executive functions," and these tend to vary between theorists. Borkowski and Burke (1996) observed that a major impediment to progress in the study of EF was the ambiguity of the construct and resultant lack of shared meaning throughout different disciplines within which EF are important (i.e., cognitive psychology, developmental psychology, neuropsychology, and education). The central mechanism in EF has been variously hypothesized as working memory (Pennington, Bennetto, McAleer, & Roberts, 1996; Smith & Jonides, 1999), attention (Barkley, 1996), information processing (Borkowski & Burke, 1996), and inhibition (Denckla, 1996). Various cognitive models have combined some of these concepts in their definitions, such as Norman and Shallice's (1986) Control of Action model which included an executive Supervisory Attentional System (SAS) to cope with novel information, and Baddeley's (1986) working memory model which included a central executive that was responsible for the selection, initiation, and termination of processing routines (i.e., encoding, storing, and retrieving). Each of these theoretical models is important in helping to understand the concept of EF, but they are somewhat narrow in their purely cognitive interpretations of the concept.

A broader conceptualization, involving multiple processes, was presented by Pennington and Ozonoff (1996), and this definition was employed herein. The reason for this selection was three-fold: their definition clearly outlines cognitive components of EF that are accessible to direct measurement using clinical measures, they provide a theory to conceptually link these component processes, and this definition of EF is relevant to clinical problems/assessment involving EF and potential relationships between deficits

and disorders. These authors (see also Welsh & Pennington, 1988), define EF as "the ability to maintain an appropriate problem-solving set for attainment of a future goal. This set can involve one or more of the following: (a) an intention to inhibit a response or to defer it to a later more appropriate time, (b) a strategic plan of action sequences, and (c) a mental representation of the task, including the relevant stimulus information encoded into memory and the desired future goal-state" (pp. 201-202). Thus, multiple processes are included in this description.

Pennington and Ozonoff (1996) detail two additional concepts that are central to their definition of EF. The first is the idea that the selection of an action is specific to and appropriate for the context within which the action is required. The ability to choose a context-specific action is particularly important when other actions are available that would be inappropriate to the particular context. Secondly, the selection of an action depends upon the integration and satisfaction of constraints from a variety of domains including, but not limited to, memory, perception, motivation, and affect. These concepts help to explain the heterogeneity of EF processes, their particular relevance in novel contexts, and the importance of other cognitive domains in performance on EF tasks. It also explains the applicability of executive abilities to many aspects of human behavior, as they integrate and influence cognitive as well as social, emotional, and motivational drive states in the attainment of future goals.

While Pennington & Ozonoff's (1996) definition guides a theoretical understanding of the EF concept, it still leaves the specific EF processes somewhat vague and abstract. Thus, more practically, tasks they consider to assess "executive functions" are those that are thought to involve set-shifting and set maintenance, interference

control, inhibition, integration across space and time, planning, and working memory (Pennington & Ozonoff, 1996). These six cognitive operations thus comprise a single conceptual model of EF that may be measured during a clinical neuropsychological examination. That model guided the current work. An issue that it highlights, however, is that EF is composed of multiple processes (Ward, Roberts, & Phillips, 2001), which complicates the discussion of EF as a single unitary construct.

The question of unity versus diversity of processes within the EF construct and its associated clinical measures has been examined recently in both normal adult (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000) and neurological populations (Duncan, Johnson, Swales, & Freer, 1997). Both groups of researchers concluded that there is support for *both* unity and diversity, or multiplicity, in understanding EF. Diversity is exemplified in EF tasks both through clinical observations as well as research findings. For example, clinical observations that some people perform poorly on one EF task but normally on others highlights the diversity of EF tasks. Duncan and colleagues (1997) tested this finding empirically and found a similar effect in that performances on tests assessing EF tended to correlate weakly with one another; however, note that is not a consistent finding (Burgess, 1997; Hanes, Andrewes, Smith, & Pantelis, 1996; Miyake et al., 2000). Providing additional support for the diversity of EF processes, subcomponent analyses have revealed stronger relationships between tasks that assess a single component of EF (i.e., set shifting) than between tasks that assess different components (Miyake et al., 2000), and convergent validity has been demonstrated for these component processes (Salthouse, Atkinson, & Berish, 2003). Therefore, there appear to be multiple processes involved in the EF construct.

On the other hand, lending support to the unity of the EF construct, there also appears to be an underlying shared mechanism or ability that contributes to performance across different EF tasks (Duncan et al., 1997; Hanes et al., 1996; Miyake et al., 2000; Salthouse et al., 2003). Some have suggested that this higher order factor is the general intelligence factor or *g* (Salthouse et al., 2003), therefore criticizing the lack of divergent validity of the EF construct. However, not everyone has agreed with this interpretation as the opposite can be argued, that components of EF underlie IQ (Conway, Kane, & Engle, 2003; Kane & Engle, 2002). Regardless, while *g* contributes to performance across a wide range of EF abilities as well as the measurement of other cognitive domains, other shared mechanisms have been suggested which more uniquely differentiate EF from other cognitive constructs. For instance, individuals with a head injury showed a common deficit of *goal neglect*, or a tendency to disregard the requirements of tasks despite a conscious awareness of the rules, which contributed to impaired performance across EF tasks (Duncan et al., 1997). Similarly, it has been hypothesized that the active maintenance of goals and other task-relevant information in working memory is crucial to performance across EF tasks (Miyake et al., 2000). Such findings provide support for the unity of the EF construct.

Therefore, although there is not yet consensus regarding the number or nature of separable components of EF (Salthouse et al., 2003), tasks assessing EF appear to represent "unique aspects of executive functioning with some overlapping of variance" (Delis, Kaplan, & Kramer, 2001, p. 82). It appears as though multiple components are involved in the EF construct, but these component processes may be partially unified by a shared ability, such as goal maintenance, which is required across EF tasks. This unity

and diversity of EF processes provides the opportunity to examine EF from a holistic perspective, with a focus on the combined measurement of EF, as well as from a component perspective, with more of a focus on individual processes.

Measurement of Executive Functions

Similar to the difficulties with understanding the concept of executive function, a number of issues have been raised about the tasks used to measure EF. One main problem in measuring EF is task impurity (Miyake et al., 2000). Since EF recruit other cognitive processes in their activity, all tasks assessing EF involve other operations to some degree. This is more of an issue with the molar tasks used in clinical practice than cognitively-based molecular tasks. Molar tasks are complex and as such draw upon a number of cognitive domains. These tasks were designed as "sign tests" to detect brain damage, not to isolate component processes (Lezak, Howieson, & Loring, 2004).

So-called molar clinical measures have both strengths and weaknesses when it comes to assessing psychopathology. With regard to weaknesses, four specific problems with such molar tasks are that they may lack: (1) strong theoretical foundations; (2) the ability to identify component processes that contribute to performance; (3) consistently reliable and normally distributed performance; and (4) sensitivity to the same underlying processes across the range of performance (Pennington & Ozonoff, 1996). Therefore, despite obvious functional EF impairments in the "real world," injured individuals may perform normally on standard EF tests (Eslinger & Damasio, 1985). It has been suggested that the ability to accurately assess EF in laboratory tasks may be precluded by the methods in which tasks are administered: clinicians provide structure and organization to the task, and there is less emphasis on the participant discovering or

creating the solution (Burgess, 1997; Denckla, 1996; Rabbitt, 1997). Therefore, potential problems with the sensitivity and specificity of molar EF tasks in head-injured populations, and the manner in which they are administered, have called into question how validly EF is measured by common clinical tasks.

Providing a balance to these issues, however, the molar tasks have a number of strengths that enable them to provide unique contributions to clinical assessments. Specifically, these include: (1) task complexity that enables for the simultaneous measurement of multiple integrated processes; (2) widespread clinical applicability and ease/portability of administration; (3) extensive clinical validation literature (detailed later); (4) availability of national population norms in many instances; and (5) availability of neuroimaging data so that their substrates are partially understood (detailed later). Thus, there are distinct strengths for molar tasks.

To further elaborate on the strengths of molar tasks, it may be erroneous to believe that what are considered problems with molar tasks could be fixed without losing some inherent aspects of the EF concept. In other words, the fact that EF tasks appear to have low sensitivity and assess multiple interacting processes may not necessarily reflect weaknesses in the tasks. Instead, they may result to some degree from exactly what we are trying to measure, so that removing them may actually invalidate the measurement of EF. For instance, the tasks' low reliability, which has been criticized and likely contributes to the observed low correlations between tasks (Salthouse et al., 2003), may result in part from one of the main foundations of EF tasks: they are designed to assess responses to novelty, and as such they are most valid the first time the task is administered (Burgess, 1997), or when the task is not remembered.

Further, since EF typically refers to the coordination of multiple cognitive processes, and not one single operation, it may be difficult, and perhaps defeat the purpose of measuring EF, to distinguish the effects of constituent processes from EF processes in performance (Salthouse et al., 2003). To split these components completely in an effort to focus solely on molecular processes may result in a loss of the very construct that we are attempting to measure. The clinical integrity of the EF processes may be maintained with these molar tasks, more so than it would be if they were broken into parts.

Finally, although measurement issues should always be kept in mind with regard to interpretation of task performance, at this time molar EF tasks are widely used in clinical practice and research (Lezak et al., 2004; Retzlaff, Butler, & Vanderploeg, 1992). It is therefore important to understand how these particular tasks are affected by the presence of psychiatric disorders. Their inclusion in this study provides clinical applicability and facilitates comparison with previous research in the area.

Therefore, an important asset of molar tasks is that they are clinically applicable and may be used to distinguish between normal and abnormal performance (Lezak et al., 2004). They provide the opportunity to assess multiple interacting processes to determine the overall integrity of EF processes in tandem. Molecular tasks, on the other hand, can assess "purer" sub-components, which may remove the potentially confounding effects of other cognitive processes and offset the difficulties in interpreting performance on molar tasks. The complexities of EF measurement cannot be easily solved; however, the advantages and disadvantages associated with the various measurement approaches may be balanced by the use of multiple tests, which assess both

molar and molecular processes to some extent. Therefore, the approach adopted here was to include representatives of both types of tasks, while attempting to capture the EF processes suggested by Pennington & Ozonoff (1996). This may provide the needed flexibility to look at component as well as holistic EF processes.

Complications in the measurement of EF have led to increased use of latent measurement techniques in recent years (Friedman, Miyake, Corley, Young, deFries, & Hewitt, 2006; Friedman & Miyake, 2004; Nigg, Stavro, Ettenhofer, Hambrick, Miller, & Henderson, 2005; Salthouse et al., 2003). Such methods provide a means to reduce the effects of task impurity and heterogeneity amongst individual EF tests by pooling the shared variance from several indices of EF. This maximizes both construct-relevant variance and therefore increases reliability and interpretability when including multiple different measures of EF. Such an approach was utilized, along with other methods, in the present examination.

To appreciate how both component and holistic EF processes may be supported by neural structures, some understanding of the anatomy of the frontal lobe region is needed. This description can provide a conceptual anatomic basis for the *componential model* of the relationship between EF and psychopathology, and aids in interpreting regions of activation in neuroimaging data for tasks and disorders to be described later.

Functional Significance of Frontal-Subcortical Circuits

The frontal lobes of the brain, particularly the prefrontal cortex, are most highly developed in humans (Petrides & Pandya, 2002). They are the site where partially overlapping systems integrate highly-processed external sensory and multimodal information from posterior cortical areas (Petrides & Pandya, 2002) with internal

cognitive and emotional responses to modulate motivation and facilitate motor responses (Lichter & Cummings, 2001). Prefrontal circuits processing cognitive and/or emotional information may be involved in the manifestation of psychopathology.

It is possible that EF problems associated with frontal-subcortical regions contribute to psychopathology in a top-down information-processing manner. Poor modulation of attention and other cognitive processes may interact with temperament or personality factors (i.e., negative affect or low positive affect) to cause pathological changes in mood and behavior. Information-processing theories have received support in the development of anxiety and depression (see Vasey, Dangleish, & Silverman, 2003). On the other hand, positive affect has been shown to improve cognition, possibly through increases in dopamine in frontal-subcortical pathways (Ashby, Isen, & Turken, 1999). Thus, the lack of or generally low positive affect associated with various psychiatric conditions may lead to problems with cognition. These theories provide means by which cognition may lead to symptoms of psychopathology as well as for symptoms of psychopathology to cause cognitive problems. While the specific direction of effects remains unclear, these ideas highlight the importance of the prefrontal region of the brain. A brief overview of the neuroanatomy and functional significance of the prefrontal cortex to EF processes and psychopathology is provided here. A more detailed description is provided in the Appendix.

The circuitry linking the prefrontal cortex with other brain regions provides a neuroanatomical basis for functional localization in terms of circuits, rather than single structures. Distinctions in circuitry have been noted for the dorsolateral, medial (i.e., anterior cingulate), and orbitofrontal regions of the prefrontal cortex (Middleton & Strick,

2002). There appears to be partial specificity within the frontal lobes relating these different circuits to different behaviors (Fuster, 1997) as well as EF component processes (Rezai, Andreasen, Alliger, Cohen et al., 1993).

The dorsolateral prefrontal cortex appears to be involved in the implementation of control and active manipulation of information (i.e., working memory; Smith & Jonides, 1999). Injury in this region is associated with a "frontal abulic syndrome" (Mesulam, 2002), which involves a disruption of "intensive and selective" attention (Fuster, 1997, p. 172) and is characterized by a loss of initiative and creativity, reduced ability to concentrate, and a tendency towards emotional apathy and flat affect. Medial regions such as the anterior cingulate cortex are activated in conditions requiring performance monitoring, response selection (i.e., resolution of cognitive conflict or interference control), and the modulation of attention and motivation (Devinsky, Morrell, & Vogt, 1995; Kerns, Cohen, MacDonald, Cho, Stenger, & Carter, 2004; Smith & Jonides, 1999; Stuss, Floden, Alexander, Levine, & Katz, 2001). Too much anterior cingulate activity may be associated with obsessive-compulsive and tic-like symptoms, while too little activity has been related to diminished self-awareness, apathy, and depression (Devinsky et al., 1995; Fuster, 1997). The dorsolateral and anterior cingulate regions appear to provide complementary cognitive activities, with the dorsolateral cortex executing control, and the cingulate cortex selecting, monitoring, and assessing performance (Kerns et al., 2004).

Damage to orbitofrontal regions seems to spare most cognitive functions (Fuster, 1997), but they appear to be involved in using reward to guide actions as lateral regions are likely to be activated for suppression of a previously rewarded response (Elliott,

Dolan, & Frith, 2000). Thus, along with more ventrolateral regions (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2004; Konishi, Nakajima, Uchida, Hideyuki, Kameyama, & Miyashita, 1999), the orbitofrontal cortex may play a role in response inhibition tasks (Casey, Castellanos, Giedd, & Marsh, 1997), which are important to many executive models. Injury here results in a "frontal disinhibition syndrome" (Mesulam, 2002), which is characterized by deficits in the "exclusionary" aspect of attention (Fuster, 1997, p. 174). Individuals with this disorder have difficulty suppressing interference from external or internal stimuli. The result is behavioral excesses with too much drive and impulsivity, lack of judgment or ability to learn from experience, and disregard for social conventions.

This interpretation of functional localization in the prefrontal cortex provides some intriguing and potentially heuristic hypotheses regarding psychiatric behavior disorders. For instance, based on its symptom links with damage to the dorsolateral and medial regions, depression may involve deficits on tasks assessing perseverative responding, planning, working memory, verbal fluency, temporal organization of behavior, and interference control. ADHD, with its surface similarity to symptoms that follow damage to dorsolateral and orbitofrontal regions, may be associated with similar impairments to those hypothesized for depression, with the addition of response inhibition and excluding interference control due to a focus on orbitofrontal, not medial, dysfunctions. Individuals with ASPD may have problems with response inhibition tasks because of the parallels with orbitofrontal lobe damage. Alcohol and drug abuse disorders do not fit neatly into this theory, but their symptomatology may correspond to the behavioral effects following orbitofrontal and dorsolateral lobe damage, and therefore

they may be associated with many of the same deficits as ADHD. Finally, the anterior cingulate regions may be important for anxiety disorders.

How have these sorts of suppositions panned out? In reality, there are varying levels of support for differential componential deficits from studies of EF and the individual disorders (to be detailed below). Further complicating clarity on this issue is the frequent comorbidity between psychiatric disorders (Kessler et al., 2005a; Kessler et al., 2005b), which is often not addressed adequately in neuropsychological studies. This made pertinent an examination of EF deficits in psychopathology that attempted to explicitly assess the contributions of individual as well as comorbid disorders to more fully understand the relationship between EF and psychopathology. Based on the above-mentioned neuroanatomy literature, there could be some partial differentiation of EF component processes mapping onto disorders. However, given that this was not a straightforward association, other models were considered to explain EF and psychopathology.

Following is a review of recent studies done on EF deficits and brain function for the individual disorders that were included in the present study. This overview will illustrate the complexities and similarities in the literature across studies. The effects of comorbidity will also be noted where relevant. Thereafter, the issue of comorbidity will be addressed more directly.

EF in Key Psychopathologies

As mentioned, because EF are potentially relevant to so many disorders, some decisions had to be made regarding which disorders to include in the present study. Selection criteria included prevalence of the disorders in the general population,

frequency of comorbid presentations, and similarities in symptomatology. Further, all of the disorders that were selected for inclusion were associated with EF deficits in some manner, and until now their frequent co-occurrence (Kessler et al., 2005a; Kessler et al., 2005b; Kessler et al., 1994) had made it difficult to isolate their individual neuropsychological correlates. Thus, the disorders included are: childhood externalizing disorders (i.e., ADHD, CD, and ODD), antisocial personality disorder (ASPD), alcoholism, drug dependence, major depressive disorder (MDD), and anxiety disorders. Selectivity was required in view of the size of some of these literatures. Therefore, recent reviews, meta-analyses, and major studies conducted in the past ten years are emphasized. Further, clinical neuropsychological measures are emphasized, with less focus placed upon experimental studies. A table is presented in Table 1 of Appendix B to summarize the main patterns of EF deficits across disorders and regional involvement that are suggested by the following reviews.

ADHD and Externalizing Disorders Typically Diagnosed in Childhood (Manifestations in Adulthood)

Many articles have been published on neuropsychological functions and ADHD, with a particular emphasis on EF task performance because of the frequent behavioral comparisons between individuals with ADHD and those with frontal lobe damage (Pennington & Ozonoff, 1996). The vast literature has covered the performance of children, adolescents, and, more recently, adults on a very wide range of cognitive tests with widely varying results. Recent reviews and meta-analyses have attempted to synthesize the vast literature (Berlin, 2003; Sergeant et al., 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). More recently, attention has turned towards adult ADHD,

and this summary will focus upon these studies as the present examination included adults. Numerous articles also suggest there are associations between EF and disruptive behavior disorders diagnosed in childhood, such as oppositional defiant disorder (ODD) and conduct disorder (CD; Pennington & Ozonoff, 1996; Willcutt et al., 2005). These disorders are frequently comorbid with childhood ADHD (Kuhne, Schachar, & Tannock, 1997), and shared genetic risk factors for these disorders and EF deficits have been suggested (Coolidge, Thede, & Young, 2000). However, the relationship between childhood diagnoses of CD and ODD and adult neuropsychological functioning has not been directly studied. Preliminary information is provided by studies of EF and antisocial personality disorder, a possible adult manifestation of CD, which is reviewed below. Therefore, this section will focus upon EF deficits in adult ADHD.

Neuropsychological test performance. Adults with ADHD have shown deficits on a wide range of tasks assessing EF processes. Impairments have been seen on tasks assessing response inhibition, cognitive flexibility, set-shifting and maintenance, verbal fluency, working memory, planning, decision making, and strategy formation (Johnson, Epstein, Waid, Latham, Voronin, & Anton, 2001; Murphy, Barkley, & Bush, 2001; Nigg et al., 2005; Schweitzer, Faber, Grafton, Tune, Hoffman, & Kilts, 2000; Seidman, Biederman, Weber, Hatch, & Faraone, 1998; Walker, Shores, Trollor, Lee, & Sachdev, 2000). Other studies have found that individuals with ADHD have performed normally on EF tasks which assessed interference control, working memory, and planning (Holdnack, Moberg, Arnold, Gur, et al., 1995; Riccio, Wolfe, Davis, Romine, George, & Lee, 2005; Riccio, Wolfe, Romine, Davis, & Sullivan, 2004; Weyandt et al., 1998), but

often the sample size was small and power was low. Thus, many EF deficits have been reported.

Similarly, in their review of the adult ADHD literature, Woods, Lovejoy, & Ball (2002) found that compared to normal controls, adults with ADHD showed selective deficits in divided and sustained attention, verbal fluency, auditory verbal list learning, planning/organization, behavioral inhibition/impulsivity, cognitive flexibility, and speed of information processing. Most of these impairments involve EF abilities. Based upon their findings for the neuropsychological profile of adults with ADHD, Woods et al. (2002) concluded that the disorder represented a disruption of the dorsolateral prefrontal cortex, and to a lesser extent the orbitofrontal cortex. Further, they (Woods et al., 2002) suggested that ADHD adults could not be differentiated from individuals with other disorders using neuropsychological test performance (Riccio et al., 2005; Riccio et al., 2004; Walker et al., 2000; Weyandt et al., 1998). However, poor controls for subclinical ADHD symptoms in these studies may have contributed to these findings. Therefore, EF test results supported dorsolateral prefrontal, and possibly orbitofrontal, dysfunction. Reduced sensitivitity to discriminate individuals with ADHD from other psychiatric disorders may be partially related to poor controls for subclinical symptomatology.

Recent meta-analyses are particularly helpful in the present context because they provide effect sizes for several widely used tasks that assess different EF processes. The most relevant analyses to the present study, due to their focus on adults with ADHD, were done by Hervey, Epstein, & Curry (2004) and Boonstra, Oosterlaan, Sergeant, & Buitelaar (2005). An examination of different EF processes shows that certain tasks are more likely to show group differences than others within each domain. Problems with

response inhibition have been considered central to ADHD in children (Pennington & Ozonoff, 1996), and the largest effect size for tasks in this EF domain was found for the Stop Signal Reaction Time (SSRT) variable (d = 0.85), a measure of response inhibition from the Stop Signal Task (Hervey et al., 2004). This result is in accordance with the findings from child cognitive studies, as group differences are most consistently seen for SSRT in EF tasks (Willcutt et al., 2005) and group differences were recently found in the largest study to date of adults with ADHD (Nigg et al., 2005).

Such strong findings are not always seen for tasks that include some response inhibition demands. Despite a small to large effect sizes for speed of information processing on the color, word, and color-word trials of the Stroop task (d = 0.30, 0.23, and 0.47, respectively for Hervey et al., 2004; d = 0.62, 0.60, and 0.89, respectively for Boonstra et al., 2005) the effect size for Stroop Interference, which is primarily a measure of interference control that involves some response inhibition, was almost negligible in ADHD adults (d = 0.15 for Hervey et al., 2004; d = 0.13 for Boonsta et al., 2005). This suggests that adults with ADHD may have slower processing speed times, consistent with results from individual studies (Corbett & Stanczak, 1999; Johnson et al., 2001; Nigg et al., 2005; Walker et al., 2000), but do not experience additional impairment from the interference control demands of the task. However, this has, perhaps somewhat misleadingly, been interpreted as support for deficits simply in response inhibition (Boonstra et al., 2005). Although a large study supported interference deficits in adults with ADHD (Murphy et al., 2001), most studies have generally suggested that Stroop interference is not performed more poorly by adults with ADHD (Johnson et al., 2001; Lovejoy, Ball, Keats, Stutts, Spain, Janda et al., 1999; Nigg et al., 2005; Riccio et al.,

2005; Walker et al., 2000). It is possible that the motor requirements in the Stop task may have contributed to deficits in the ADHD adults, as adults with ADHD have shown deficits on tasks assessing motor but not cognitive inhibition (Nigg, Butler, Huang-Pollock, & Henderson, 2002), and increased motor task demands contribute to deficits in performance across tasks with ADHD adults (Hervey et al., 2004). Therefore, ADHD adults do not appear to have deficits in cognitive interference control but do for more motoric response inhibition tasks.

As for other aspects of EF, adults with ADHD showed moderate to large effect sizes for tasks that assessed working memory (d = 0.44 - 0.83), verbal fluency (d = 0.62 - 0.63), and planning (d = 1.09; Boonstra et al., 2005; Hervey et al., 2004). However, in individual studies with smaller sample sizes these results were not always sustained (Riccio et al., 2005; Riccio et al., 2004; Weyandt et al., 1998). With regards to set-shifting abilities, adults with ADHD performed more poorly on some tasks in this domain (i.e., Trail Making Test B; d = 0.65 - 0.68), but tended not to on others (i.e., Wisconsin Card Sorting Task (WCST); d = 0.02 - 0.12; Boonstra et al., 2005; Hervey et al., 2004). A similar pattern was seen in another meta-analytic review which included studies of children, adolescents, and adults (Frazier, Demaree, & Youngstrom, 2004). Deficits on the WCST are not consistently observed in adults with ADHD (Johnson et al., 2001; Riccio et al., 2005; Riccio et al., 2004), although they have been demonstrated in a large study (Nigg et al., 2005). Trail Making Test B requires motor control and cognitive set-shifting, while WCST requires working memory and conceptual-level responding in addition to set-shifting. Therefore, similar to the results for response inhibition, it appears as though the motor and time pressure demands for the Trail Making Test may

have contributed to increased impairments in the ADHD group. Hervey et al. (2004) noted that across domains, ADHD adults' performance tended to deviate more and more from controls as task demands such as motor, time, and complexity increased. Therefore, although both WCST and Trail Making Test B are arguably set-shifting tasks, the additional demands created by the time pressure and greater motor demand of the Trail Making Test B appear to make it more sensitive to ADHD adults' set-shifting impairments.

The largest studies done to date suggest that there are deficits across a wide range of EF abilities such as fluency, working memory, set-shifting, and response inhibition (Murphy et al., 2001; Nigg et al., 2005). Therefore, some of the discrepant findings for these processes may have resulted from small sample sizes in the individual studies. Overall, tasks that appear to tap orbitofrontal and dorsolateral processes and which involve more demands on speed, motor control, and complexity are better able to differentiate between ADHD adults and healthy controls.

Effects of comorbidity on neuropsychological test performance. High rates of antisocial behavior, substance abuse, anxiety, and mood disorders are seen in adults with ADHD (Biederman, Faraone, Spencer, Wilens et al., 1993; Biederman, Wilens, Spencer, Faraone et al., 1996). Individuals with comorbid disorders are often excluded from studies of adults with ADHD. When this constraint is not imposed, high rates of the co-occurring disorders are commonly reported, but not necessarily controlled, for adults with ADHD (Corbett & Stanczak, 1999; Riccio et al., 2005; Riccio et al., 2004). When neuropsychological test results were statistically adjusted for the presence of comorbid conditions, ADHD deficits remained robust in adult studies (Nigg et al., 2005; Seidman

et al., 1998) and in a meta-analytic review of pediatric/adolescent studies (Willcutt et al., 2005). While the presence of a comorbid Axis I disorder has resulted in elevated EF deficits (Downey, Stelson, Pomerleau, & Giordani, 1997), this is not a consistent finding (Murphy et al., 2001), but this latter negative finding may have been due to low statistical power after splitting a continuous variable to define comorbid depression in adults with ADHD (Hervey et al., 2004). Overall, comorbidity effects have not been able to explain ADHD deficits, yet have not been fully mapped.

Neuroimaging studies. A recent review of neuroimaging studies in ADHD suggested that abnormalities in structure and function have been found in the lateral prefrontal cortex, dorsal anterior cingulate cortex, basal ganglia (expecially caudate), corpus callosum, and cerebellum (Seidman, Valera, & Bush, 2004). An early study suggested that ADHD adults had lower prefrontal activity in response to a cognitive challenge compared to controls (Zametkin, Nordahl, Gross, King et al., 1990). Differences in neural activation were seen with a working memory task, as adults with ADHD had more diffuse activation and lacked task-related frontal activation compared to controls (Schweitzer et al., 2000). Adolescents with ADHD showed reduced activation of the right inferior prefrontal cortex during successful response inhibition on the Stop Signal Task (Rubia, Smith, Brammer, Toone, & Taylor, 2005). Thus, abnormalities in the fronto-striatal circuits appear to be relevant to the cognitive deficits seen in ADHD (Seidman et al., 2004).

Taken together, the results of neuropsychological testing and neuroimaging implicate the involvement of fronto-striatal circuits in ADHD. Individual EF tasks show differential sensitivity to impairments in cognitive performance, but the pattern of deficits

suggest that the inferior/orbitofrontal and dorsolateral prefrontal cortex and associated subcortical circuitry may be particularly important for the deficits seen in ADHD.

Antisocial personality disorder

Antisocial personality disorder (ASPD), an adult version of CD, has received a great deal of attention in the neuropsychological and neurological literature as researchers have attempted to understand the cognitive, biological, and social mechanisms that contribute to its development. However, inconsistencies in the definition and operationalization of antisocial behavior have contributed to lack of cohesion in the literature (Morgan & Lilienfeld, 2000). Three main approaches have dominated the literature: (1) the clinical diagnosis of ASPD, defined by the DSM-IV as a pervasive pattern of disregarding and violating the rights of others with a childhood history of CD (American Psychiatric Association, 1994); (2) the personality dimension of psychopathy, which involves a constellation of personality traits such as lack of remorse or sincerity and impoverished emotional reactions, and is assessed using multiple methods (Cleckley, 1941; Hare, 1996); and (3) the legal concepts of criminality and delinquency. These definitions of antisocial behavior show considerable overlap and intercorrelations, but they are distinct (Morgan & Lilienfeld, 2000). In the interest of consistency, the present paper will focus on clinically-based DSM definitions of ASPD, but other definitions of antisocial behavior will be covered when they help to elucidate the literature.

Neuropsychological test performance and effects of comorbidity. A fairly recent meta-analysis (Morgan & Lilienfeld, 2000) included studies using all of these operationalizations of antisocial behavior and examined effect size differences between individuals with antisocial behavior and controls on six widely used measures of EF:

Category Test, Porteus Mazes Test, Stroop Interference Test, Trailmaking Test Part B, WCST perseverative errors, and verbal fluency tests. EF processes that are assessed with these tasks include set-shifting and maintenance, working memory, interference control, cognitive flexibility, and response inhibition. Across studies and different antisocial behavior definitions, there was a medium weighted mean effect size (d = .62); the effect sizes for criminality and delinquency were in the large range (d = 1.09 and .86, respectively), CD and psychopathy were in the small to medium range (d = .40 and .29, respectively), and ASPD (DSM-III or DSM-IIIR) had negligible but statistically significant effect sizes (d = .10) (Morgan & Lilienfeld, 2000). It should be noted that very few studies have been conducted using DSM definitions of ASPD. Nonetheless, these findings suggest a weak relationship between EF deficits and ASPD.

Studies done since this meta-analysis have corroborated Morgan and Lilienfeld's (2000) findings that individuals with ASPD may not perform more poorly than controls on typical tests of EF. Individuals with ASPD did not perform more poorly than normal (Barkataki, Kumari, Das, Hill, Morris, O'Connell et al., 2005; Stevens, Kaplan, & Hesselbrock, 2003) or psychiatric controls (Crowell, Kieffer, Kugeares, & Vanderploeg, 2003) on the WCST, a measure of concept formation and working memory. Similar null effects were seen for tasks assessing set-shifting, planning, and interference control (Barkataki et al., 2005; Stevens et al., 2003), although this is not a consistent finding (Dolan & Park, 2002). Moreover, individuals with ASPD *plus* the personality dimension of psychopathy have shown deficits in performance on these processes (Dinn & Harris, 2000). It may be that individuals with ASPD are more likely to show deficits in EF

performance when they have other comorbid psychopathology, as this was also found for substance use disorder (Malloy, Noel, Longabaugh, & Beattie, 1990).

Unlike the null findings seen with most EF processes, males with ASPD alone have shown differences from controls on response inhibition tasks (Dinn & Harris, 2000; Dolan & Park, 2002; note that Dinn & Harris only approached significance). These results suggest that ASPD alone may not be associated with deficits on tasks assessing typical EF processes such as set-shifting, working memory, and interference control, but do show deficits on response inhibition. Response inhibition processes appear to rely upon different neural networks in the prefrontal cortex (Aron et al., 2004), suggesting that ASPD may primarily be associated with dysfunction in lateral-ventral (i.e., orbitofrontal) regions of the prefrontal cortex. Similar discrepancies in findings with psychopaths (Gorenstein, 1982; Hart, Forth, & Hare, 1990; Lapierre, Braun, & Hodgins, 1995; Pham, Vanderstukken, Philippot, & Vanderlinden, 2003; Sutker & Allain, 1987) also provide support for this regional involvement.

Neuroimaging and lesion studies. Brain lesion studies show parallels between orbitofrontal lobe damage and antisocial behavior disorders. Cases of "acquired sociopathy" have been reported following damage to the orbitofrontal region of the brain (Blair & Cipolotti, 2000), and the resultant syndrome is characterized by personality changes and cognitive deficits on inhibition tasks (Fuster, 1997; Malloy, Bihrle, Duffy, & Cimino, 1993), similar to those seen in individuals with ASPD (Dinn & Harris, 2000; Dolan & Park, 2002). MRI has revealed reduced prefrontal gray matter volume in uninstitutionalized men with ASPD, suggesting evidence of a structural brain deficit in

that region of the brain (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000). Such findings provide support for cerebral dysfunction being involved in the disorder.

However, when regions of the prefrontal cortex were assessed in adults with ASPD and alcoholism, Laakso and colleagues (2002) found that only duration of alcohol use and education predicted their volume deficits. This suggests that comorbid pathology may be important in brain dysfunctions and cognitive problems. Further supporting this idea, while ASPD has been noted as an outcome for a subset of children with ADHD, perhaps mediated by deficits in EF (McKay & Halperin, 2001), antisocial behaviors in adolescents with ADHD do not individually contribute to cognitive deficits seen on any typical EF processes (Déry, Toupin, Pauzé, Mercier, & Fortin, 1999). Therefore, ASPD appears to be associated with certain specific cognitive deficits that may partly involve dysfunctions in the orbitofrontal prefrontal cortex. However, more general EF deficits may not been seen except in association with correlates of ASPD such as comorbid disorders.

Taken together, these results suggested that individuals with ASPD would not perform poorly on some of the more common tasks assessing major EF processes. More general deficits in EF may be seen when there are comorbid disorders such as ADHD and alcoholism. Behavioral parallels exist between damage to the orbitofrontal cortex and the symptomatology of ASPD, and response inhibition deficits in individuals with ASPD further support the possible involvement of this region of the brain. However, it may be difficult (or nearly impossible) to fully separate ASPD from comorbid disorders such as alcoholism and ADHD in order to determine their individual contributions to

neuropsychological impairment due to the strong overlap in symptomatology between these disorders.

Alcoholism

Neuropsychological test performance. Alcohol dependence has been associated with deficits in a wide range of EF processes. These deficits are so frequently observed that a 'frontal hypothesis' has been proposed. As a possible explanation for the cognitive impairments that follow chronic alcohol abuse, this hypothesis suggests that the frontal lobes are particularly susceptible to alcohol-related damage (Ratti, Bo, Giardini, & Soragna, 2002). Chronic alcoholics have performed more poorly than controls on tests assessing working memory, cognitive set-shifting, abstract reasoning, fluency tests, response inhibition, and interference control (Adams, Gilman, Koeppe, Kluin et al., 1993; Brokate, Hildebrandt, Eling, Fichtner, Runge, & Timm, 2003; Dao-Castellana, Samson, Legault, Martinot, Aubin, Crouzel et al., 1998; Hoffman, Hall, & Bartsch, 1987; Poon, Puttler, Zucker, Nigg, & Fitzgerald, 1999; Ratti et al., 2002; Uekermann et al., 2003). Thus, deficits have been found across a wide range of individual EF processes (Ratti et al., 2002).

To increase power, many studies have examined combined or composite scores from tests assessing general cognitive domains. When using this type of an analysis, adults with alcohol dependence have shown deficits on EF factor scores which included processes such as working memory, set-shifting, conceptual reasoning, and interference control (Goldstein, Leskovjan, Hoff, Hitzemann, Bashan, Khalsa et al., 2004b; Selby & Azrin, 1998; Sullivan, Fama, Rosenbloom, & Pfefferbaum, 2002). It should be noted that when results for individual tests were analyzed in these studies, few differences were

found in task performance, which suggested the need for a composite analysis. It may be that the impairment was mild in these studies, and could only be detected through analysis of the EF construct as a whole and not in component parts. Different levels of severity for alcohol abuse/dependence may have resulted in weaker findings in some studies versus others. However, although there appears to be some decreases in deficits with long-term abstinence (Selby & Azrin, 1998), EF impairment persists (Munro, Saxton, & Butters, 2000). Therefore, similar to ADHD, EF deficits are often noted in adults with alcohol dependence, even with remittance of the disorder, although the specific level and type of impairment tends to vary across studies.

Effects of comorbidity and genetic liability on neuropsychological test performance. Again, the issue of comorbidity is important for research on alcoholism. In a recent study on the neuropsychological performance of 43 alcoholic women, only 11 were free of other lifetime Axis I comorbidities (Sullivan et al., 2002). Nine of the comorbid women met criteria for one other disorder, while the remainder met criteria for two or more lifetime Axis I disorders; depression and drug abuse were most frequently diagnosed. Comorbid disorders were not taken into account in their analyses, however, so it can be questioned whether their finding that alcoholic women performed more poorly on an EF composite was due to alcohol dependence or other comorbid disorder. Uekermann and colleagues (2003) examined the potential effect of depression upon neuropsychological performance in alcoholics. While adult alcoholics performed more poorly on EF measures than controls, there were no differences in comparison to individuals with alcoholism and depression (Uekermann et al., 2003). In males, ASPD is frequently comorbid with alcoholism (Kessler et al., 1997), and the association and

interaction between these two disorders has been a focus as a possible second type of alcoholism (Zucker, Ellis, Bingham, & Fitzgerald, 1996; Zucker, Ellis, & Fitzgerald, 1992; Zucker, Ellis, Fitzgerald, & Bingham, 1996). In neuropsychological studies, it has been shown that alcoholic individuals with ASPD perform more poorly on neuropsychological tasks than pure alcoholics (Giancola & Moss, 1998; Malloy, Noel, Rogers, Longabaugh et al., 1989), although this is not a consistent finding (Hoffman et al., 1987; Sutker & Allain, 1987). Thus, results vary with regard to the effect that comorbid disorders have on the cognitive performance of adults with alcoholism. ASPD has been the most heavily studied disorder in this regard. Although results are not consistent, they suggest that the presence of a comorbid disorder is likely to be important.

Further complicating the findings on alcoholism is a related line of research suggesting that EF deficits may actually precede alcohol use and that these deficits are risk factors for the development of problem drinking (Nigg, Glass, Wong, Poon, Jester, Fitzgerald et al., 2004). Alcoholism has been shown to be heritable (Knopik, Heath, Madden, Bucholz, Slutske, Nelson et al., 2004), and a number of recent studies have used the high-risk paradigm to examine neuropsychological functioning in the children of alcoholic parents. Findings indicate that the sons of alcoholics show greater EF deficits compared to the offspring of non-alcoholic control parents (Pihl, Peterson, & Finn, 1990). A family history of alcoholism has been associated with deficits in EF abilities such as response inhibition (Nigg et al., 2004), while inconsistent results have been obtained for the presence of conceptual set-shifting deficits in children of alcoholics (Corral, Holguín, & Cadaveira, 2003; Corral, Holguín, & Cadaveira, 1999). The presence of familial comorbidity, particularly ASPD, may also contribute to certain cognitive deficits. Family

history of *both* alcoholism and ASPD appears to be associated with a different set of cognitive deficits than those seen with alcoholism alone, as they involve general intelligence and reward-response (Nigg et al., 2004). Stevens and colleagues (2003) found that planning errors were increased in individuals with a family history of alcoholism, but there was an interaction effect between family history of alcoholism and ASPD, which resulted in difficulties inhibiting prepotent motor responses as well.

These precursor EF deficits appear to increase risk for the development of alcohol problems (Giancola, Shoal, & Mezzich, 2001; Nigg, Wong, Martel, Jester, Puttler, Glass et al., 2006). Although it has been suggested that this relationship is fully mediated by comorbid antisocial behavior (Giancola et al., 2001), such findings may only hold for general substance disorders as opposed to alcoholism per se. For instance, even after controlling for child externalizing behaviors, response inhibition deficits in children predicted later alcohol-related behaviors and problems (Nigg et al., 2006). Therefore, family history of alcoholism, or alcoholism and ASPD, appears to be associated with EF deficits which may place adolescents at increased risk for developing alcohol problems themselves.

Neuroimaging studies. Neuroimaging research has supported frontal lobe differences in alcoholism. While chronic alcoholics have lower global rates of metabolism (Volkow, Hitzemann, Wang, Fowler et al., 1992), selective hypometabolism has also been found in the frontal lobes (Volkow et al., 1992), and a post-mortem study showed that alcoholics have fewer neurons in the frontal lobes compared with non-alcoholic controls (Harper & Kril, 1985). A large percentage of recovered alcoholics, studied after withdrawal symptoms had remitted, showed hypoperfusion of the frontal

lobes, with reduced rCBF being related to duration of drinking and presence of comorbid antisocial personality disorder (Kuruoglu, Arikan, Vural, Karatas et al., 1996). Some findings suggest that the frontal dysfunction is isolated to the mediofrontal region as selective hypometabolism has been found in the medial part of the frontal lobes, which includes the anterior cingulate gyrus (Adams et al., 1993; Dao-Castellana et al., 1998). Dao-Castellana and colleagues (1998) found that healthy, neurologically intact adult alcoholics primarily had hypometabolism in the mediofrontal region (including the anterior cingulate gyrus), as well as dysfunction in the left dorsolateral prefrontal cortex, but not the orbitofrontal cortex (Dao-Castellana et al., 1998). Others have also found differences in metabolism in the anterior cingulate cortex and dorsolateral prefrontal cortex (Goldstein et al., 2004b). These findings had neurobehavioral implications as hypometabolism in the mediofrontal lobes was correlated with impaired performance on verbal fluency and slower speed on the Stroop color-word condition, while the left dorsolateral hypometabolism was related to increased errors on the Stroop test (Dao-Castellana et al., 1998). Thus, neuropsychological deficits are correlated with metabolic abnormalities in the frontal lobes of chronic alcoholics. However, with time, frontal brain abnormalities may subside following abstinence (Gansler, Harris, Oscar-Berman, Streeter, Lewis, Ahmed et al., 2000).

Taken together, these results suggest that chronic alcohol dependence is associated with deficits in EF, but EF may be both a contributor and an outcome. First, the consistency of these impairments, in conjunction with neuroimaging findings, has prompted researchers to suggest a frontal lobe hypothesis, involving the dorsolateral, medial, and orbitofrontal regions (the latter being based on response inhibition deficits),

to explain some of the cognitive changes following heavy alcohol abuse. Second, however, EF deficits are associated with a family history of alcoholism, and therefore the cognitive impairments may actually precede and increase risk for the onset of alcohol use disorders. Finally, comorbid disorders such as ASPD may contribute to the cognitive profile by amplifying the deficits associated with alcohol use as well as the familial risk outcomes. Therefore, it appears as though there are multiple routes by which alcohol can contribute to EF impairments. Each of these pathways - family history of alcoholism/ASPD, chronic use, and antisocial comorbidity - may interact to produce the observed deficits on neuropsychological tests of EF.

Drug Dependence

Studies on drug use tend to include different definitions of substance use and methods of diagnosis. A recent review included both abuse and dependence and noted that there is a general paucity of studies on EF and drug use (Lundqvist, 2005). Based on this, the present review will include findings for heavy abuse and dependence, although the focus is upon dependence. Despite the inherent difficulties in the analysis, some studies have been able to isolate the cognitive profiles for abuse of different drugs. Data collected from a large epidemiological study suggested that marijuana and cocaine were the two most commonly abused drugs (Petry, Stinson, & Grant, 2005), which has also been seen in treatment populations (Miller, Klamen, Hoffmann, & Flaherty, 1996). Therefore, my review will focus on these two drugs.

Neuropsychological test performance. Generally mild and inconsistent neurocognitive deficits have been seen in groups with substance disorders. Chronic cocaine users showed less severe deficits on an EF composite than individuals with

alcoholism, although no differences were seen on the individual tests (Goldstein et al., 2004b). Similar findings were seen in another study that attempted to isolate the specific deficits associated with cocaine abuse and dependence (Selby & Azrin, 1998). Cocaine users did not perform differently from controls on tests assessing neuropsychological functioning, while poly-substance and alcohol abuse/dependence were associated with a number of cognitive impairments, including deficits in set-shifting, interference control, and verbal fluency. A recent meta-analysis on the cognitive effects of cocaine abuse (Jovanovski, Erb, & Zakzanis, 2005) found that the median effect size for a wide variety of tests was 0.35. However, a number of EF tests had effect sizes greater than this median effect; large effect sizes were seen for a general EF factor score, and a conceptual reasoning test, while medium effect sizes were obtained for an interference control test (Stroop interference), and set-shifting test (Trail Making Test, B), and small for another set-shifting test that involved working memory (WCST). This suggested that chronic cocaine users do show some mild dose-related (Bolla, Rothman, & Cadet, 1999) neurocognitive deficits, particularly in conceptual reasoning, psychomotor set-shifting, and interference control. Differences in inclusion criteria (i.e., abuse versus dependence) which affect amount and frequency of drug use, as well as small sample sizes, likely contributed to a weak ability to detect differences between drug users and healthy controls in individual studies.

Marijuana is also a commonly abused substance, but few studies have examined its relationship with EF. Heavy marijuana users had more perseverative errors than light users on the WCST, a test of working memory and set-shifting, following at least one day of abstinence (Pope & Yurgelun-Todd, 1996). These deficits appear to continue through

even longer periods of abstinence. Bolla and colleagues (2002) found that there were performance decrements on tests of memory and EF processes, such as set-shifting and interference control, in long-term users following a month of abstinence. Such deficits are not consistently seen (Eldreth, Matochik, Cadet, & Bolla, 2004; Gruber & Yurgelun-Todd, 2005), but similar to cocaine there appears to be a dose-related effect of marijuana use, with amount, not duration, being related to cognitive impairment (Bolla et al., 2002; Bolla et al., 1999). Thus, dose-related EF deficits are sometimes seen with marijuana use; although deficits are inconsistent, they appear to remain at least following short-term periods of abstinence.

Effects of comorbidity on neuropsychological test performance. Few studies of the neuropsychological effects of substance use have clear implications for the individual deficits associated with drug dependence, as it is difficult to isolate participants who do not have comorbid substance (i.e., alcoholism or other drugs) or other disorders. The importance of these factors was evident from a recent latent variable analysis of cognitive performance in drug-abusing patients (Fals-Stewart & Bates, 2003). It was shown that alcohol use and *number* of current substance dependence diagnoses were important contributors to current EF abilities, along with education and IQ. Further, these deficits have been proposed to precede and, along with family history of substance use, increase risk for drug use (Giancola & Tarter, 1999). These findings suggest that comorbid disorders contribute considerably to the cognitive deficits seen in substance use disorders, and make it difficult to interpret any individual contributions.

Neuroimaging studies. Frontal lobe functioning and associated cognitive deficits have been related to the cycle of addiction. A recent review suggested that the

orbitofrontal and anterior cingulate circuits are dysfunctional in individuals with addictions, thus contributing to lack of inhibitory control over reward-related behavior (Lubman, Yücel, & Pantelis, 2004). Others have also noted that these regions are most consistently implicated in the stages of addiction such as intoxication, craving, and binging, and they are deactivated during withdrawal (Goldstein & Volkow, 2002; Volkow, Ding, Fowler, & Wang, 1996).

These findings have implications for functional imaging. Frequent cocaine users had reduced activity in the anterior cingulate and right prefrontal cortex while completing a response inhibition task which involved working memory demands (Hester & Garavan, 2004). Structural changes are also evident in prefrontal regions; decreased grey matter was found for cocaine-dependent adults in the orbitofrontal and anterior cingulate regions of the brain, along with the insula and some areas in the temporal lobe (Franklin, Acton, Maldjian, Gray, Croft, Dackis et al., 2002). Frequent marijuana users also show functional abnormalities in prefrontal activity. On an interference control task, the Stroop, marijuana smokers demonstrated a different pattern of anterior cingulate activity (as well as more diffuse dorsolateral activity) than control participants, although no differences were noted in task performance between the groups (Gruber & Yurgelun-Todd, 2005). These dysfunctions are still seen even following a 25-day period of abstinence, as Eldreth and colleagues (2004) also found that chronic marijuana users showed a pattern of hypoactivity in the left anterior cingulate and lateral prefrontal cortex, and hyperactivity in the hippocampus even though they did not perform differently from controls on a modified version of the Stroop interference task. These results suggest that there are persistent metabolic changes which affect the prefrontal

regions of the brain (Eldreth et al., 2004). At rest, frequent marijuana users also have hypoactivity in ventral regions of the brain following approximately 26 hours of abstinence (Block, O'Leary, Hichwa, Augustinack, Ponto, Ghoneim et al., 2000), but no structural changes are noted in the brain (Block, O'Leary, Ehrhardt, Augustinack, Ghoneim, Arndt et al., 2000). Therefore, marijuana and cocaine use are associated with functional and structural dysfunctions (the latter only seen for cocaine) in the prefrontal regions of the brain. In particular, the anterior cingulate and orbitofrontal regions appear to be involved in the cycle of addiction.

Taken together, mild EF deficits have been observed with heavy marijuana and cocaine use. These cognitive impairments appear to be dose-related and are related to dysfunctions in prefrontal and associated subcortical regions of the brain, particularly the orbitofrontal and anterior cingulate circuits. The pattern of deficits suggests that comorbid disorders, polysubstance use, familial risk, and preexisting EF deficits may be important to EF impairment. The similarities in the EF deficits across the reviewed drugs suggest that substance dependence disorders should be combined to form one group in the present analyses (i.e., drug dependence). However, alcoholism is associated with more consistent and specific effects, and thus was analyzed separately.

Depression

Neuropsychological test performance. Unipolar depression has been associated with a range of neuropsychological deficits in EF. Research has found that patients have shown consistent deficits on EF tasks during episodes of major depressive disorder. Multiple studies have found impaired set-shifting and maintenance, working memory, interference control, perseverative control, response inhibition, and concept formation

(Austin, Mitchell, Wilhelm, Parker, Hickie, Brodaty et al., 1999; Austin, Ross, Murray, O'Carroll, et al., 1992; Channon, 1996; Fossati et al., 1999; George, Ketter, Parekh, Rosinsky et al., 1997b; Kaiser, Unger, Kiefer, Markela, Mundt, & Weisbrod, 2003; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999; Moritz et al., 2002; Paradiso, Lamberty, Garvey, & Robinson, 1997; Trichard, Martinot, Alagille, Masure et al., 1995). Severity of depressive symptomatology has also been correlated with performance on the WCST, a task which involves set-shifting, concept formation, and working memory (Merriam et al., 1999), and number of episodes and hospitalizations were related to greater cognitive impairment (Purcell, Maruff, Kyrios, & Pantelis, 1998). Chronicity of the disorder may be particularly important to cognitive deficits (Richard et al., 2003). Therefore, there appears to be a strong link between depressive symptoms and EF impairment.

It is sensible that being depressed would weaken cognitive efficiency and problem solving; however, such deficits may last even after the disorder has remitted. Non-symptomatic males with a chronic history of unipolar depression performed more poorly than controls on tasks assessing set-shifting, working memory, and interference control (Paradiso et al., 1997). Again, severity appears to exacerbate this effect. Frequency of affective episodes appears to be a factor in longer term deficits, as patients with recurrent affective episodes, as opposed to a single depressive episode, showed general cognitive deficits during the euthymic phase (Kessing, 1998). However, patients with recurrent affective episodes also had higher levels of subclinical depression, which correlated with some cognitive test results, suggesting that residual symptomatology may account for some of the enduring neuropsychological deficits.

Neuroimaging studies. Neuroimaging studies also support frontal lobe dysfunctions in depressed patients. Unipolar depressed patients show reduced glucose metabolism in the pre-frontal cortex (Baxter, Schwartz, Phelps, Mazziotta et al., 1989; Martinot, Hardy, Feline, Huret et al., 1990), with a possible lateralization effect (Kimbrell, Ketter, George, Little, Benson, Willis et al., 2002). In general, unipolar depressed patients, compared to healthy controls, have decreased dorsolateral and dorsomedial prefrontal regional activity, as well as decreased metabolism in areas of the anterior cingulate gyrus (see reviews: Dougherty & Rauch, 1997; Drevets, 2000; Drevets, Price, Simpson, Todd et al., 1997). Similar to the results from neuropsychological task performance, it is difficult to determine is whether this is a state or trait phenomenon as some effects do not remit with cessation of symptoms. Increased ventrolateral prefrontal/paralimbic metabolism has also been observed (Drevets, Videen, Price, Preskorn et al., 1992); this effect tends to normalize following antidepressant treatment (Drevets, 2000). Thus, patients with depression show widespread prefrontal dysfunctions. Specifically, there is hypometabolism in the dorsolateral and dorsomedial prefrontal cortex and anterior cingulate regions, and increased activity in the ventrolateral prefrontal area.

The findings from neuroimaging studies appear to have functional implications. The dorsal anterior cingulate area appears to be involved in the attentional and cognitive features of depression (Flint, Black, Campbell-Taylor, Gailey et al., 1993), and prefrontal hypometabolism is correlated with severity of features of depression (Kimbrell et al., 2002). Cortical activation has been evaluated during neuropsychological test performance, and depressed patients demonstrate different patterns of activity than

controls. Depressed patients had normal cerebral activity, as measured by event-related potentials, while completing a task which required simple responses to stimuli, but frontotemportal activity was reduced when response inhibition demands were included (Kaiser et al., 2003). During the Stroop task, which assesses interference control, patients with depression had little activation in the anterior cingulate cortex, which is normally activated by controls, but increased activation in the left dorsolateral prefrontal cortex (George, Ketter, Parekh, Rosinsky et al., 1997a). While completing a planning task, depressed patients had no significant activation in the cingulate cortex and striatum and low levels of activity in other prefrontal areas, all of which are typically highly involved in performance by control participants (Elliott, Baker, Rogers, O'Leary et al., 1997). Thus, a general prefrontal dysfunction marked by particular deficits in the cingulate-striatal circuit may be associated with some of the EF deficits observed in depressed patients (Videbach, Ravnkilde, Pedersen, Egander, Landbo, Rasmussen et al., 2001).

Taken together, depressed patients, even those in the euthymic phase, appear to show consistent deficits on a wide range of EF functions. Cognitive deficits appear to be related to severity and number of depressive episodes. Neuroimaging findings support a generalized dysfunction in the prefrontal cortex, as abnormal patterns of activity have been found in the dorsolateral, ventrolateral, and cingulate regions of the brain. These results may be specific to EF deficits or they may reflect a more generalized pattern of cognitive deficits. Given this, it will be important to determine whether any EF deficits can be better accounted for by generalized processing speed deficits. No studies could be located to specifically assess the effect of comorbid disorders upon performance on EF tasks.

Anxiety Disorders

Neuropsychological test performance and neuroimaging studies. Compared to the other disorders covered here, much less attention has been paid to the relationship between EF impairment and anxiety disorders. Sub-clinical anxiety is widely recognized as disruptive to testing as it can adversely affect test performance and cloud interpretation of results (Lezak et al., 2004). However, research has not supported a detrimental effect upon EF abilities such as working memory and set-shifting for experimentally-induced anxiety (Martin & Franzen, 1989) or levels of state or trait anxiety (Gladsjo, Rapaport, McKinney, Lucas, Rabin, Oliver et al., 1998; Waldstein, Ryan, Jennings, Muldoon et al., 1997), although males' performance on a task assessing interference control was adversely affected by induced anxiety (Martin & Franzen, 1989). Therefore, the effects of subclinical levels of anxiety upon neuropsychological test performance are variable and may be somewhat gender specific.

Research on clinical anxiety disorders has predominantly focused upon OCD (Airaksinen et al., 2005). The disorder has frequently been associated with specific EF deficits that are related to frontostriatal dysfunction. These suppositions are partially based on findings of deficits in response inhibition, planning, set-shifting and maintenance, working memory, and interference control (Aycicegi, Dinn, Harris, & Erkmen, 2003; Basso, Bornstein, Carona, & Morton, 2001; Boldrini et al., 2005; Moritz et al., 2002; Penadés, Catalán, Andrés, Salamero, & Gastó, 2005; van den Heuvel, Veltman, Groenewegen, Cath, van Balkom, van Hartskamp et al., 2005). However, the results for the individual studies were inconsistent and the deficits often varied between studies. Suggestions have been made that the primary dysfunction is in the orbitofrontal

cortex (Aycicegi et al., 2003; Basso et al., 2001), but neuroimaging has also shown dysfunctions in the dorsolateral and anterior cingulate regions (van den Heuvel et al., 2005; Van Veen & Carter, 2002). Therefore, general prefrontal dysfunction has been supported by neuropsychological and neuroimaging research. The effects following anterior cingulate damage, however, suggest this region may be of primary interest.

The relationship between EF deficits and other anxiety disorders has received much less attention through neuropsychological studies, and the results are somewhat less compelling. Individuals with panic disorder/agoraphobia have demonstrated intact EF abilities such as working memory, cognitive flexibility, set-shifting, and planning (Asmundson et al., 1995; Boldrini et al., 2005; Gladsjo et al., 1998; Purcell et al., 1998). Compared to controls, adults with panic disorder have shown set-shifting deficits, but this effect disappeared after individuals with an alcohol abuse disorder were removed from analyses, possibly as a result of reduced sample size (Airaksinen et al., 2005). One study also noted a trend towards verbal fluency deficits (Gladsjo et al., 1998). Adults with social phobia tended towards reduced verbal fluency (Airaksinen et al., 2005) and showed impaired performance on a set-shifting task (Cohen, Hollander, DeCaria, Stein et al., 1996); however, other studies do not support such findings (Asmundson et al., 1995; Sachs, Anderer, Margreiter, Semlitsch, Saletu, & Katschnig, 2004). Generalized anxiety disorder (GAD) has been associated with deficits in interference control (Dibartolo, Brown, & Barlow, 1997). No EF impairment has been associated with specific phobia in the literature, although only one study could be found that included this disorder (Airaksinen et al., 2005). Thus, there are some weak findings for EF deficits in

individuals with panic disorder/agoraphobia, social phobia, and GAD, while none have been associated with specific phobia.

The association between EF deficits and post-traumatic stress disorder (PTSD) is somewhat stronger. Impaired performance has been observed on tasks assessing set-shifting, set maintenance, and working memory (Beckham, Crawford, & Feldman, 1998; Koenen, Driver, Oscar-Berman, Wolfe, Folsom, Huang et al., 2001; Stein, Kennedy, & Twamley, 2002). However, such findings may be associated with severity of current psychopathology and limited to lower functioning samples as college students with PTSD did not show any deficits across a wide range of EF tasks (Twamley, Hami, & Stein, 2004). Therefore, deficits in anxiety disorders may be related to severity of the disorder, as suggested by the findings with PTSD.

It has been suggested that anxiety as a trait or a disorder is related to the inability to control cognitive interference, and thus that there are weaknesses in cognitive control (Eysenck & Calvo, 1992). However, it was noted that such deficits would be more apparent on tasks that involved greater cognitive load, particularly those that require efficiency as opposed to effectiveness (Eysenck & Calvo, 1992). This theory has received some support (Calvo & Eysenck, 1996; Hopko, Ashcraft, Gute, Ruggiero, & Lewis, 1998). Thus, previous studies may have missed this effect because the tasks they used may not have put enough demands on speed, working memory, and interference control.

The lack of strong connection between anxiety disorders and EF deficits may be due to emphasis on neural systems outside of the frontal region in maintenance of these disorders. One of the most prominent theories of anxiety was originally proposed by

Gray (1982) and was recently updated (Gray & McNaughton, 1995). This theory involves the septo-hippocampal system, which includes the hippocampus, septal nuclei, dentate gyrus, subiculum, and parahippocampal gyrus. The primary involvement of these systems may explain the paucity of support for EF deficits in anxiety disorders, and findings of memory and learning deficits (Airaksinen et al., 2005; Boldrini et al., 2005; Sachs et al., 2004). However, a review of neuroimaging in anxiety disorders suggested that the orbitofrontal and anterior cingulate cortices are implicated in nearly all manifestations of anxiety (Malizia, 1999), with a focus on increased right frontal activity (Keller, Nitschke, Bhargava, Deldin, Gergen, Miller et al., 2000). It is possible that along with not including measures with large enough task demands to differentiate between adults with anxiety disorders and controls, previous studies may have been hindered by sample sizes that were too small to detect effects on measures associated with frontostriatal functioning.

Taken together, only OCD has been strongly related to EF deficits. Due to the weak findings and lack of real divergent findings across the other anxiety disorder, anxiety disorders were combined to examine the EF effects in related groups of disorders for the present study. Despite the weak findings, anxiety disorders are the most commonly diagnosed psychiatric disorders in the general population (Kessler et al., 2005a), and therefore should be evaluated in some manner in the present study. The large sample size in the present study increased the ability to detect any EF deficits in anxiety disorders. Further, their inclusion enhanced the ability to examine the effects of internalizing symptoms on cognitive functioning. Thus, despite the weak support for EF impairment, anxiety disorders were included in the present study.

Summary

As can be seen from this selective review of the vast literatures examining neuropsychological functioning in individuals with psychiatric disorders, there appears to be support for some deficits in EF with each of these disorders. Yet, the findings also tend to vary considerably, with less support for some disorders (i.e., anxiety disorders, ASPD, and drug use) versus others (i.e., alcoholism, ADHD, and depression). Further, within each of the individual disorders, support for EF deficits is variable and inconsistent, often affected by the specific EF tests used, sample sizes, and presence of comorbid disorders. For instance, the apparent weak support for EF deficits in ASPD may simply be due to very specific regional involvement of the orbitofrontal cortex which is not associated with typical EF processes. As well, while most anxiety disorders are only weakly related to EF deficits, few studies with small sample sizes have hindered the ability to detect any significant effects. Finally, strong relationships between disorders, such as those seen between drug and alcohol use disorders, may create the appearance of EF deficits that are only related to one of these disorders. Despite these drawbacks and variable findings, some differential patterns of deficits can be seen (summarized in Table 1 of Appendix B), providing a theoretical basis for the componential model examining the individual disorders.

However, the results also demonstrated that there are parallels in the literature and interactions between disorders. These substantiated the need to evaluate the relationship between EF deficits and psychopathology at multiple diagnostic levels. As mentioned, inadequate controls for comorbidity have made it difficult to tease apart the independent effects for individual disorders. The parallels in the literature make it pertinent to

understand whether the deficits were differentiable or shared amongst the disorders. The focus now turns to a discussion of the complex problem of comorbidity.

The Problem of Psychiatric Comorbidity

Given the overlap in symptomatology and high rates of comorbidity between many of these disorders, it is questionable whether they should be separated and analyzed individually. To do so may remove core aspects of the disorder that contribute to cognitive deficits. On the other hand, failure to control these effects makes interpretation difficult as comorbidity is recognized as a major impediment to understanding the specificity of deficits to individual psychiatric disorders (Angold et al., 1999; Sergeant et al., 2002).

The importance of understanding the effect of comorbidity is underscored by the frequent occurrences of multiple disorders. The National Comorbidity Study has assessed the patterns of lifetime comorbidity in a large, population-based sample for the disorders of interest for this study. More than half of all individuals who have ever met criteria for a psychiatric disorder have had two or more different lifetime conditions (Kessler et al., 2005a; Kessler et al., 1994). It is certainly a major issue for the disorders reviewed above. Commonly associated disorders include ADHD with ASPD, and mood, anxiety, and substance use disorders (Biederman et al., 1993; Biederman et al., 1996); ASPD with anxiety disorders and substance abuse/dependence (Goodwin & Hamilton, 2003; Petry et al., 2005); alcohol abuse with anxiety and affective disorders in females and other substance and antisocial disorders in males (Kessler et al., 1997); substance disorders with other substance, mood, and anxiety disorders, and ASPD (Agosti, Nunes, & Levin, 2002; Falck, Wang, Siegal, & Carlson, 2004; Miller et al., 1996; Skinstad &

Swain, 2001); depression with anxiety and eating disorders, substance dependence (alcohol and drugs), and ASPD (Biederman, Petty, Faraone, Hirshfeld-Becker, Henin, Pollack et al., 2005; Niles, Mori, Lambert, & Wolf, 2005; Rush, Zimmerman, Wisniewski, Fava, Hollon, Warden et al., 2005); and anxiety disorders with other anxiety, eating, and mood disorders (Belzer & Schneier, 2004; Hunt, Slade, & Andrews, 2004; Sareen, Stein, Cox, & Hassard, 2004). Thus, overlap and co-occurrence of disorders is frequently seen, particularly amongst the disorders of interest in this proposed study

Yet, as noted, many psychiatric studies of EF fail to control for the presence of comorbid syndromes, and without doing so it is impossible to determine whether the outcome is specific to the disorder under question, an associated condition, or some combination of both disorders. Several conceptual models have been proposed to explain the co-occurrence of two disorders (whether concurrently or successively) in the same individual (Wonderlich & Mitchell, 1997). Rejected explanations that cannot adequately account for the rates of comorbidity in most instances include chance co-occurrences of the individual disorders (Lilienfeld, Waldman, & Israel, 1994) and comorbidity as an artifact of research methodology (Angold et al., 1999). Moreover, despite criticisms that the diagnostic system inappropriately separates certain disorders (Krueger, 1999) and includes too many overlapping symptoms (Angold et al., 1999), the taxonomic issues likewise do not completely account for the high rates of comorbidity (Angold et al., 1999).

Theoretical models for comorbid presentations that still remain viable at least for the disorders being considered in the proposed study include the following: (1) the presence of a disorder increasing risk for the development of another disorder; (2)

multiple behavioral manifestations of the same underlying risk factor; and (3) quantitatively different expressions of the same underlying risk factor or disorder (Krueger, 1999; Wonderlich & Mitchell, 1997). Therefore, comorbidity is conceptualized herein as a real phenomenon that can occur for multiple reasons.

The importance of understanding comorbidity comes in part from findings that suggest it can affect the presentation of individual disorders. A number of disorders show different characteristics when they have been preceded by another disorder (i.e., dysthymia and MDD; Kovacs, 1996), and a worse overall outcome has been found for the concurrent overlap of two disorders than would be found for either disorder alone (i.e., ADHD plus an internalizing or externalizing disorder; Angold et al., 1999). In general, comorbidity has been associated with greater severity of psychopathology (Angold et al., 1999; Kessler et al., 2005b). Angold and colleagues (1999) suggested that descriptions of disorders and thus their treatment could be improved by examining the effects of comorbidity. They indicated that certain disorders, such as ADHD and conduct disorder, could be defined by their comorbid conditions because the comorbid presentations were strikingly different from those associated with either of the individual, "pure" forms of the component disorders. Thus, presence of comorbidity has been shown to change the symptom presentations and outcomes of disorders in a manner that may support the diagnosis of a different disorder or a subtype of the disorders in question (Angold et al., 1999). In light of this issue, an examination of EF deficits in multiple psychiatric disorders should specifically evaluate the effects of comorbidity.

Despite the potential confounding effect of comorbid disorders on EF, they have often been neglected in studies of psychopathology and neuropsychological assessment.

An evaluation of psychopathology other than the main disorder in question is not often referenced in studies of EF. When it is evaluated in some manner, it is usually to screen out participants for substance use disorders which could affect sober testing. Attempts to specifically address the potential confound of comorbid disorders often involves excluding participants who meet criteria for any DSM-IV Axis I (or, less frequently, Axis II) disorder aside from the main disorder under question. This effort to isolate the neuropsychological findings to the disorder under study raises a problem, however. That is, given the frequent presentations of comorbid disorders in the general population, the ecological validity of the results may be compromised by excluding so many naturalistic cases (Downey et al., 1997; Kessler et al., 2005a; Kessler et al., 1994; Krueger, 1999). To do so may simply exclude the most severe cases (Angold et al., 1999; Kessler et al., 2005b), and thus lead to an underestimation of EF impairment and poor generalizability. Further, the sole exclusion of current, and not lifetime disorders, overlooks possible persisting EF impairment after disorders have remitted (Kessing, 1998; Munro et al., 2000; Paradiso et al., 1997), which could confound results. Therefore, neuropsychological studies do not usually evaluate the effects of comorbidity in a manner that could help to elucidate its effects upon performance.

As shown in the review of EF studies for the individual disorders, some studies have specifically considered the effects of comorbidity in their evaluation of neuropsychological test performance. Their results highlight the importance of including some assessment of comorbidity as the possibility of an additive neuropsychological dysfunction has received some support (i.e., Downey et al., 1997; Riordan et al., 1999). These studies suggest that comorbid conditions may affect cognitive performance of

individuals with psychiatric disorders, perhaps by amplifying cognitive deficits. On the other hand, performance on neuropsychological tests has not always been affected by comorbid conditions (i.e., Katz, Wood, Goldstein, Auchenbach, & Geckle, 1998; Uekermann et al., 2003). Many of these studies with null effects have been hampered by small sample sizes, particularly once diagnostic groups were separated into those with and without a comorbid condition. Questionable methods for diagnosing comorbid disorders have also been used. Although the few instances where comorbidity was focused upon provided inconsistent results, their findings highlighted the fact that comorbidity could be important to EF impairment. The role of comorbidity is too rarely focused upon in neuropsychological studies, and more clarity is needed on this issue.

Multiple possible hypotheses may be proposed to account for the manner by which comorbid disorders could affect neuropsychological test performance. Specific effects could result, wherein only certain comorbid disorders contributed to EF impairment. Another possibility is that comorbidity is related to increased deficits, regardless of the specific disorders under question. In other words, increased *numbers* of comorbid disorders would be associated with increased neuropsychological deficits. Frost and colleagues (1989) found that although different disorders varied in their cognitive impairment profiles, the presence of multiple conditions was the best predictor of neuropsychological dysfunction. This suggests that just the presence of comorbidity may increase neuropsychological dysfunction, regardless of the results for the individual disorders. Similar findings resulted from a study of adults with ADHD, where number of comorbid disorders was related to the degree of attentional deficits (Taylor & Miller, 1997). Comorbidity is strongly related to severity of psychopathology (Angold et al.,

1999; Kessler et al., 2005b), and this may be the important factor in neuropsychological deficits. Thus, it is unclear whether EF deficits are associated with specific symptom presentations or are merely a marker of nonspecific psychopathology associated with increased numbers of disorders.

Taken together, the presence of comorbid disorders appears to have potentially significant effects upon neuropsychological test profiles, but results thus far have been inconsistent and appropriate studies are few. The lack of focus upon the effects of comorbidity, resulting lack of consistency in the manner with which comorbidity has been dealt, different methods for diagnosing the primary and comorbid disorders, and small sample sizes have complicated any conclusions about specificity in neuropsychological studies. Remaining questions include whether comorbidity affects cognitive performance, whether any effect is only apparent for certain disorders and not for others, and whether EF deficits are associated with specific syndrome constellations or are simply related to psychopathology in a nonspecific manner as part of the "burden of comorbidity," as hinted at earlier in the basic hypothetical models outlined.

These issues were specifically addressed within the present study by focusing on a selected subset of common psychiatric disorders as defined by the DSM-IV diagnostic criteria. In addition, broader, dimensional categories of psychopathology were used to implement a shared-symptom-based analysis as described below. Four models of the relationship between EF and psychopathology were tested to attempt to better understand how claims can be made regarding such wide-ranging involvement of EF deficits in many different disorders. These models moved from specific to more generalized definitions of psychopathology.

Study Objectives

The present study sought to examine the profile of EF deficits and psychiatric disorders in five forms of psychopathology that had been associated in some manner with neuropsychological EF deficits: ADHD, ASPD, alcohol dependence, drug dependence, depression, and anxiety disorders. Previous research in this area failed to account well for comorbidity; this was a specific focus of interest in this study, in order to understand the individual as well as combined contributions to EF impairment. It was important to determine whether EF simply represented a nonspecific marker of disturbance or a key etiological clue, in order to understand why the relationship between EF and psychopathology is apparently believed to be so wide-spread. Tests assessing processing speed, considered a reflection of general cognitive functioning, were included as non-executive neuropsychological measures to help differentiate whether any neuropsychological deficits were specific to EF or were simply a reflection of general neurocognitive impairment.

To recap, four models were tested, which represent four possible explanations for the puzzling extensiveness of EF and psychopathology. The Componential Model hypothesized that each disorder was associated with a different pattern of EF deficits. As highlighted by the review of the neuropsychological literature, there was some suggestion that this may be part of the story. The componential model was examined using a profile analysis to determine whether there are differentiable deficits in individual EF processes (i.e., set-shifting, working memory, response inhibition, and interference control) for each of the psychiatric disorders. Thus, although most disorders appeared to be related to EF deficits, in reality the deficits would be differentiable and not shared across disorders.

The second model, Comorbidity-Specificity, suggested that only some, but not all, disorders were related to more globally-defined EF deficits. This solution also received some support as noted in the literature review earlier. Such an explanation would suggest that the high frequency of comorbidity between disorders, which has been poorly controlled in most studies, had made it appear as though EF deficits were widespread across psychopathology. By looking at the unique contribution of the individual disorders to EF deficits, it was possible to determine whether certain, but not all, disorders were associated with EF deficits and thus accounting for the perceived widespread effects.

The third model, Comorbidity-Nonspecificity, suggested that EF deficits were simply non-specific markers for dysfunction, so that number rather than form of psychopathology contributes to EF deficits. As noted earlier, this model has also received support in some instances. This model suggested that regardless of the particular conditions involved, having more disorders would lead to increased EF impairment.

Finally, the fourth model, dimension-specificity, suggested that the reason that EF deficits were so widely associated with psychiatric disorders was due to shared underlying dimensions of psychopathology. The idea was that the EF deficits were associated with a common dysfunction shared across many disorders, and thus each of these disorders appeared to be individually associated with impairment. The contributions of these superordinate factors, which may represent shared underlying psychopathological dysfunctions amongst disorders, was assessed by examining the

differential effects of "internalizing" versus "externalizing" disorders (see Krueger, 1999) upon the manifestation of EF deficits.

It was possible that one or more of these models would be better able to capture the relationship between EF deficits and psychopathology, or that none would completely capture the complexity of the association. Analyses attempted to take into account the possible contributions of single and multiple disorders, and provide room for a broader examination of the possible contributions of shared "symptomatology." It was intended that these multiple levels of analysis would help to clarify the reasons for the extensive literature identifying relationships between EF and multiple forms of psychopathology.

Methods

Two large samples from two separate, but related, community-based studies were combined for data analyses to assess the relationship between psychopathology and EF. This was a secondary data analysis using already existing data. Fresh data collection was not feasible given the difficulty in obtaining large samples with a wide range of psychopathology to meet the study objectives. The first sample that will be described, the ADHD sample, consisted of adults who were primarily recruited based upon presence of ADHD and controls without ADHD. The second sample consisted of men who were recruited based upon presence of alcohol dependence (with a secondary focus upon ASPD), control men without alcoholism or other such drug use disorder, and their spouses. Many of the participants who met criteria for ADHD or alcoholism also met criteria for additional comorbid disorders, so there was ample representation of ASPD, drug dependence, depression, and anxiety. Further, the control groups for each sample did not meet criteria for the primary disorder of interest (i.e., ADHD or alcoholism), but other psychiatric disorders were allowed to vary (with some exceptions, as described below). Disorders also were free to vary for the spouses in the alcoholism study. Therefore, within the control groups and alcoholism study spouses, psychiatric disorders were adequately represented, as were numbers of individuals with no psychiatric diagnoses for comparison purposes. In total, 641 participants were included in analyses (described in greater detail below).

Sample 1: ADHD Adults and Controls

Participants

Recruitment. Adult participants were recruited from the community via public advertisements and then evaluated in a standard multistage screening and diagnostic evaluation procedure. Prospective participants contacted the project office at which point key rule-outs were checked (age 18-40, no sensory-motor handicap, no neurological illness, no head injury with loss of consciousness, and native English-speaking). Eligible participants were then scheduled for the diagnostic visit wherein they completed semi-structured clinical interviews to further evaluate ADHD and comorbid conditions. The study was described in full detail to all potential participants at their first visit (i.e., prior to the clinical interview). Written informed consent was then obtained from all participants.

Assessment of psychopathology. Potential participants were assessed for current and lifetime childhood and adult disorders, and they provided self-reported levels of impairment for those disorders. Adult Axis I disorders were assessed during a face-to-face interview with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1997). This interview assessed symptoms of the following disorders: MDD, dysthymic disorder, bipolar disorder, substance abuse and dependence, psychotic symptoms, GAD, PTSD, OCD, panic disorder, agoraphobia, simple phobia, social phobia, and eating disorders. ASPD and other personality disorders were assessed with the SCID-II. Disorders that are typically seen in childhood, such as ADHD, CD, and ODD, were assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Puig-Antich & Ryan, 1986). Previously published procedures

for assessing adults for these typically childhood-related disorders were followed (Biederman, Faraone, Keenan, Benjamin et al., 1992; Biederman, Faraone, Keenan, Knee et al., 1990), and the K-SADS interview was worded appropriately to assess both childhood and adult symptoms. These interviews were administered by masters-level clinicians following extensive training, and participants provided self-reported information about their symptoms. Autistic disorder was screened by the clinician using added symptom questions and was a rule-out.

The assessment of adult ADHD requires retrospective assessment of their childhood ADHD status to establish childhood onset by age 12, as well as inclusion of informant interviews to verify symptoms and impairment (Wender, Wolf, & Wasserstein, 2001). Due to the retrospective nature of the interview for the childhood disorders, informants were contacted to verify symptoms and impairment. Two informants were contacted: (1) a 'retrospective' informant (usually a parent) to report on childhood symptoms ADHD, CD, and ODD using modules from the K-SADS; and (2) a 'peer' informant who could report on current levels of ADHD symptomatology using the K-SADS module as well as other current antisocial symptomatology. All informant interviews were conducted by telephone after appropriate consent procedures. To ensure that prospective ADHD participants exceeded normative cutoffs for level of ADHD symptoms, participants and informants completed additional ratings scales (see Nigg et al., 2005).

Diagnostic procedures. A diagnostic team that included a licensed clinical social worker, a licensed clinical psychologist, and a board certified psychiatrist evaluated the item coding for ADHD. A best estimate diagnosis was reached for ADHD status based

upon self and informant ratings. Each team member independently reviewed all available information from SCID, K-SADS, and rating scales to arrive at a clinical judgment about all additional Axis I and II disorders. The DSM-IV criteria regarding comorbidity were carefully followed in all cases, so that although comorbid disorders were diagnosed when present, ADHD was not diagnosed if clinicians judged that symptoms were *better explained* by a co-occurring mood or other major disorder (American Psychiatric Association, 1994). Evidence of impairment was required to make diagnoses. Individuals were classified for each adult disorder according to the following scale: (1) Definite, meets full criteria; (2) Probable, falls one symptom short of full criteria; (3) Possible, falls two symptoms short of full criteria; and (4) No diagnosis, falls three or more symptoms short of full criteria. The rating scale for the K-SADS was different for the childhood disorders: (1) Definite, meets full criteria; (2) Subthreshold, meets criteria for more than half of the symptoms; and (3) No diagnosis, meets criteria for fewer than half of the symptoms. Inter-rater agreement on presence or absence of ADHD (definite) and other disorders were satisfactory (Nigg et al., 2005).

Exclusionary criteria. Potential participants were excluded from the ADHD and the non-ADHD groups if they had a current major depressive or manic/hypomanic episode, current severe substance dependence preventing sober testing, subthreshold childhood ADHD, history of psychosis, history of autism, FSIQ < 75, history of head injury with loss of consciousness (if determined to be of moderate severity), sensory-motor handicap, neurological illness, native language not English, or currently prescribed anti-psychotic, anti-depressant, or anti-convulsant medications. For the non-ADHD group additional exclusions were antisocial or borderline personality disorder, past

bipolar disorder, or a previously diagnosed learning disorder. Bipolar disorder was an exclusion for any individual in the present study due to its potential to confound neuropsychological test results. Other psychiatric disorders were free to vary.

Criteria for testing. Participants that met inclusion criteria were asked to return for neuropsychological testing at the lab offices on the Michigan State University campus. Participants had to be sober during testing. They were checked for recent alcohol, marijuana, and other medication consumption prior to testing. A number of individuals were taking regular psychostimulant medications (Adderall, Ritalin, Concerta, and Focalin in this sample). They were tested after a minimum of 24 hours (for short acting preparations) to 48 hour washout (for long acting preparations); actual mean washout time was 63.8 hours.

Final sample. 424 adults passed through the initial screen and completed the screening rating scale and the diagnostic screen visit. The diagnostic procedures qualified 195 of them (46%) between the ages of 18 and 37 for the study, grouped into an ADHD group (n = 105), and a non-ADHD control group (n = 90) and these 195 completed the neuropsychological battery and were available for the present study. All participants completed at least three of the four neuropsychological measures in this study. Presence or absence (i.e., 0 or 1) of disorders were recoded for the following lifetime and current diagnoses: MDD, dysthymia, bipolar I, alcohol dependence, drug dependence (any type), agoraphobia without panic disorder, panic disorder, social phobia, specific phobia, OCD, PTSD, GAD, antisocial personality disorder, conduct disorder, ODD, and ADHD. Four individuals met criteria for panic disorder; although DSM-IV panic disorder could not be diagnosed retrospectively in the alcoholism study and thus was not included in the

present analyses, these individuals were retained in the study but not defined as having panic disorder. This was unlikely to affect analyses as there were no significant correlations between lifetime or current panic disorder diagnosis and neuropsychological variables of interest. Two participants were removed from analyses because they met criteria for bipolar I disorder (to avoid confounding neuropsychological test results since this was not a focus of analyses), leaving $n = 193$ participants.

Sample 2: Alcoholism Study

Participants

The second sample consisted of parents (dads and moms) from families who participated in the Michigan Longitudinal Study (MLS, also referred to herein as the alcoholism study), an ongoing longitudinal study on the development and stability/change of alcohol problems/abuse/dependence (Zucker et al., 2001). All families were recruited based upon the alcoholism status of the father, and given the interest in development of alcoholism, families were only included in the study if they had at least one biological male child. All families were initially told that they were being recruited to participate in a longitudinal study of child development and family health. More detailed information was provided if requested. Neuropsychological testing has been conducted for both children and adults; only data from the adult samples were included in the present study, so the description of study methodology will focus upon their recruitment.

Data have been collected at 3-year intervals since initial family contact (i.e., Wave 1). Parental consent and child assent was obtained from all participants by the Field Coordinator at the first contact visit of Wave 1. At the end of each wave of data

collection, request for permission to re-contact the family in three years was obtained, and written consent was re-established at each new wave. Intellectual functioning data were collected at Waves 2 and 4. At Wave 5, neuropsychological testing was administered to all parents participating in the study. Wave 5 testing has been completed for all families.

Three hundred and eleven families initially agreed to participate in the study. The MLS has maintained contact with 100% of all still living participants from Wave 1 data collection. Only a small percentage of families are no longer willing to participate in data collection, and the sample currently contains more than 90% of the original participants.

Recruitment. Three subsets of families were originally recruited into the Longitudinal Study. The three subsets were recruited to represent varying levels of risk for development of alcoholism in the children. The subset of families included in the present analyses are: (1) Court Alcoholic (n = 159), a court-recruited alcoholic family group that included at least one parent with alcoholism, and often, with ASPD; (2) Community Alcoholic (n = 91), a community-recruited alcoholic family group; and (3) Control Group (n = 61), a matched group of community-recruited, non-substance abusing parents and their offspring.

Families in the Court Alcoholic group were initially identified using court records from four counties in Michigan. All men with drunk-driving convictions involving a blood alcohol concentration of at least 0.15% for a first conviction, or 0.12% if they had been involved in multiple convictions, were potential study participants. Along with conviction status, men who were included in the study had to meet Feighner and colleagues (1972) criteria for probable or definite alcoholism (assessed using the Short

Michigan Alcoholism Screening Test (SMAST; Selzer, Vinokur, & van Rooijen, 1975), have a male child between the ages of 3.0 and 6.0 currently living in the home, be living with the boy's biological mother at the time of first contact, and identify as Caucasian. Seventy-nine percent of the men identified through this method allowed the probation officers from the district courts to release their contact information. Of those contacted, 92% agreed to participate in the study. This recruitment strategy provided a large number of alcoholic fathers with comorbid ASPD. Mother's alcohol status was not a factor in study inclusion or exclusion.

Control group families were of a similar composition (i.e., biological father and mother, together at the time of first contact, with their 3-5 year old male child living in the home), but were recruited using a yoking procedure and door-to-door survey methods in the same neighborhoods where the Court Alcoholic families resided. The canvas team would begin a door-to-door search two blocks away from a court alcoholic family's residence for intact families with a male child whose age was within six months of the alcoholic family's son, but where neither the mother nor father met criteria for either probable or definite alcoholism or other drug abuse/dependence using the Feighner et al. (1972) criteria.

While canvassing the neighborhoods another subset of alcoholic families was found, called the Community Alcoholic Group. These families were also intact with a male child within six months of the court alcoholic family's child, but the father met criteria for probable or definite alcoholism during the initial screening procedure. However, these fathers did not have any recent drunk driving or drug involved arrest record. They were considered to fall into a moderate risk category for the male child to

develop problems with alcohol and provided a diagnostic comparison group. All 61 families agreed to participate in the study.

Note that familial configurations have changed over the tenure of the study, and new family members (e.g., step-parents, younger siblings) have been added to assessment protocols.

Diagnostic procedures. As mentioned, preliminary alcoholism diagnoses were made using Feighner criteria for a probable or definite diagnosis of alcoholism. Although DSM diagnoses were not a criterion for study inclusion, data that were collected through SMAST, the Drinking and Drug History Questionnaire (DDHQ; Zucker, Fitzgerald, & Noll, 1980), the Antisocial Behavior Inventory (ASB; Zucker, Noll, Hamm, Fitzgerald, & Sullivan, 1994; Zucker et al., 1996) and the Diagnostic Interview Schedule, Version III (DIS; Robins, Helzer, Croughtan, & Ratcliff, 1980) were later used to establish DSM–IV alcohol-related and ASPD diagnoses. Inter-rater reliability for these diagnoses was excellent (Zucker et al., 1996).

During Wave 1, information on lifetime diagnoses was collected; at each follow-up assessment, diagnostic information was obtained for the intervening three years between data collection waves. Lifetime diagnoses were created by combining information gathered at these five different time points for the disorders of interest in the present study. "Current" diagnoses were those that the participants met criteria for near the time of neuropsychological assessment (i.e., within three years prior to Wave 5). At each wave of data collection, diagnostic information was collected using the Diagnostic Interview Schedule (DIS) appropriate for the version of the DSM that was current at that time. Therefore, diagnostic classification systems used during the tenure

of the study included the DSM-III, DSM-III-R, and DSM-IV. All diagnostic information was recently converted to DSM-IV standards. Diagnostic information was collected for the following disorders: MDD, dysthymia, mania/hypomania, schizophrenia, eating disorders, specific phobia, social phobia, agoraphobia, panic, GAD, PTSD, OCD, separation anxiety disorder, ODD, ADHD, and ASPD. As mentioned above, additional collateral questionnaire and interview information was used along with DIS results to refine alcohol dependence and ASPD diagnoses since these were the focus of the alcoholism study. Further, in the alcoholism group, participants were considered to meet criteria for ASPD whether or not they met criteria for childhood CD. This exception was made because the retrospective nature of the assessment made it difficult to definitively determine presence or absence of the childhood CD. (However, note that in the ADHD group care had been taken to ensure the validity of retrospective CD diagnoses by contacting a parent, so ASPD criteria did require a history of CD in that sample.)

Exclusionary criteria. Fetal alcohol effects in the target male child were exclusionary for a family's participation for all groups. Any participants who met criteria for lifetime diagnoses of psychosis, bipolar disorder, neurological illness, and FSIQ < 75 at any time point were removed from the data sets due to the potentially confounding effects upon neuropsychological data.

Criteria for testing. Examiners traveled to the families' homes in order to administer the neuropsychological test battery. Privacy and minimal distractions were ensured throughout testing. Participants were not allowed to have drunk more than two alcoholic beverages during the hour prior to testing. Information was collected on medication and drug use prior to testing.

Final sample. Seven hundred and thirty-eight individuals participated in some part of the alcoholism study. Since neuropsychological tests were administered at only T5, and this was an important element of the present study, individuals who had completed fewer than three out of the four tasks included in this study (i.e., Trail Making Test, Stroop Interference, Stop Signal Test, and WCST) were eliminated from further analyses. This resulted in the following participants being removed from the database: participants who had not completed any of the neuropsychological tasks at T5 (n = 247), and participants with only one (n = 4) or two (n = 22) tasks completed.

As mentioned, diagnostic information for the alcoholism sample was based upon information evaluated and collapsed across five data collection waves. These diagnoses were recoded into presence or absence (i.e., 0 or 1) of disorder for lifetime (i.e., at any of the five time points), or current (i.e., since the previous data collection wave, or within the three years prior to neuropsychological data collection at T5). If information on a diagnosis was missing for any time point, the disorder was considered "absent" at that time. Diagnoses recoded for analyses were: MDD (single or recurrent episodes), dysthymia, bipolar I, schizophrenia, schizophreniform disorder, schizoaffective disorder, agoraphobia without panic disorder, social phobia, specific phobia, OCD, PTSD, GAD, alcohol dependence, drug dependence (any type), antisocial personality disorder (with or without presence of conduct disorder), conduct disorder, ODD, and ADHD.

In order to match with exclusion criteria in the ADHD study, further rule outs were made for the following issues from the sample of n = 465 participants: schizophrenia-spectrum disorder or history of psychosis (n = 10), bipolar I disorder (n = 9), epilepsy (n = 1), and anti-psychotic and anti-mania medications (n = 2). Thirty-nine

participants said they had experienced a head injury, and 29 participants endorsed a loss of consciousness. However, these participants were retained in analyses since people tend to misunderstand and over-endorse these experiences, the extent of these injuries was not followed up on in the alcoholism study, and mild head injuries do not appear to be associated with deficits on tasks similar to those included in the present study (Ettenhofer, 2006; note that there were also no significant correlations with tasks in the present data, r = -.06 - .07). Four hundred and forty-eight participants were included in analyses.

Neuropsychological Test Battery

Except for the estimate of Full Scale IQ (FSIQ) and location of the testing, the specific test forms and administration practices were very similar between the samples. Therefore, the IQ estimation will be explained separately for each sample, but the EF tasks will be explained together.

Full Scale IQ (FSIQ)

Sample 1: ADHD adults. FSIQ was estimated with a five subtest short form of the Wechsler Adult Intelligence Scales, Third Edition (WAIS-III; Sattler & Ryan, 1999; Wechsler, 1997): Picture Completion, Vocabulary, Similarities, Arithmetic, and Matrix Reasoning. Reliability and validity for this short form are adequate (Sattler & Ryan, 1999).

Sample 2: MLS/Alcohol parents. Four subtests of the WAIS, Revised Edition (WAIS-R; Wechsler, 1981) were administered at Waves 2 and 4: Picture Completion, Information, Arithmetic, and Block Design. This short form has been shown to be a valid estimate of full scale IQ (Reynolds, Willson, & Clark, 1983). The results from Wave 4,

the most recent testing, were used in our analyses to provide the most accurate estimate of parents' intellectual functioning. There is an approximately six-year interval between the first and second test administrations for the parents in the alcohol study, suggesting that retest effects were unlikely; IQ correlation between T2 and T4 assessments were .79, alpha = .88.

Neuropsychological Tests

The tasks that were selected for inclusion in the present study are widely-used clinical measures that assess EF and the integrity of the frontal lobes and associated circuitry. Given the difficulties inherent in measuring EF and the importance of demonstrating frontal involvement for tasks included in EF profiles (Sergeant et al., 2002), the following is a brief review of lesion and imaging studies for the EF tasks included in the present study, suggesting regions of activation that appear to be necessary for task activity. This information is important to understand the basis for the componential model, which examined the profile of EF deficits associated with the individual disorders. Although the following review highlights the involvement of the prefrontal cortex in each of these tasks, it also underscores the regional differentiation of underlying neural circuits for different EF processes, which provides the theoretical basis for the componential model.

Trail Making Test. The Trail Making Test (Trails) is a widely-used, timed paper-and-pencil test consisting of two parts (Reitan, 1958). In Part A, the participant draws a line connecting numbered circles in sequential order. In Part B, the participant draws a line connecting numbered and lettered circles, switching between numbers and letters in alphabetic-numerical order. Scores on each part of the Trails test are determined by the

time (in seconds) required to complete each trial. Whereas performance on Part A depends largely upon psychomotor speed and visual search abilities, Part B also requires working memory and cognitive flexibility as the participant must maintain two mental sets and alternate between them (Arbuthnott & Frank, 2000). For analyses using speed variables, Trails A time was used as a measure of motor speed with higher scores indicating slower speed. To assess set-shifting, a component of EF, a Trails B Residual score was created by removing the effects of Trails A performance from Trails B (done separately within the individual samples). Higher scores indicated poor performance.

Despite the widespread use of Trails as a frontal lobe task, few studies have been done to validate such an application. No imaging studies are available for the Trail Making Test due to its motor requirements, but a few studies have attempted to measure the effect of lesion damage upon performance. One group of researchers found no differences between patients with frontal and non-frontal lesion damage on Trails A, but discrepancies in performance on Trails B (Ettlin, Kischka, Beckson, Gaggiotti, Rauchfleisch, & Benson, 2000). This follows the expected pattern, as Trails B is thought to be a measure of executive or frontal functioning due to its set-switching component, while Trails A involves motor speed and visual scanning (Crowe, 1998). The findings of a recent meta-analysis, however, were at odds with this hypothesis, as there was a much larger effect size for Trails A in comparisons between frontal and non-frontal patients (Demakis, 2004). Other researchers have also failed to differentiate frontal from more posterior damage using the Trail Making Test (Anderson, Bigler, & Blatter, 1995; Reitan & Wolfson, 1995).

Two explanations may account for this failure to find frontal lobe specificity. Firstly, the effect of damage to specific regions of the frontal lobes may have been lost by combining studies that included any type of frontal lobe damage. Supporting this possibility is the finding that patients with damage to the dorsolateral prefrontal cortex showed the greatest impairment on Trails B, while damage to inferior frontal (ventral-medial/orbitofrontal) and anterior cingulate regions had little effect on performance of this task (Stuss, Bisschop, Alexander, Levine, Katz, & Izukawa, 2001a). The results of this study also suggested that frontal lobe patients were slower than patients with posterior lesions on Trails A, Trails B, and a proportional score intended to isolate the executive aspects of Trails B performance. Further, only frontal lobe patients made more than one error. These findings suggest that the Trail Making Test is sensitive to frontal lobe damage, but perhaps more selectively for damage to the dorsolateral region.

Secondly, a derived score, similar to that used in the previously mentioned study (Stuss et al., 2001a) may be more effective in differentiating frontal from non-frontal damage. As mentioned, Trails A performance involves visual scanning abilities and motor speed. By removing these effects from Trails B performance, a more pure measure of executive abilities may be derived which more selectively assess the putative EF set-shifting functions of the frontal lobes (Arbuthnott & Frank, 2000).

Taken together, despite varied findings, the Trail Making Test appears to involve the frontal lobes in performance, and perhaps selectively reflects the integrity of the dorsolateral region. The isolation of the EF components of the task using a derived score may better differentiate between frontal and non-frontal performance.

The Stroop Color-Word Test (Stroop). The Stroop Test (Golden, 1978) is a well-known task which assesses the abilities to control interfering information and response conflict. Three conditions are performed under a time pressure, each with separate stimulus cards with five rows of twenty-five items. Participants are directed to read down these rows as quickly as possible without making any errors. The number of items completed after forty-five seconds is the total score for each condition. In the first condition, Word Reading, the participant reads color words (i.e., red, blue, and green) that are printed in black ink. For the second condition, Color Naming, the stimulus card has rows of X's that are printed in different colored ink (i.e., XXXX) and participants name the color of the ink for each item. In the final condition, Color-Word, participants must name the color of the ink for color words (i.e., red, blue, and green) that are printed in an incongruent color. Naming the ink and not reading the word requires considerable effort as reading is an overlearned activity, and thus participants must suppress the prepotent response (Ward et al., 2001). Similar to the Trails derived score, an interference residual score was created that removed Word Reading and Color Naming performance from Color Word results (done separately in the individual samples). This provided a purer measure of interference control as it removed the effects of processing speed; higher scores indicated better performance. For analyses using speed measures, Word Reading and Color Naming were included as measures of processing speed, with higher scores indicating faster performance.

The primary EF component assessed by the Stroop task is interference control, as measured by the incongruent condition. The primary region of activation during the Stroop effect appears to be the anterior cingulate cortex (Smith & Jonides, 1999).

Different aspects of the task appear to activate different frontal lobe regions, with the left dorsolateral cortex activated during color naming for both congruent and incongruent conditions (MacDonald, Cohen, Stenger, & Carter, 2000), while anterior cingulate activation is specific to the incongruent naming condition (Bench, Frith, Grasby, Friston, et al., 1993; MacDonald et al., 2000; Ravnkilde, Videbech, Rosenberg, Gjedde, & Gade, 2002). Activation has also been seen in the right superior mesial frontal lobe during the Stroop effect (Larrue, Celsis, Bes, & Marc-Vergnes, 1994). Therefore, the medial region and particularly the anterior cingulate cortex have been shown to be challenged during the incongruent condition of the Stroop task.

Lesion studies have also suggested that frontal regions, particularly the anterior cingulate cortex, are important to Stroop performance. A recent meta-analysis of lesion studies found that there were moderate effects sizes for discriminating frontal from non-frontal lesions on Stroop Word, Color, and Color-Word (Demakis, 2004). In one study, damage to left mid-dorsal anterior cingulate cortex, but not the same region on in the right hemisphere, resulted in consistently lower accuracy on incongruent trials, with deficits in maintaining task set and inhibiting the automatic response to read the words (Swick & Jovanovic, 2002). Another study that included patients with single, focal brain lesions in frontal and non-frontal regions found that only patients with frontal damage had significant impairment (Stuss et al., 2001b). They were slower overall on all conditions, and similar to the results of imaging studies, damage to the left dorsolateral frontal lobe resulted in increased errors and slowness in response speed for color naming, while bilateral superior medial frontal damage (i.e., anterior cingulate) was associated with increased errors and slowness in response time for the incongruent condition.

Increased errors have also been noted in right frontal lobe patients (Vendrell, Junqué, Pujol, Jurado et al., 1995).

Taken together, these imaging and lesion studies suggest that the Stroop task selectively involves the frontal lobes. The task discriminates between frontal and non-frontal patients, and primarily activates regions of the superior frontal lobe such as the anterior cingulate cortex. Therefore, the Stroop task appears to be a good measure of the integrity of the anterior cingulate region of the brain.

Wisconsin Card Sorting Test (WCST). The WCST is a widely-used computer-administered task assessing working memory, concept formation, and set-shifting (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Participants were shown a computer screen with four patterned "key" cards to which they needed to match a stimulus card which appeared at the bottom of the screen. There were three different principles by which the stimulus card could be matched to a key card: color, shape, or number. Using feedback from the computer (i.e., "right" or "wrong") participants had to deduce how to sort the cards. Once they had figured out what principle to use in sorting the cards, the category remained the same for ten cards, at which point the sorting principle switched. In the alcohol group, up to 124 trials were administered. A shorter version of the task was administered in the ADHD group, so up to 64 trials were administered. These tasks are considered to be comparable (Axelrod, 2002; Love, Greve, Sherwin, & Mathias, 2003; Sherer, Nick, Millis, & Novack, 2003). Participant performance was evaluated using the standard scores for number of perseverative errors (i.e., continuing to sort using an incorrect principle). Higher scores indicated better performance on this task.

Despite its widespread use (Retzlaff et al., 1992), the many and varied task demands associated with the WCST have made it difficult to achieve consistent results across lesion studies with regard to the involvement of the frontal lobes (Stuss, Levine, Alexander, Hong, Palumbo, Hamer et al., 2000). This task involves working memory, set-shifting and maintenance, abstract conceptualization, and responding to feedback. While a number of studies have found that individuals with damage to frontal regions of the brain perform more poorly on the task, specifically making increased perseverative errors (Goldstein, Obrzut, John, Ledakis, & Armstrong, 2004a), other studies have produced negative findings. Patients with posterior damage have also performed poorly on the task, while frontal lobe patients have performed normally (Anderson et al., 1991). In a study of patients with stable focal lesions there were no significant differences between frontal and non-frontal patients on WCST performance (Anderson et al., 1991). These authors suggested that impaired performance on the WCST could not be interpreted in isolation as a marker of frontal lobe damage.

However, similar to some of the studies with other EF tasks, it may be that distinct regions of the frontal lobes are involved with task performance, and combining frontal patients into a single group may result in a loss of information. While Anderson et al. (1991) did not find any effect using sub-region analyses, perhaps due to small sample sizes, others have found that damage to the dorsolateral (Milner, 1963) as well as superior medial prefrontal regions (Stuss et al., 2000) were related to poor performance on perseverative errors. Further, unilateral and bilateral lesions to the inferior medial regions of the frontal lobes (i.e., orbitofrontal) had little effect upon these measures of task performance (Stuss et al., 2000). These authors suggested that the WCST was

sensitive to focal frontal lesions, but that their results supported a differentiation of processes within the frontal lobes.

Support for these results come from a recent meta-analytic review which found that participants with frontal damage showed poorer performance on all variables of the WCST except for nonperseverative errors (Demakis, 2003). Strikingly, in moderator analyses there was a large effect size for damage to the dorsolateral prefrontal cortex on a composite WCST variable. These lesion results suggest that the dorsolateral prefrontal cortex contributes to performance on commonly assessed variables of the WCST.

The lesion data is substantiated by the findings from imaging studies. They show activation of the dorsolateral prefrontal cortex during task performance (Berman, Ostrem, Randolph, Gold et al., 1995; Rezai et al., 1993). The right dorsolateral frontal-subcortical (i.e., caudate nucleus) circuit was found to be critical for WCST performance as the activation of this circuit was associated with reduced perseverative responses in patients with a history of closed head injury (Lombardi, Andreason, Sirocco, Rio, Gross, Umhau et al., 1999). Other researchers have found localized blood flow to the left dorsolateral frontal regions (Rezai et al., 1993), even following training and practice on the test (Berman et al., 1995), suggesting that the working memory components of the task may be largely responsible for the involvement of this region (Berman et al., 1995). Therefore, the results of neuroimaging studies provide additional evidence for discrete regional activation of the dorsolateral prefrontal cortex in task performance on the WCST. Although different regions of the frontal lobes may be involved in performance on different aspects of the task (Stuss et al., 2000), perseverative errors appears to be a sensitive indicator of the functional integrity of the dorsolateral prefrontal cortex.

Logan Stop Task (Stop). The Stop task (Logan, 1994) is a dual-task computer paradigm to assess response suppression or inhibition in a rapid decision context. Procedures were the same as those used by Logan, Schachar, & Tannock (1997). The computer screen displayed an X or an O on a black and white screen and individuals were required to respond to these stimuli by pressing designated buttons labeled 'X' and 'O' as quickly as possible using their dominant hand. They were to withhold responding when they heard a tone. Four blocks of 64 trials were administered following two practice blocks of 32 trials each. We used the tracking version of the stop task, which provides the most valid estimates of stop signal reaction time (Band, Van Der Molen, & Logan, 2003). The time of the stop signal tone was varied in a stochastic procedure to maintain accuracy at 50%, so that stop signal reaction time (SSRT) was computed as the difference between stop signal delay and go speed (Logan, 1994). In this study, we used stop signal reaction time (response inhibition) as a measure of the time needed to inhibit a response (i.e., an EF process), and variability of the go reaction time (RT variability) as a measure of response variability on trials that they did not have to inhibit responding. Both of these are related to EF, and higher score indicated poorer performance (i.e., slower inhibition or more response variability).

Across studies, performance on the Stop task has been shown to be mediated by the prefrontal cortex. Patients with frontal lobe damage have longer SSRTs than orthopaedic and normal controls (Aron et al., 2003; Rieger, Gauggel, & Burmeister, 2003); in other words, frontal patients require a longer delay to successfully inhibit their response. This is not a consistent finding (Dimitrov, Nakic, Elpern-Waxman, Granetz, O'Grady, Phipps et al., 2003), but, as with other EF tasks, some variation may occur

based upon the specific location of the damage within the frontal lobes. For instance, within frontal lobe patients those with right hemisphere or bilateral lesions have significantly longer SSRTs than patients with left lesions (Rieger et al., 2003). Therefore, although the lesion results are not consistent in separating frontal from non-frontal patients, they suggest that the right frontal circuits are involved in the inhibition of ongoing responses.

Imaging data support the lesion results, and suggest discrete activation of a region of the prefrontal cortex in task performance. In healthy adults, a bilateral middle and inferior frontal system appears to be predominantly involved in response inhibition (Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons et al., 2000). In a sample of right frontal lobe patients, Aron and colleagues (2003) found that damage to the inferior cortex, specifically the pars triangularis, accounted for the variability in SSRT. These authors indicated that low variability in damage to orbitofrontal and medial frontal regions left open the possibility that other regions may be involved. The involvement of the right inferior frontal cortex in successful response inhibition was also seen in a study of normal controls (Rubia, Smith, Brammer, & Taylor, 2003), and a recent review suggested that it was a commonly recruited region across studies of response inhibition (Aron et al., 2004). In children, the activity in the prefrontal cortex as well as basal ganglia has been shown to be important to task performance (Casey et al., 1997). Therefore, lesion and imaging data have pointed to a specific role of the right frontal cortex, specifically inferior and orbitofrontal regions and their striatal connections, in response inhibition as measured by SSRT.

A measure that recently received attention as an index of regulatory control, perhaps related to executive control but also possibily related to other processes such as arousal, is variability of response time, such as that measured by the variability of the go response (RT variability) in the Stop task. Intra-individual performance variability on an executive function task has been associated with superior and dorsolateral prefrontal brain lesions in adults (Stuss et al., 2003). Variability of response time has been shown to be related to neurocognitive impairment in aging (Dixon, Garrett, Lentz, MacDonald, Strauss, & Hultsch, 2007). Functional imaging using a Go/No-Go task revealed that go response variability is related to response inhibition, and involves an overlapping neural network that includes bilateral middle frontal regions, along with right inferior parietal and thalamic regions (Bellgrove, Hester, & Garavan, 2004). These results were interpreted as suggesting that the increased frontal activation that is associated with higher intra-individual response time variability reflects the need for executive control to maintain task performance (Bellgrove et al., 2004). Caudate and prefrontal regions were also recruited in children with high response variability (Simmonds, Fotedar, Suskauer, Pekar, Denckla, & Mostofsky, 2007). Again, this supports the idea that prefrontal areas are needed for maintenance of task performance in conditions of behavioral inconsistency (Simmonds et al., 2007). Therefore, response variability, or RT Variability, appears to be a measure of executive control that is related to response inhibition and relies upon prefrontal networks.

Results

Data Preparation

Data cleaning. As recommended in recent methodological texts, extreme outliers ($z > 4.0$ and more than .5 SD from next score) were truncated to within .5 SD of the next nearest score to prevent undue influence of single scores on linear models and reduce type I and type II error (see Wilcox, Keselman, & Kowalchuk, 1998). Data preparation was completed in the two groups separately.

Three scores were adjusted in the ADHD group using the above-described method for removing outliers: one for Trails B (from 137.37 to 113.17), one for Stroop Color-Word (102 truncated to 101), and one for Response Inhibition (from 625.33 to 480.67). The expectation maximization (EM) method of data imputation was used to impute missing data in each of the samples individually, and 1.6% of the cognitive variables were imputed in the ADHD group. Residual scores were created for the Stroop and the Trails task as described above under task descriptions. Standardized z-scores were also created for each task included in analyses using the mean and standard deviation of the ADHD sample control group (i.e., individuals with no lifetime disorders).

For the MLS/alcoholism group, a total of 10 outliers were adjusted: three for Trails A (79.57, 88.00, and 100.00 truncated to 71.5), three for Trails B (196.56, 198.13, and 200.00 truncated to 173.33), two for Response Inhibition (569.00 and 598.00 to 564.69), and two for WCST perseverative errors (55.00 and 76.00 to 51.55). Using EM, 5.8% of the cognitive variables were imputed in the alcoholism group. Residual scores were created for the Stroop and Trails, and standardized *z*-scores were created for each

task based on the mean and standard deviation of the alcoholism sample control group (i.e., individuals with no lifetime disorders).

Statistical Analyses. Different statistical approaches were used to examine the explanatory power of the four models hypothesized to account for the extensive relationship between psychiatric disorders and EF. With the *Componential Model* it was hypothesized that deficits in some, but not all, components of EF would be associated with certain disorders. This was tested using profile analysis, essentially a repeated measures multivariate analysis of variance (MANOVA) except all observations are taken at a single time point. This allows one to test for differences in the *patterns* of performance across multiple tests (Atchinson, Bradshaw, & Massman, 2004; Tabachnick & Fidell, 1996). Multiple regression analyses were used to examine the *Comorbidity-Specificity Model*, or the possibility that only one or a few disorders were related to EF deficits. Both multiple regression analyses and univariate ANOVA tests were used to examine whether number of disorders was important to neuropsychological test results for the *Comorbidity-Nonspecificity Model*. Finally, structural equation modeling with latent factors was used to examine the relative relationships between general psychopathology and performance on neuropsychological tests assessing speed and EF for the *Dimension-Specificity Model*.

Note that the primary focus for all analyses was upon lifetime diagnoses. However, to examine whether there were differential effects, all analyses were repeated to assess current disorders (i.e., disorders that were present when neuropsychological testing was conducted for the ADHD sample, and within the past three years for the alcoholism sample). Disorders were coded as being present or absent (i.e., 0 or 1). As

well, most analyses were conducted with an EF composite variable (consisting of Trails Residual, Stroop Residual, Response Inhibition, RT Variability, and WCST perseverative errors), a speed composite variable to test for differential cognitive effects (consisting of Trails A, Stroop Word, and Stroop Color), and the individual EF tests.

The AMOS 5.0 (2003) statistical package, using the Maximum Likelihood method, was employed for all latent variable and structural analyses. For analyses relying on SEM analyses, multiple fit analyses are reported and interpreted as outlined by Kline (2004): (1) Pearson chi-square for which nonsignificant values signify good fit, and a χ^2/df ratio < 3 is acceptable; (2) Goodness of Fit Index (GFI; Joreskog & Sorbom, 1981) for which a value > .90 is considered a good fit; (3) Comparative Fit Index (CFI; Bentler, 1990) for which a value > .90 is considered a good fit; and (4) Root Mean Square Error of Approximation (RMSEA; Steiger, 1990) for which a value of .08 is considered acceptable and .05 is considered good (lower is better). The SPSS 15.0 (2006) statistical package was used to perform all other statistical analyses.

Post-hoc power analyses were based on calculations provided by the power program G*POWER 3.0.3 (Faul, Erdfelder, Lang, & Buchner, in press). A p value of .05 was used for all calculations. With a sample size of 641, the present study had adequate power to detect small effects ($f = 0.10$; $f^2 = 0.02$) for all analyses. Power was greater than .90 to detect a significant overall omnibus F in the repeated measure MANOVA analysis for both the within and between factor effects with seven comparison groups, and greater than .77 for the test of the interaction. For regression analyses, power was greater than .77 to detect a significant overall R^2 in the omnibus test with one to six predictors for a small effect. The power to detect effects for the omnibus ANOVA F-test with four

groups was greater than .90. Power for medium effects exceeded .90 for all analyses. For the structural model, Kline (2004) recommended that the ratio of number of cases to free parameters should be 20:1, but that a 10:1 ratio is more realistic and adequate for power in SEM analyses. The largest structural model comparing the relative relationships between psychiatric disorders and cognitive test performance contained 66 parameters, 44 of which were freely estimated, so the ratio of sample size to free parameters exceeded Kline's (2004) recommendations.

Sample Description

Data were merged between the two groups to create one large sample. Demographic data are presented in Table 2. As is apparent, the samples differed on their mean age and FSIQ score, as the ADHD sample was younger and had a higher mean IQ score. The distribution of males and females was equal between the samples, and although there was a trend towards the ADHD study participants having more years of education than the alcoholism group, this difference did not reach significance. As is expected with an older sample (and due to the family-based recruitment strategy), a larger proportion of the alcoholism sample reported that they were married or living with a partner. Average personal income in the ADHD sample was $26,987. Given the young nature of this sample, reported parental income is also informative as to SES (*M*=$72,000 (*SD*=$25,592)). Mean reported family income in the alcoholism sample at the time of testing was $58,677 (*SD*=$26,355). Note that this represents a considerable improvement over family income at the beginning of the study ($35,649 (*SD*=16,967)). Thus, the ADHD sample was from a slightly higher SES, but both samples included considerable variability in income levels.

The distribution of lifetime and current disorders in the two samples are presented in Tables 3 and 4. Given the multiple differences in sample characteristics, particularly age, SES, study recruitment objectives, and inclusion/exclusion criteria, differences in the rates of disorders were not unexpected. In general, the alcoholism sample was a more disordered population. For individual lifetime disorders, the alcoholism group had higher rates of MDD, dysthymia, specific phobia, alcohol dependence, conduct disorder, and ASPD, while the ADHD group had higher rates of ADHD and ODD. No differences were seen for lifetime rates of GAD, agoraphobia, PTSD, OCD, or drug dependence. For composite "any depression" and "any anxiety" variables, the alcoholism group had a greater frequency of both types of disorders. Taken together, combining the samples provided large distributions of a range of different disorders, particularly when using composite variables.

The number of individuals who met criteria for any type of psychopathology near the time of testing did not differ between the samples. Differences were nonetheless noted in distribution of individual disorders between samples, as the alcoholism group had higher rates of MDD (a considerable difference because current MDD was an exclusionary criterion in the ADHD group), and a trend towards higher rates of alcoholism. The ADHD group demonstrated higher rates of dysthymia, GAD, and ADHD. This latter difference was striking because adult ADHD was not evaluated in the alcoholism sample. Note that the variables for, and thus rates of, current and lifetime ASPD are the same because it is considered a lifetime disorder. For composite variables, the alcoholism group had higher rates of any depressive disorders, and the ADHD group had higher rates of any anxiety disorders. For the combined group, there were relatively

high rates of most disorders when considering composite depressive and anxiety disorders, although the rate of drug dependence was very low. It is likely that individuals who were heavily involved with drugs at the time of testing able to commit to either study. Therefore, there were many differences across the samples in distributions of specific disorders for both lifetime and current diagnoses. However, this was expected based on differences in individual study objectives and thus sample characteristics.

Cognitive test performance also differed across the two samples on many tasks (see Table 5). Again, however, this was expected based upon differences in age, IQ, and SES across the populations. Note that the means for Stroop Residual and Trails Residual did not differ, despite differences in Stroop Color, Stroop Color-Word, and Trails A and B, since the residuals were created separately in the two samples and sample-dependent differences were effectively eliminated. Differences were also seen for RT Variability and WCST perseverative errors. In all cases, the ADHD participants' performance was better than the alcoholism participants.

The mean cognitive test performances associated with the different lifetime and current disorders in the combined sample are presented in Tables 6 and 7. Note that these means are for overlapping diagnostic groups, and individuals in these groups may have comorbid pathology. Correlations amongst the tasks included in this study are provided in Tables 8 through 10 for the combined, alcoholism, and ADHD samples, respectively. The sample is further characterized in correlation tables detailing relationships amongst lifetime and current disorders in Tables 11 through 16.

Checks on the Validity of Combining the Alcoholism and ADHD Samples

The combination of two separate samples in the present study raised concerns about conducting and interpreting analyses. While data were combined in order to obtain a large sample with a range of disorders to conduct meaningful analyses, it clearly raises concerns about the above-noted differences in the samples, and how those may contribute to results. One means to deal with this issue is to control for "sample" in all analyses. However, the two samples have very different distributions of disorders, and controlling for the sample of origin may result in unintentionally controlling for presence of disorders; in other words, controlling for the variable of interest. Therefore, alternative means were implemented to control for sample differences in this study. These included: (1) controlling for variables that differed notably between the samples in all analyses (i.e., FSIQ and age); (2) where appropriate, standardizing scores separately in the two samples based on the mean of the individual samples' control groups (i.e., individuals with no disorders)[1]; and (3) confirmatory factor analyses (CFAs) were used with single- and multiple-group analyses to examine the stability of the covariance structures between the two samples.

CFAs were conducted on all composite/latent variables (e.g., EF, processing speed, depression, anxiety disorders, childhood externalizing disorders, etc.; see results below) to evaluate their structure in the combined and individual samples in order to

[1] Certain analyses required that test performance be standardized into a common metric (e.g., profile analysis, creation of EF composite score). When this was required (i.e., MANOVA for Analysis 1, linear regressions for Analyses 2 and 3), participants' performances on each of the tasks of interest were standardized separately in the two samples to reduce sample-dependent differences. Therefore, participants from the ADHD sample were standardized on the means and standard deviations of controls within the ADHD sample, and participants in the alcoholism sample were standardized on controls within the alcoholism sample. By standardizing these EF scores within the individual samples, sample-dependent differences were removed to ensure that test performance was not solely based upon differences in sample. Similarly, residual variables for the Stroop and Trails EF measures were created individually in the separate samples in order to reduce sample-based discrepancies.

justify their inclusion in structural analyses, as well as to provide a basis for creating composite variables for other statistical analyses. Variables were first analyzed with the samples combined to determine a best-fitting baseline model. Follow-up analyses were then conducted using single- and multiple-group confirmatory factor analyses to ensure that there was measurement invariance, or equivalence in the covariance structure, for latent variables between the alcoholism and ADHD samples. In other words, given that two different samples were included in this study, these analyses evaluated the legitimacy of interpreting combined analyses (Kline, 2004).

Therefore, in confirmatory factor analyses, the following was conducted for each latent variable: (1) Combined-group analyses were performed to determine a best-fitting baseline model using model fit for each of the proposed latent/composite variables; (2) Single-group analyses were performed in which the best-fitting baseline model was analyzed *separately* in the alcohol and ADHD groups and model fit was evaluated; and (3) Multiple-group analyses were performed in order to evaluate the measurement model in both groups *simultaneously* with varying levels of cross-group equality constraints. For the multiple-group analysis, if there was no significant difference in fit (as determined by the difference in χ^2) of an unconstrained model to those with equality-constrained loadings, then the indicators were judged to assess the factors comparably in each group; conversely, significant loss of fit would suggest that group membership moderated the relations specified in the model (Kline, 2004). Therefore, CFAs were conducted prior to hypothesis testing in order to validate composite variables, evaluate the structure of relationships within combined and separate samples, and determine the legitimacy of interpreting analyses with the samples combined.

Confirmatory Factor Analyses to Establish Latent Variables for Psychiatric Disorders and Cognitive Tests

The structural model for psychopathology was initially based on a three-factor hierarchical structure similar to that found by Krueger (1999) to explain patterns of comorbidity. This model suggests that psychiatric disorders fall along two main dimensions associated with internalizing (which included two sub-factors) and externalizing symptoms. A variant of this model was replicated within the present study to determine whether a similar pattern of comorbidity existed. The initially hypothesized model with relations between disorders is presented in Figure 1. Some notable differences between the model in Figure 1 and that presented by Krueger (1999) reflect changes in the diagnostic criteria (he used DSM-III-R) and the inclusion of additional disorders in the present study. For instance, Krueger (1999) did not include PTSD, OCD, or the childhood externalizing disorders (i.e., ADHD, ODD, CD) in his study, and he did include panic disorder but it was not be included in the present study as it could not be diagnosed retrospectively in the alcoholism group. CFAs were used to determine whether the model based on Krueger's findings also represented the structure of internalizing and externalizing DSM-IV disorders in the present study.

Internalizing disorders. As shown in Figure 1, a hierarchical latent model based on Krueger's findings for internalizing disorders was initially tested. It included two latent subfactors, one for "anxious-misery" (i.e., GAD, MDD, dysthymia), and another for "fear" (i.e., social phobia, simple phobia, agoraphobia, OCD, and PTSD). In Krueger's model, the two latent factors (anxious-misery and fear) were subfactors of the internalizing factor, so these factors were correlated in the present analyses. However,

this model was untenable, as it would not converge appropriately (i.e., the covariance matrix was not positive definite) and estimates could not be interpreted. This occurred even when the model only included the same disorders as Krueger (1999) included in his internalizing model.[2]

To better understand the relationships in the data, an exploratory factor analysis using principal components with varimax rotation was conducted on the remaining internalizing disorders (i.e., GAD, social phobia, specific phobia, OCD, PTSD, MDD, and dysthmia). Factor cutoffs were based on eigenvalues greater than or equal to 1.0. Variables were considered to load significantly on a factor when factor loadings exceeded 0.4 in magnitude. Two factors were found, comprising a total of 40.5% of the variance. The first and largest factor (eigenvalue = 1.72) included social phobia, OCD, and GAD, while the second factor (eigenvalue = 1.12) included MDD, dysthymia, and PTSD. Specific phobia did not load on either factor, but when a three factor solution was allowed the third factor (eigenvalue = .98) included only specific phobia.

Therefore, the relationships amongst disorders in the present study differed considerably from those found by Krueger (1999), as well as Watson (2005), both of whom found that GAD loaded significantly on a factor with MDD and dysthymia (as well as PTSD when it was included in analyses (Cox, Clara, & Enns, 2002). The inconsistency in findings may be due to differences in the nature of the samples included in previous studies compared to this one (see Watson, 2005 for a full review of

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[2] In an attempt to improve the model, agoraphobia was removed from analyses due to extremely low factor loading suggesting poor fit ($\beta = .08$, $p > .05$), and small sample size ($n = 8$). There was a small negative relationship between agoraphobia and Trails Residual ($r = -.08$), but correlations with other cognitive variables were not significant ($r = -.04$ to $.05$), so dropping this variable was unlikely to affect later analyses. However, the model remained untenable and did not converge appropriately (i.e., covariance matrix was not positive definite).

limitations of diagnosis-based analyses). Specific issues that may have affected relationships in the present study compared to Krueger's (1999) report included the two-sample design with differences in inclusion and exclusion criteria in the two samples, resulting in differences in the distributions of disorders. Further, this may be a more affected sample due to the clinically-based nature of the research questions. Importantly, when Krueger (1999) reanalyzed his data within a treatment-seeking subsample, he found that internalizing disorders were best described by a single latent factor. The present study likely is most reflective of a treatment-seeking or clinical sample, in that there was an emphasis upon recruiting specific disordered populations in both the alcoholic and the ADHD samples, along with matched controls. The rates of disorders therefore obviously do not match the population.

Other issues that may have affected relationships amongst internalizing disorders included the changes in the diagnostic exclusions and criteria across the different editions of the DSM that were used in the retrospective diagnosis of disorders in the alcoholism sample. As well, the presence of multiple symptom dimensions in many of the anxiety disorders tends to affect correlations within and between syndromes and makes it difficult to create an adequate taxonomy for structural analyses (Watson, 2005). In particular, PTSD did not fit clearly into the present results in that it loaded with the depressive, not anxiety, disorders in exploratory factor analyses, contrary to prior studies. Yet overall, the appropriate conceptual placement of PTSD amongst other disorders remains somewhat unclear (Watson, 2005). Theoretically, the appropriate placement of PTSD is problematic, as it requires an external experience and is "therefore a less meaningful indicator of a latent, endogenous 'core psychopathological process'" (Krueger, 1999, p.

922). Therefore, Krueger (1999) did not include PTSD in his study, although a follow-up re-analysis of his data suggested that PTSD loaded only weakly onto the general "anxious-misery" factor (Cox et al., 2002).

Given these considerations, PTSD was dropped from the model and the remaining internalizing disorders were analyzed as a single factor, which provided the best representation of the current data. Because the exploratory factor analysis demonstrated that MDD and dysthymia loaded together, their errors were correlated. The resultant model is presented in Figure 3. The model fit well (χ^2 (8) = 8.30, $p > .05$, GFI = .996, CFI = .998, RMSEA = .008), and all factor loadings were significant.

Running this model in the two samples individually demonstrated that model fit was acceptable for both samples (Alcohol: χ^2 (8) = 3.83, $p > .05$, GFI = .997, CFI = 1.00, RMSEA = .00; ADHD: χ^2 (8) = 14.40, $p > .05$, GFI = .98, CFI = .88, RMSEA = .07), although the model more accurately depicted the relationships in the alcoholism than in the ADHD group. When the multiple-group analysis was conducted, there was a significant difference between the baseline, freely estimated model in the combined sample and the constrained model (χ^2 (22) = 48.17, $p < .01$, GFI = .98, CFI = .82, RMSEA = .04; χ^2 difference (14) = 39.87, $p < .01$). In the individual groups, the greatest discrepancy in loadings appeared to be for the "specific phobia" indicator since it reached significance in the alcohol group (r = .25), but not in the ADHD group (r = .02). Therefore, this loading was allowed to be freely estimated (χ^2 (21) = 39.97, $p < .01$, GFI = .98, CFI = .87, RMSEA = .04; change in χ^2 (13) = 31.67, $p < .01$). The models were still significantly different between samples, so another constraint was released for the "social phobia" factor loading but the fit remained significantly different from baseline (χ^2 (20) =

32.39 $p < .05$, GFI = .99, CFI = .92, RMSEA = .03; change in χ^2 (12) = 24.09, $p < .01$). Therefore, the factor loading for dysthymia was also released, and the difference from the baseline unconstrained model was no longer significant (χ^2 (19) = 29.53, $p > .05$, GFI = .99, CFI = .93, RMSEA = .03; change in χ^2 (11) = 15.79, $p > .05$).

Thus, three out of six factor loadings had to be released to reach model fit equivalence between the samples, although fit was quite good after releasing two loadings and chi square difference is heavily susceptible sample size. This suggests that there were differences in the structure of relations between the ADHD and alcoholism samples. However, given the differences in recruitment and inclusion/exclusion criteria in the two samples that contributed to differences in distributions of internalizing disorders (see Table 3), along with the above-described problems associated with analyzing the structure of anxiety disorders, this was a somewhat expected and was viewed as an acceptable and interpretable result. Therefore, the best-fitting baseline model for internalizing disorders was retained and considered to be interpretable in SEM analyses with the combined sample. Note, however, that separate composite variables were used for "any depression" and "any anxiety" in all non-SEM analyses, with the latter also including agoraphobia and PTSD to best reflect the full range of anxiety disorder diagnoses in the sample (results were the same regardless of which anxiety composite was included).

Externalizing disorders. A latent variable for externalizing disorders was tested that included alcohol dependence, drug dependence, ASPD, and child externalizing disorders (i.e., ADHD, CD, and ODD). The model is presented in Figure 4, and fit

statistics suggested that it described the relationships in the model well (χ^2 (2) = 8.32, $p <$ .05; GFI = .99, CFI = .95, RMSEA = .07).

When the model was tested in the individual samples, model fit was good and all factor loadings were significant (alcohol: χ^2 (2) = 5.60, $p > .05$, GFI = .99, CFI = .98, RMSEA = .06; ADHD: χ^2 (2) = 1.27, $p > .05$, GFI = .997, CFI = 1.00, RMSEA = .00). A multiple-group analysis with all factor loadings constrained was not significantly different from the baseline, combined sample model (χ^2 (7) = 14.44, $p < .05$, GFI = .99, CFI = .96, RMSEA = .04; change in χ^2 (5) = 6.12, $p > .05$), suggesting that the model could be interpreted in the combined sample.

Cognitive tasks. The latent variable including non-standardized scores for all of the EF tasks (i.e., WCST, Stroop residual, Trails residual, Response Inhibition, and RT Variability, with the two latter variables' errors correlated due to their dependency) fit well and all factor loadings were significant (χ^2 (4) = 1.50, $p > .05$; GFI = .999, CFI = 1.00, RMSEA = 0.00). This model is presented in Figure 5. Non-standardized scores were used because this analysis depends upon lack of equality in covariance structures. The model fit well in the individual samples (alcohol: χ^2 (4) = 4.20, $p > .05$; GFI = .996, CFI = .999, RMSEA=0.01 although Response Inhibition was not significant at .16; ADHD: χ^2 (4) = 11.47, $p < .05$; GFI = .98, CFI = .85, RMSEA=0.01 and all factor loadings were significant). Fit for the multiple-group analysis with all factor loadings constrained was significantly different from the freely-estimated baseline model (χ^2 (12) = 19.50, $p > .05$; GFI = .99, CFI = .97, RMSEA=0.03; χ^2 difference (8) = 18.00, $p < .05$). The difference in model fit remained significant even after removing one or two of the constraints. Therefore, it appears that the difference between the groups was due to

differences in the structure of relationships due to consistent sample/methodological differences that could not be easily overcome. As will be demonstrated below, however, stability and equivalence were improved in a larger measurement model that also included processing speed tasks.

Fit statistics for a latent variable including all of the speed tasks (i.e., Stroop Color, Stroop Word, Trails A) could not be tested since the model was just-identified. However, model fit was adequate for a larger measurement model that correlated the EF and processing speed latent variables (χ^2 (18) = 93.21, $p < .05$; GFI=.97, CFI=.92, RMSEA=0.08). The model is presented in Figure 6.

Individual sample analysis of the EF and speed measurement model in Figure 6 demonstrated that fit was adequate in both groups (alcohol: χ^2 (18) = 73.97, $p < .05$; GFI = .96, CFI = .92, RMSEA = 0.08; ADHD: χ^2 (18) = 73.97, $p < .05$; GFI = .96, CFI = .92, RMSEA = 0.08). However, it should be noted that the factor loading for Stroop Residual on the EF variable was not significant in either the ADHD or the alcohol group. Despite this, the task was retained in the model since this factor loading was significant in the combined sample, which was the focus of the present study. Therefore, taken together, the model appeared to fit adequately and similarly in both individual samples. This was confirmed by the multiple-group analysis with all factor loadings constrained, as the fit was not significantly different from the baseline, freely-estimated model (χ^2 (42) = 111.76, $p < .05$; GFI = .96, CFI = .92, RMSEA = 0.05; change in χ^2 (24) = 37.79, $p >$ .05). A more stringent test of sample equivalence was then conducted, and the correlation between the EF and Speed factors was constrained in the multiple-group; this model was also not significantly different from the baseline analysis (χ^2 (43) = 112.62, p

$< .05$; GFI = .96, CFI = .93, RMSEA = 0.05; change in χ^2 (25) = 19.41, $p > .05$). Taken together, these findings suggest that the measurement model including both EF and speed may be interpreted with the two samples combined.

Therefore, these preliminary stage analyses suggested that including both the EF and speed latent variables together in a measurement model provides stability for each individual cognitive factor, and thus results may be interpreted with the combined samples. This sample equivalence could not be adequately achieved with the EF latent factor alone, even after releasing a number of the constraints, suggesting there were significant structural differences moderated by group membership even though the EF factor fit well in each of the individual samples and in the combined sample. Since combined-sample analyses could not be clearly interpreted with only the EF factor, all structural analyses included the full cognitive measurement model (i.e., both EF and speed factors correlated), while analyses focusing on only one or the other cognitive domain included manifest variables (i.e., standardized composite scores). With these decisions about measurement models resolved, the analysis proceeded to test the four models described in the hypotheses on page 60.

Tests of Hypotheses

Analysis 1: Testing the Componential Model for Disorder-Specific Patterns of EF Test Performance

Profile analysis was used to test the hypothesis that there would be differences in the pattern of deficits between different disorders. In other words, this assessed the possibility that different disorders were associated with deficits in different EF processes. This allowed for an examination of group (i.e., disorder) differences on test performance

across Stroop Residual, Trails Residual, Response Inhibition, RT Variability, and WCST perseverative errors. Disorders included were "any depression," "any anxiety," alcoholism, drug dependence, ASPD, and childhood externalizing/adult ADHD. Profile analysis using repeated measures MANOVA is superior to using a series of univariate analyses on individual tests because it allows a test of significant *patterns* of performance across multiple tests (Atchinson et al., 2004; Tabachnick & Fidell, 1996).

For this study, group was entered into the analysis as a between-subjects factor, and EF tests were entered as the within-subject factors. Profile analysis tests three separate aspects of the data: levels, flatness, and parallelism. Differences in the *levels* of the profiles would suggest overall performance differences between disorder groups, and were followed up with post-hoc Tukey tests. *Flatness* was tested but was of less interest for present purposes because it simply assessed whether the groups combined performed differently on the EF tests (i.e., differences in the means of the EF tests), which were interpreted by examining mean differences. Deviations from *parallelism* in the disorder profiles were the main focus of this analysis; these would be suggested by a significant interaction of group and test, and were interpreted with follow-up univariate ANOVAs and Tukey tests. The interaction analysis provided the ability to determine whether disorder groups performed differently across different components of EF processes.

Multivariate analysis of covariance (MANCOVA) was used to assess how the effects of possible moderating variables such as age, gender, and IQ affected the pattern of performance or interaction between disorder group and test performance. In order to make comparisons across tests, all scores were transformed into a common metric using

z-scores based on the mean and standard deviation of the control groups in the individual samples.

Individuals were assigned to discrete, non-overlapping groups for analysis based on their status for disorders/classes of disorders (i.e., controls, individuals with various single disorders, and individuals with multiple disorders). For lifetime analyses, the disorder variable defined individuals as follows: controls (n = 170), any depression only (n = 58), any anxiety only (n = 33), alcoholism only (n = 61), childhood externalizing disorders only (n = 46), and comorbid disorders (n = 269). For current analyses participants were defined as current: controls (n = 360), any depression only (n = 61), any anxiety only (n = 30), alcoholism only (n = 16), ASPD only (n = 36), adult ADHD only (n = 49), and comorbid disorders (n = 88). Lifetime ASPD (n = 4) and current/lifetime drug dependence (n = 0; n = 1) could not be included in analyses as few individuals met criteria for only these diagnoses. Figures 7 and 8 present the standardized mean scores for the EF tests for the non-overlapping lifetime and current diagnostic groups included in this analysis. For informational purposes, the mean EF scores for the overlapping diagnostic groups (i.e., individuals could meet criteria for multiple disorders, so a single individual could be included in multiple disorder groups) are in Figures 9 and 10.

Lifetime analyses demonstrated that the main between-subject effect of group was significant (F (1, 5, 631) = 3.22, $p < .01$). Post-hoc Tukey tests indicated that the anxiety disorder group performed significantly better than both the child externalizing group ($p < .05$) and the comorbid group ($p < .05$) across EF tests. The main within-subject effect of test (F (4, 628) = .98, $p > .05$) and the test-by-disorder interaction were not significant (F (20, 2084) = 1.00, $p > .05$). These results suggest that for lifetime disorders there are

differences in overall EF test performance between certain disorders (but not significantly different from controls). However, the pattern of performance is not significantly different across tests based on disorder status. Results remained the same after covarying age, gender, and IQ.

For current diagnoses, the main effect of disorder status was significant (F (1, 6, 633) = 4.61, $p < .01$). Post-hoc Tukey tests indicated that there were significant differences between the control group and the ADHD and ASPD groups ($p < .05$), and the anxiety disorder group and the alcoholism, ASPD, and ADHD groups ($p < .05$). The main within-subjects effect of test was significant (F (4, 630) = 3.70, $p < .01$), which simply means that there were differences in the EF test means. Of greater interest, however, was the significant test-by-disorder interaction (F (24, 2199) = 1.63, $p < .05$). Here, the quadratic and order-4 within-subjects contrasts were significant (quadratic: F (6) = 2.30, $p < .05$; order-4: $F(6) = 3.06$, $p < .01$), suggesting there were quadratic and quartic trends in the data. The curved profiles with poorer performance on Trails Residual, Response Inhibition, and RT Variability for alcoholism, ADHD, and ASPD in Figure 8 depict this relationship. Therefore, this analysis found differences in EF results due to current disorder status and specific test, and the differences across tests varied based upon group membership.

Univariate ANOVAs with post-hoc Tukey analyses were conducted for each test to better understand the test-by-disorder interaction. There were significant group (i.e., disorder) differences on Trails Residual (F (6, 633) = 2.78, $p < .01$), Response Inhibition (F (6, 633) = 3.88, $p < .01$), and RT Variability (F (6, 633) = 2.68, $p < .05$). Follow-up Tukey tests indicated that participants with ADHD performed significantly worse than

those with anxiety disorders on Trails Residual ($p < .05$). On Response Inhibition, alcoholics performed significantly worse than controls, anxiety disordered, and comorbid participants ($p < .05$). No individual comparisons reached significance for RT Variability, but there was a trend for the ADHD group to perform more poorly than controls ($p = .07$). Although differences did not reach significance, the ASPD group also tended to perform more poorly than other groups on these three measures, while depressed and, surprisingly, comorbid participants tended to perform similarly to controls. When age, gender, and FSIQ were covaried in MANCOVA, the main effects of disorder and test remained significant, but the test-by-disorder interaction was no longer significant. Thus, these covariates appeared to account for the interaction, and when controlled support for the componential model is reduced.

Summary of analysis for model 1. Partial support was provided for a componential model in the profile analysis, but only with current diagnoses, where participants with ADHD and alcoholism demonstrated different patterns of performance across EF tests from some other groups. Current ADHD was associated with poorer Trails Residual and RT Variability (the latter was a trend), and current alcoholism was associated with deficits in Response Inhibition. RT Variability deficits in the ASPD group approached, but did not reach, significance. Support for the componential model disappeared when age, gender, and FSIQ were covaried in current analyses. Differences in global EF performance between disorders and between tests remained significant, but these did not interact. The componential model did not receive support in lifetime diagnoses, as the *pattern* of performance across EF tests did not differ based on disorder status, although there were differences in overall EF performance between individuals

with anxiety disorders and those with childhood externalizing or comorbid disorders. In general, comorbid disorder presentation was not related to greater EF impairment. Overall, the weak support for the componential model in the profile analysis suggested that this model failed to adequately explain the relationship between psychiatric disorders and EF. Support for disorder-specific effects was suggested, however, and with these results in mind, the following analysis further elucidated the effects of disorder status upon global and specific EF test performance.

Analysis 2: Testing the Comorbidity-Specificity Model that Only One or a Few Disorders Are Uniquely Associated with EF Deficits

Multiple regression analyses were conducted to examine whether only certain disorders were associated with EF deficits. Then, high levels of comorbidity amongst disorders may account for the appearance of more widespread deficits. Predictors were dummy-coded variables for presence/absence of each disorder (i.e., any depression, any anxiety disorder, alcoholism, drug dependence, ASPD (lifetime), and childhood externalizing disorders/adult ADHD). Predictors were entered in a single block, with the outcome variable being the composite EF score. This allowed for an examination of the unique contribution of individual disorders to EF test performance. To assess for differential effects with other cognitive processes, this regression was repeated with the processing speed composite variable and individual EF tests. The effects of age, gender, and IQ were covaried.

The results of the linear multiple regression analysis for lifetime diagnoses and EF composite are presented in Table 17. As can be seen, only childhood externalizing disorders significantly predicted the EF composite score, with presence of a childhood

externalizing disorder being related to poorer performance on EF tasks, and all lifetime disorders together accounting for 3% of the variance in the EF composite score. To better understand the contributions of individual disorders to this result, this analysis was repeated with the childhood externalizing disorders separated into CD, ODD, and ADHD. Here, only ADHD was significantly predictive of EF composite score ($\beta = -.20$, $p < .01$), suggesting that ADHD accounted for the predictive power of the childhood externalizing disorders. Similar results were found for current disorders, as only adult ADHD significantly predicted poorer performance on EF tests (see Table 18). Together, all of the current disorders accounted for 4% of the variance in EF performance.

While age and IQ were also significant predictors of EF composite score ($\beta = .10$, $p < .05$ for age; $\beta = -.35$, $p < .01$ for IQ; $\beta = -.07$, $p = .06$ for gender with males trending towards better performance), these results remained the same for lifetime disorders even after age, gender, and IQ were controlled ($\beta = -.14$, $p < .05$ for lifetime childhood externalizing; $\beta = -.23$, $p < .01$ for lifetime ADHD). The same results were seen for current disorders, where both gender ($\beta = -.09$, $p < .05$, with males performing better) and IQ ($\beta = .36$, $p < .01$) were significant predictors, but adult ADHD remained significant ($\beta = -.21$, $p < .01$) even after controlling for age ($\beta = .08$, $p = .08$), gender, and IQ. Therefore, for both lifetime and current analyses, only ADHD was significantly related to performance on EF tests. Bivariate correlations also showed that only ADHD was related to EF composite (results not shown).

Regression analyses were also performed with the individual tests, using the standardized test performance. There were no significant predictors for Stroop Residual. Of the lifetime disorders, only childhood externalizing disorders significantly predicted

poorer performance on Trails Residual ($\beta = .16, p < .01$), RT Variability ($\beta = .16, p < .01$), and approached significance for WCST ($\beta = -.08, p = .06$). Breaking the childhood externalizing disorders down into the individual disorders (ADHD, ODD, and CD) demonstrated that ADHD was accounting for these relationships. Anxiety disorders significantly predicted Response Inhibition score ($\beta = -.11, p < .01$) and approached significance with RT Variability ($\beta = -.08, p = .06$), predicting *better* performance on these measures; when broken into the individual disorders no one anxiety disorder was significantly related to either measure. When FSIQ, age, and gender were added to the regression equation, childhood externalizing disorders remained significantly related to Trails Residual and RT Variability, although the relationship with WCST was no longer significant, and anxiety remained a significant predictor of better Response Inhibition score (results not shown). Surprisingly, alcoholism became a significant predictor of better Stroop Residual score after covarying these variables ($\beta = .09, p < .05$).

For current disorders, regression analyses suggested that ADHD significantly predicted Trails Residual ($\beta = .13, p < .01$), Response Inhibition ($\beta = .11, p < .01$), and RT Variability ($\beta = .19, p < .01$). Alcoholism significantly predicted Response Inhibition ($\beta = .08, p < .05$) and RT Variability ($\beta = .09, p < .05$), and ASPD approached significance in predicting Trails Residual ($\beta = .07, p = .07$). No disorders significantly predicted Stroop or WCST. After controlling for age, FSIQ, and gender, ADHD remained a significant predictor of Trails Residual, Response Inhibition, and RT Variability. Alcoholism no longer significantly predicted Response Inhibition but predicted RT Variability, and ASPD demonstrated a trend towards better WCST

performance ($\beta = .08, p = .06$) while anxiety demonstrated a trend towards better Response Inhibition ($\beta = -.07, p = .08$).

Finally, regression analyses were repeated with the speed composite score (see Tables 19 and 20). For lifetime disorders, alcohol dependence and childhood externalizing disorders (shown to be predominantly ADHD ($\beta = -.10, p < .05$) when broken into component parts) were significantly related to speed. When age ($\beta = -.08, p = .09$), gender ($\beta = -.17, p < .01$ with males being faster), and IQ ($\beta = .33, p < .01$) were controlled, only childhood externalizing disorders (i.e., ADHD) remained significant. For current disorders, only ASPD significantly predicted slower speed, although this result appeared to be due to sample-related issues as only adult ADHD significantly predicted slower speed after controlling for age ($\beta = -.06, p > .05$), gender ($\beta = -.18, p < .01$ with males being faster), and IQ ($\beta = .35, p < .01$).

Summary of analysis for model 2. Only current and lifetime ADHD were unique predictors of poorer performance on global EF measures when controlling for the effects of other disorders, and these results remained after controlling for age, gender, and IQ. While global effects were seen, only some of the individual EF tests were related to ADHD, suggesting that these associations may be driving the overall, global score. ADHD predicted poorer performance on Trails Residual and RT Variability (current and lifetime) and Response Inhibition (current). A trend towards more WCST perseverative errors disappeared after controlling for FSIQ. With regard to individual tests, current alcoholism was also related to poorer RT Variability and Response Inhibition and a trend was seen between ASPD and Trails Residual (none of these results remained with covariates). Lifetime, but not current, anxiety predicted better performance on Response

Inhibition and RT Variability before controlling for covariates (the latter was a trend). Thus, the robust relationship between ADHD and global and individual EF effects provided strong support for the Comorbidity-Specificity Model.

The individual test effects also suggested that the Componential Model is important to the relationship between EF and ADHD. Although weaker, the associations between alcoholism and individual EF processes also provided support for both models. However, ADHD was also associated with slower processing speed, suggesting that cognitive effects are not specific to the EF domain.

Analysis 3: Testing the Comorbidity-Nonspecificity Model that Number of Disorders Predicts Performance on EF Tests

This analysis examined the possibility that *number of disorders* rather than type of disorder, contributed to EF deficits. A variable was created to define individuals with: (1) no disorders; (2) one disorder; (3) two disorders; and (4) three or more disorders. Disorders that were included in lifetime analyses were: MDD, dysthymia, GAD, OCD, PTSD, agoraphobia without panic disorder, social phobia, specific phobia, alcohol dependence, drug dependence, ASPD, ODD, CD, and ADHD. In current-diagnosis analyses, the following disorders were included in the determination of number of disorders at the time of testing: MDD, dysthymia, GAD, OCD, PTSD, social phobia, specific phobia, alcohol dependence, drug dependence, ASPD (lifetime), and adult ADHD. Agoraphobia without panic disorder was not included in analyses on current disorder status because no participants met criteria for agoraphobia near the time of testing.

The effects of number of disorders on EF test performance were assessed using multiple regression as well as mean difference (i.e., ANOVA with post-hoc Tukey tests) analyses. Predictor variables included the composite EF variable, the composite speed variable (to determine whether any effect of comorbidity cut across neurocognitive domains), and the five individual EF tests (to determine whether certain tests were more strongly related to comorbidity than others). Age ($\beta = .18$, $p < .01$), gender ($\beta = -.07$, $p = .05$), and IQ ($\beta = .34$, $p < .01$) were covaried.

The distributions of numbers of lifetime and current disorders in the present study are presented in Tables 21 and 22. Individuals who met criteria for three or more disorders were collapsed into a single group for analyses. The regression of the EF composite variable upon number of lifetime disorders was not significant ($\beta = -0.052$, $p = .193$). When considering current disorders, the regression was significant ($\beta = -.104$, $p = 0.008$). The relationship was small, but suggested that having more current comorbid disorders was significantly related to poorer performance on EF tasks. However, this association was no longer significant when controlling for age, gender, and FSIQ.

ANOVA also indicated that there was not a significant difference in the mean EF composite score between groups for lifetime disorders ($F(3, 637) = .942$, $p = 0.42$). The omnibus test for current disorders suggested that there was a significant difference in mean EF composite score between the groups ($F(3, 637) = 2.67$, $p = 0.047$), but none of the individual mean differences reached significance in post-hoc Tukey's tests. Therefore, having a greater number of disorders near the time of testing, but not throughout the lifetime, did appear to be linearly related to poorer performance on EF tasks. However, there were no significant group differences in the EF composite score.

Further, independent samples *t*-tests demonstrated that simply having any disorder at all was significantly related to performance on EF tests for current diagnoses ($t = 2.52$, $p = .01$) but not for lifetime disorders ($t = 1.68$, $p = .09$). These results suggested that, perhaps, *presence* of a current disorder was more important than *number* of current disorders in EF task performance. Further, presence versus absence of lifetime disorders in general did not result in significant differences in EF test performance.

When considering the individual EF tests, regression results indicated that there was no predictive relationship between number of disorders across the lifetime and performance on any of the individual tests (results not presented). ANOVA results demonstrated no mean differences between groups (results not presented). For current diagnoses, number of disorders significantly predicted Trails Residual ($\beta = .086$, $p = .029$), while Stroop ($\beta = -.072$, $p = .070$) and RT Variability ($\beta = .076$, $p = .053$) approached significance. WCST ($\beta = -.001$, $p = .979$) and Response Inhibition ($\beta = .055$, $p = .166$) were not significant predicted by number of disorders. No relationships remained significant when controlling for age, gender, and FSIQ. Significant mean differences were observed for Trails Residual (F (3, 637) = 3.09, $p = .03$) and Response Inhibition (F (3, 637) = 3.96, $p < .01$). Post-hoc Tukey tests indicated that the difference for Trails Residual was between participants with no disorders ($M = -0.76$, $SD = 17.67$) and those with three or more disorders ($M = 9.51$, $SD = 24.70$), who performed significantly more poorly. For Response Inhibition, a significant difference was seen between individuals with no disorders ($M = 241.37$, SD = 68.34) and those with one disorder ($M = 262.97$, SD = 82.93), with the latter performing significantly worse. Therefore, there was a linear relationship between number of disorders and performance

on Trails Residual, and mean differences between controls and individuals with three or more disorders. A mean difference in Response Inhibition time was seen for controls and individuals with one disorder.

Number of lifetime disorders did significantly predict performance on the speed composite variable (β = -.170, p < .01), as did number of current disorders (β = -.083, p = .036), although the latter result was no longer significant when controlling for age (β = -.01, p > .05), gender (β = -.19, p < .01), and FSIQ (β = .34, p < .01). The omnibus ANOVA F-test was significant for lifetime disorders (F (3, 637) = 6.87, p < .01), with a significant difference between speed task means for individuals with no disorders (M = 0.00, SD = 2.48) and those with one (M = -0.67, SD = 2.34), two (M = -0.75, SD = 2.50), and three or more disorders (M = -1.22, SD = 2.52). There were no mean differences for current disorders (results not shown).

Summary of analysis for model 3. Taken together, number of lifetime disorders was not associated with EF performance. A small but significant linear relationship was seen between frequencies of current disorders and performance upon EF (particularly Trails Residual and Response Inhibition) and speed tasks; however, differences in age, gender, and FSIQ appear to account for these relationships. Further, *presence* of a current disorder, rather than the number of disorders, appeared to be more important to EF performance. A more robust and enduring relationship existed between lifetime disorders and performance on speed tasks, with increasing number of disorders contributing linearly to slower speed. In all, the Comorbidity-Nonspecificity hypothesis that EF deficits were nonspecifically related to number of disorders was not supported.

Analysis 4: Testing the Dimension-Specificity Model that Shared Underlying Dimensions of Psychopathology are Differentially Related to Cognitive Task Performance

Latent factors and structural equation modeling (SEM) were used to examine the relative relationships between general dimensions of psychopathology and performance on neuropsychological tests assessing speed and EF. Individual latent variables included in this analysis were validated in the previously presented CFAs.[3]

The measurement model for the large model examining relationships between lifetime disorders and performance on EF and processing speed tasks is presented in Figure 11. Although not perfect, fit for this model was adequate (χ^2 (127) = 287.37, $p <$ .01; GFI = .95, CFI = .88, RMSEA = 0.04), particularly considering that the focus of this model was to analyze specifically-defined a-priori relationships as opposed to capturing all possible relationships between variables in the model. In other words, the reduced model fit indicates that there are relationships within the data that are not represented in the model, but fit was considered to be adequate to interpret the path coefficients. All factor loadings for the individual latent variables were significant. Correlations between the externalizing factor and both cognitive domains were significant, as well as between the two cognitive domains (i.e. EF and speed).

The structural model to examine the predictive relationships for lifetime internalizing and externalizing disorders upon EF and speed latent variables is presented in Figure 12. Fit was adequate, and fit did not change from the measurement model (χ^2 (127) = 287.37, $p <$ .01; GFI = .95, CFI = .88, RMSEA = 0.04). The externalizing latent variable significantly predicted both the executive and the speed latent factors. However,

[3] Note that standardized test scores were not used in any of the latent, measurement, or structural models, because SEM relies upon an analysis of covariance---that analysis would be undermined if these variances were equalized.

the internalizing latent factor did not significantly predict either of the cognitive variables. Therefore, there was a differential relationship between disorder and cognitive performance for the type of disorder (i.e., internalizing versus externalizing), but not for the type of cognitive ability (i.e., speed versus executive). Together, the internalizing and externalizing variables accounted for 8% of the variance in the EF factor and 11% of the variance in the speed variable. Covariates were also entered into the structural model; however, the sample size was not large enough to enter age, gender, and FSIQ simultaneously so each covariate was entered individually. Gender (β = -.01, p > .05 with EF and β = -.09, p = .07 with speed) and age (β = .53, p < .01 with EF and β = .10, p < .05 with speed) alone did not affect results. After controlling for IQ, only the relationship between externalizing and speed remained significant (β = .12, p > .05 for EF; β = .26, p < .01 for speed), likely due to the very strong relationship between FSIQ and EF (β = -.72, p < .01 with EF and β = -.30, p < .01 with speed).

When this same baseline measurement model was assessed with current disorders, fit was adequate ($\chi 2$ (127) = 340.84, p < .001, GFI = .94, CFI = .83, RMSEA = .05), but both dysthymia and ADHD demonstrated poor loadings on the internalizing and externalizing factors, respectively (β = .06 and β = -.10). The poor dysthymia loading is likely due to its small sample size, particularly in the alcoholism sample, as all of the individuals with MDD are in the alcoholism sample. The poor ADHD loading is likely also due to differences in distributions of disorders between the samples, as adult ADHD was only evaluated in the ADHD sample, while the other externalizing disorders (i.e., alcoholism, ASPD, and drug dependence) were predominantly found in the alcoholism sample. Therefore, there was almost no overlap between current diagnoses of

alcoholism, ASPD, and drug dependence and ADHD. Given the poor fit for these factors on their respective latent variables, dysthymia and ADHD were dropped from the current model. There was a significant improvement in fit for the measurement model ($\chi 2$ (97) = 213.07, $p < .001$, GFI = .96, CFI = .89, RMSEA = .04; change in $\chi 2$ (30) = 127.77, $p < .01$; see Figure 13) and all factor loadings were significant. Correlations between externalizing disorders and both cognitive domains were significant, as was the correlation between EF and speed.

When predictive relationships were examined in the structural model (see Figure 14), there was no change in fit from the measurement model ($\chi 2$ (97) = 213.07, $p < .001$, GFI = .96, CFI = .89, RMSEA = .04). Similar to the results with lifetime diagnoses, externalizing disorders significantly predicted poorer performance on both EF and speed measures. Internalizing disorders were not significant predictors of either cognitive domain. Therefore, again, there was specificity in the relationship between disorder and cognitive performance for type of disorder (i.e., externalizing, not internalizing), but not for type of cognitive task (i.e., externalizing disorders were related to both EF and speed). Note that the predictive relationships between externalizing disorders and cognitive task performance with current disorders were stronger than those for lifetime diagnoses.

Results were unchanged when gender was controlled in the model ($\beta = -.03$, $p > .05$ with EF and $\beta = .07$, $p > .05$ with speed). When age was added as a covariate ($\beta = .47$, $p < .01$ with EF and $\beta = .11$, $p < .05$ with speed), the relationship between externalizing disorders and speed remained significant ($\beta = .32$, $p > .05$), whereas the relationship between externalizing and EF approached but did not reach significance ($\beta = .33$, $p = .05$). Similarly, when FSIQ was added as a covariate, the relationship between

externalizing and EF was no longer significant ($\beta = .14, p > .05$), but the relationship between externalizing and speed remained significant ($\beta = .25, p < .05$). Again, there was a strong relationship between FSIQ and EF ($\beta = -.69, p < .01$), moreso than with speed ($\beta = -.27, p < .01$). Internalizing disorders remained unrelated to either cognitive domain in all of these covariate analyses.

Summary of analysis for model 4. The externalizing dimension of psychopathology for both lifetime and current disorders predicted both poorer EF performance and slower speed, whereas the internalizing dimension was unrelated to either cognitive test domain. Therefore, dimensional specificity was apparent with regards to psychopathology, but not with regard to cognitive domain; that is, there was not a differential cognitive deficit. However, FSIQ was strongly related to EF, and when controlled in the present analyses only the relationship between externalizing disorders and speed remained significant.

Separate Sample Analyses

It should be noted that linear regression analyses were conducted in the ADHD and alcoholism samples separately to determine equivalence of findings. In the ADHD sample, only childhood externalizing disorders/adult ADHD were related to poorer performance on the EF composite ($\beta = -.19, p < .05$ for lifetime; $\beta = -.17, p < .05$ for current) even after including age, gender, and FSIQ. Lifetime drug dependence approached significance ($\beta = -.14, p = .06$). In the alcoholism sample, no disorder groupings were related to EF composite score for lifetime analyses. Interestingly, however, when childhood externalizing disorders were separated into ADHD, ODD, and CD, ODD was significantly predictive of better EF score ($\beta = .19, p < .01$). This unusual

result will be further investigated in later studies. Alcoholism approached significance in current analyses in the alcoholism sample ($\beta = -.09, p = .08$). The small sample size for ADHD, and the fact that it was only assessed for childhood, likely prevented this disorder from demonstrating EF effects in the alcoholism sample. Therefore, separate sample analyses were similar to the findings from the combined sample, with ADHD demonstrating robust effects.

Overall Summary

Taken together, these results suggested that there is specificity in the types of disorders that are associated with EF deficits. The Comorbidity-Nonspecificity Model (Model 3) examining the effect of number of disorders from a non-specific perspective was clearly ruled out by the present results. Before controlling for age, gender, and FSIQ, a number of the other models received support and provided information about the nature of the specific relationships. The Dimension-Specific Model (Model 4) perhaps best summarizes the overall findings, with externalizing disorders, and not internalizing disorders, being related to EF deficits. Aspects of both the Comorbidity-Specificity Model and Componential Model were supported as predominantly process-specific EF deficits were associated with only ADHD, alcoholism, and ASPD (all externalizing disorders). Global EF effects appeared to be driven by individual-process weaknesses.

These results are tempered by the fact that most of the cognitive findings were non-specific in nature and crossed neurocognitive domains. Similar impairments were found for processing speed and psychopathology, and FSIQ appeared to account for performance on EF tests. When IQ was controlled in analyses, only the global and individual EF weaknesses associated with ADHD remained. Unlike the EF effects,

associations between psychiatric disorders and processing speed generally remained significant even after controlling for FSIQ. Thus, the processing speed deficits were more robust than EF effects in the present study. This suggests that slow processing speed may be a general marker of disturbance, whereas EF may be related only to particular forms of psychopathology when covariates are considered.

Discussion

The present study sought to examine the relationship between psychiatric disorders and EF deficits in six forms of psychopathology that have previously been associated, in some manner, with neuropsychological EF deficits: childhood-onset disruptive behavior disorders (i.e., ADHD, CD, and ODD), adult ADHD, alcohol dependence, drug dependence, ASPD, depression, and anxiety disorders. To better understand the widespread association between psychopathology and EF, this study focused on comorbidity amongst disorders and how they contribute to general and specific cognitive impairments.

Four different models were tested as potential explanations for this relationship. The models moved along the diagnostic hierarchy from individual disorders, to multiple or comorbid conditions, to dimensional pathology. Two models appeared to best explain the relationship between EF and psychopathology: the Dimensional Model and the Componential Model. Before discussing the significance of that conclusion, the results of each of the main hypotheses will be briefly examined in turn. Additional hypotheses that were examined within these main models, such as the specificity of EF deficits, long-term nature of disorder-related deficits, sensitivity of EF tests to pathology, and directional influences in the relationship between EF and psychiatric disorders, will also be discussed.

Examination of Hypotheses

Nonspecific EF Deficits

Nonspecific comorbidity was not significantly related to EF deficits. In profile analyses, individuals with multiple lifetime disorders had significantly poorer mean

global EF performance compared to individuals with anxiety disorders, but there were no differences from controls. Participants with multiple disorders did not demonstrate any deficits in performance in current analyses compared to other disorder groups or controls. In fact, as depicted in Figure 8, their performance on many tasks was better than that of individuals with only current ADHD, alcoholism, or ASPD. Although there was a weak linear relationship between number of current disorders and poorer EF performance, it appeared as though the important effect was simply *presence* of a disorder near the time of testing rather than comorbidity or the number of disorders.

Some differential effects suggested that current comorbidity predicted poorer performance on certain EF processes, namely set-shifting and response inhibition. Again, however, results were weak in that increasing numbers of disorders did not directly relate to worse performance on these measures.

A number of potential explanations may account for the failure of the nonspecificity hypothesis with regards to EF. Firstly, number of disorders may not be the best marker of severity of psychopathology. Increasing numbers of disorders do not necessarily reflect a concomitant increase in the level of impairment. Previous studies have found that severity of depressive symptoms and frequency/chronicity of episodes were related to cognitive impairment (Merriam et al., 1999; Purcell et al., 1998; Richard et al., 2003). Thus, other more informative markers of severity may be level of self-reported impairment associated with individual disorders, chronicity, success of treatments, relapse rates, and other indicators. Second, the definition of "current" disorders in the present study may have reduced the ability to detect effects. Current disorders were not necessarily indicative of an "acute" condition at the time of testing,

but rather a "recent" condition because individuals from the alcoholism sample were defined as having a current disorder when they met criteria for a disorder within the past three years. Some "current" diagnoses may not have been present at the time of testing, reducing their impact upon test performance. Further, current disorders may not have been concurrently diagnosed, weakening any cumulative effects of having multiple coexisting disorders. Finally, it may be that specific combinations of disorders are important to EF effects (e.g., alcoholism and ASPD; Giancola & Moss, 1998; Malloy et al., 1989). Overall, however, these results suggest that number of disorders alone does not contribute to EF problems.

Disorder-Specific EF Deficits

Given that nonspecific comorbidity was not associated with EF deficits, a comorbidity-specificity model was alternatively hypothesized to explain the relationship between psychiatric disorders and EF deficits at the level of multiple disorders. Here, it was suggested that only certain disorders were related to EF deficits, and comorbidity amongst disorders made it appear more widespread. Analyses of global EF performance showed that only certain disorders were associated with poorer performance. Mean global EF differences for lifetime diagnoses suggested that individuals with ADHD performed more poorly than individuals with anxiety disorders. No differences were seen between controls and disorder groups for lifetime diagnoses, suggesting that this ADHD effect did not reflect a clinical EF impairment. More clinically relevant results were seen for current diagnoses, as current ADHD and ASPD groups demonstrated global EF deficits compared to controls. Current alcoholics (along with ADHD and ASPD groups) performed more poorly than anxiety-disordered individuals. The small

sample size for current alcoholism may have prevented differences from controls from reaching significance. Thus, current and lifetime ADHD, ASPD, and current alcoholism were associated with weaker global EF performance.

Many individuals in the present study met criteria for multiple lifetime/current disorders, and the single-disorder analyses did not include this full range of pathology. When taking overlapping/comorbid conditions into account and controlling for their presence in regression analyses, only current and lifetime ADHD were related to the EF composite score. This was a robust effect, which remained even after controlling for other factors such as age, gender, and FSIQ. Such findings are consistent with previous findings for ADHD, as the EF deficits associated with this disorder have generally remained robust even after controlling for the presence of comorbid conditions (Nigg et al., 2005; Seidman et al., 1998; Willcutt et al., 2005). Therefore, ADHD, ASPD, and alcoholism were associated with poorer global mean EF performance, particularly when these conditions were diagnosed near the time of testing. In linear analyses, when overlap and comorbidity amongst conditions were taken into account, only ADHD was uniquely related to global EF deficits.

Process-Specific Disorder-Related EF Deficits

Specificity of the relationship between EF and psychopathology was further examined by considering different aspects of EF processes. The hypothesis that individual disorders may be associated with impaired performances in different aspects of EF processes received some support. The same disorders that were shown to be related to global effects had process-specific effects.

Profile analysis highlighted the fact that participants with current ADHD or current alcoholism tended to demonstrate relative decrements in their already poorer global EF performance (described below) on set-shifting and response inhibition, respectively. Overall, the somewhat weak componential effects in the profile analysis were surprising given that there was considerable support in the literature for process-specific EF deficits in the different disorders. Further, the graphs plotting the mean EF task performance suggest that there were additional disorder-related differences in the patterns of performance across tests for current diagnoses that did not reach significance in the profile analysis (see Figure 8). The use of single-disorder groups (resulting in an unbalanced design and reduced sample sizes) may have affected power to detect effects.

More powerful regression analyses examining the unique relationships between disorders and individual EF test performances provided similar results, along with additional effects that did not reach significance in the profile analysis. For instance, lifetime ADHD was related to greater response variability and weak set-shifting. Current disorder results were similar to those found with the profile analysis, as current ADHD was again related to deficits in set-shifting (Trails Residual) and response variability, as well as to response inhibition. Current alcoholism also predicted poorer response inhibition (although not after controlling for FSIQ), as well as greater response variability. Finally, a trend was seen for ASPD to be related to poorer set-shifting performance (i.e., Trails Residual) in current-diagnosis analyses.

Therefore, the same disorders (i.e., current and lifetime ADHD, ASPD, and current alcoholism) tended to be related to global as well as specific EF deficits. The process-specific weaknesses overlapped amongst these disorders to some degree;

decrements on the residual score from Trail Making Test were seen for current and lifetime ADHD and ASPD (the latter being a trend), and weak Response Inhibition and RT Variability were seen for both ADHD and alcoholism. Thus, the processes most sensitive to disorder-based differences were set-shifting, response inhibition, and response variability. On the other hand, anxiety disorders, depression and drug dependence did not demonstrate weaker global or component EF proceses. Other childhood-onset disorders such as CD and ODD were also not uniquely related to EF deficits, likely because these disorders are not diagnosed in adulthood and EF effects were subsumed under the adult manifestations of these disorders (e.g., alcoholism, ASPD, ADHD). Therefore, the same disorders demonstrated both global and specific EF weaknesses, suggesting that the global effects were driven by component differences to some degree. The deficits associated with ADHD, alcoholism, and ASPD tended to overlap. ADHD demonstrated the most widespread and robust effects, but the profiles of performance on EF tests for these disorders were not entirely differentiable.

Consistencies and divergences exist between these results and past research with respect to the individual disorder findings. Similar to the present study, past research on ADHD has demonstrated deficits on Trails B, Response Inhibition, and RT Variability, while deficits in WCST and Stroop Interference were rare (Boonstra et al., 2005; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Frazier et al., 2004; Hervey et al., 2004; Johnson et al., 2001; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Lovejoy et al., 1999; Murphy et al., 2001; Nigg et al., 2005; Riccio et al., 2005; Walker et al., 2000; Willcut et al., 2005). Thus, EF results for participants with ADHD were highly consistent with past literature.

More variability was noted between the present findings and past research for alcoholism. A wide range of EF deficits have been seen across previous studies on alcoholism (Adams et al., 1993; Brokate et al., 2003; Dao-Castellana et al., 1998; Hoffman et al., 1987; Poon et al., 1999; Ratti et al., 2002; Uekermann et al., 2003), but only deficits in response inhibition (before controlling for IQ) and response variability were found in the present study for alcoholism. The small sample size for current alcoholism only in the present study may have reduced the power to detect additional group differences even though the alcoholism group appeared to perform poorly on Trails Residual as well (see Figure 8). While multiple deficits have been seen across many previous studies, the specific deficits tended to differ between studies. Further, some researchers found that individual tests lacked sensitivity in this population and global, composite EF scores were required to demonstrate EF deficits (Goldstein et al., 2004b; Selby & Azrin, 1998; Sullivan et al., 2002). Thus, although specific deficits were confined to only response variability and inhibition for alcoholism, these results are not widely inconsistent with previous findings.

Contrary to expectations, ASPD was not related to deficits in response inhibition. Instead, individuals with ASPD demonstrated a trend towards poorer performance on a set-shifting task. The expectation of response inhibition deficits was based upon research suggesting that similar regions of the brain contributed to antisocial symptoms and response inhibition abilities (Blair & Cipolotti, 2000; Fuster, 1997; Rubia et al., 2000) and some findings in children that aggression is related (Kerr, Tremblay, Pagani, & Vitaro, 1997). However, response inhibition deficits have only been shown in a few studies for DSM-IV diagnoses, and deficits did not always reach full significance (Dinn

& Harris, 2000; Dolan & Park, 2002). Further, EF deficits are more commonly seen in individuals with ASPD and other comorbid conditions (Dinn & Harris, 2000; Malloy et al., 1990), so controlling for other disorders in these analyses may have reduced cognitive effects. Finally, although set-shifting deficits were rare in the limited past research on cognitive deficits in ASPD, they were noted in at least one previous study (Dolan & Park, 2002). Therefore, the present findings are also not entirely inconsistent with previous literature on ASPD.

Anxiety disorders, depression, and drug dependence were not related to EF deficits in this study. With respect to anxiety disorders, it was thought that because poor interference control may theoretically contribute to the development of anxiety (Calvo & Eysenck, 1996; Eysenck & Calvo, 1992; Hopko et al., 1998), deficits would be seen on EF tasks assessing the cognitive component of this process. However, this was not supported. Interestingly, the presence of anxiety disorders, particularly lifetime disorders, was associated with improved abilities to inhibit responses and maintain consistency in response speeds (the latter being a trend). Further, individuals with anxiety disorders performed significantly better than individuals with ADHD on a set-shifting task (i.e., Trails Residual). No individual anxiety disorders were accounting for these findings. Taken together, it may be that individuals with a personality or response styles that are vulnerable to developing anxiety disorders are more likely to be cautious, attentive, and consistent on tasks that require sustained focus.

Note that the anxiety-based enhancements in set-shifting and response inhibition and variability in the present study were generally relative to other disorders rather than control participants, and tended to disappear after controlling for age, gender, and FSIQ.

Only OCD has been associated with consistent EF deficits, and few individuals met criteria for OCD in the anxiety disorder group in this study. Thus, these results were consistent with past findings suggesting lack of support for EF deficits in anxiety. They extend prior research by suggesting that anxiety-disordered individuals show relatively better performance compared to indivduals with other pathologies on tasks assessing set-shifting, response inhibition, and response variability.

Issues specific to the individual disorders as well as to the methodology of this study may have reduced the likelihood of detecting EF effects with depression and drug dependence. With regards to depression, no individuals with current MDD were included in one of the samples (i.e., ADHD-based sample), and the definition of "current" depression in the other sample (i.e., alcoholism) included individuals who met criteria *near* the time of testing, not necessarily at the time of testing. Some studies have suggested that cognitive deficits continue even after depression has remitted (Kessing et al., 1998). However, in general, there was greater support for EF deficits in the acute phase of the disorder, and these were related to severity of symptoms, recurrence of depressive episodes, and chronicity of the disorder (Kessing et al., 1998; Paradiso et al., 1997). These key factors could not be assessed in the present examination and may have limited findings for depression and EF.

Similar factors were important in past studies of drug dependence. For instance, number of drug dependencies, presence of additional comorbid disorders, dose-related drug effects, chronicity of use, and recency of intake were shown to be significant to past associations between drug dependence and EF impairment (Bolla et al., 1999; Eldreth et al., 2004; Fals-Stewart & Bates, 2003; Goldstein et al., 2004b; Gruber et al., 2005; Selby

& Azrin, 1998). The inability to account for these factors in the present study may have impeded the ability to detect EF effects. Further, the present sample included almost no individuals who met criteria for *only* drug dependence, disrupting the ability to isolate cognitive deficits associated with this disorder. The high rate of comorbidity with drug dependence in the present study, and past findings that comorbidity was important to cognitive effects, suggests that other disorders account for the link between drug dependence and EF throughout the literature. Taken together, disorder-related and study-specific issues may be contributing to the failure to detect an EF effect for anxiety disorders, depression, and drug dependence.

To review, both disorder- and process-specific EF effects were found. The deficits in component processes across ADHD, ASPD, and alcoholism tended to overlap, but were not identical, suggesting that certain EF tests were particularly sensitive to psychopathology (i.e., Trail Making Test and Stop Signal). The presence of these disorders near the time of testing increased the likelihood of deficits, but a lifetime diagnosis of ADHD was also associated with weaker performance. Anxiety disorders, depression, and drug dependence were not associated with EF impairments.

Dimension-Specific EF Deficits

The final main hypothesis examined the relationship between psychopathology and EF at the broadest level of the diagnostic hierarchy. Here, the question was whether the wide-ranging association between psychiatric disorders and EF deficits was due to shared underlying dimensions of psychopathology. A common and accepted distinction between "internalizing" and "externalizing" disorders was used to determine whether traits/symptoms that are shared in the development and manifestation of these disorders

are differentially related to EF deficits. Previous analyses have highlighted that global and specific EF deficits were associated with the following disorders: ADHD, alcoholism, and ASPD. Depression and anxiety disorders (along with drug dependence, perhaps due to the highly comorbid nature of this disorder) did not demonstrate EF deficits. The dimensional model further emphasized the split between these types of disorders, as only externalizing disorders were related to EF deficits.

Given the strong relationship between ADHD and EF deficits in prior analyses, it is particularly striking that current externalizing disorders continued to significantly predict EF test performance even after removing the ADHD indicator from the latent factor. As well, while individual lifetime analyses tended to demonstrate weaker links between disorders and cognitive functioning, the latent lifetime externalizing factor demonstrated a strong association between disorders and EF performance in the dimensional analysis. This provides strong support for the possibility that a shared aspect of these disorders, rather than just a single disorder or type of symptom, is contributing to performance on EF tests.

ADHD was shown to be most strongly related to EF deficits in previous analyses, as the widespread relationship with component EF processes contributed to robust global effects. Alcoholism and ASPD demonstrated more sporadic relationships were fewer EF processes. It may be that a shared underlying feature of these disorders is stronger in ADHD than in other externalizing disorders, thus accounting for the more consistent relationship between ADHD and EF deficits. However, EF effects disappeared after controlling for IQ due to strong relationships between FSIQ, externalizing disorders, and EF performance. It is difficult to determine whether this is due to sample-based

differences, in that controlling for IQ actually removed disorder-related effects. Alternatively, IQ differences may be mediating the association between externalizing disorders and EF. This will be further discussed below.

Dimensional models also highlighted the lack of association between internalizing disorders and cognitive performance. Anxiety and depression have been variably associated with EF deficits in past literature, although findings were much stronger for depression. In this study, previously seen anxiety-based improvements in performance on some EF processes were perhaps washed out by the lack of association between depression and EF. Methodological issues may have also contributed to the limited shared variance between internalizing disorders to some degree. It is possible that limitations in measurement of these disorders (discussed under Limitations) weakened the ability to detect EF effects in internalizing disorders. However, these results do correspond with the findings from other analyses.

Taken together, only externalizing disorders were related to deficits in global EF processes, and internalizing disorders were not associated with EF. However, these effects disappeared after controlling for FSIQ, suggesting that FSIQ may account for the relationship between externalizing disorders and EF deficits.

Conclusions on Main Models

Integrating the results across the four main models examined in the present study, it appears as though shared underlying features of pathology and process-specific effects are contributing to the widespread relationship between EF deficits and psychiatric disorders. Individuals with externalizing disorders tended to demonstrate poorer performance on EF tests assessing set-shifting, response inhibition, and response

variability. One externalizing disorder, drug dependence, was not related to EF deficits, but detection of any associations may have been impeded by the difficulty isolating this disorder in the present sample. Study-specific methodological issues may have contributed to the failure of internalizing disorders to demonstrate an EF effect in the present study (detailed below under Limitations). It is also possible, however, that the failure to adequately assess for and control comorbid disorders in past studies produced stronger associations between these disorders and EF deficits, particularly for depression. Thus, tests of the main hypotheses provided support for dimensional and process-specific effects. Since only specific disorders are associated with EF deficits, past studies may have failed to adequately test and control for comorbid conditions.

The nature of the disorder-specific relationships within the externalizing dimension may reflect a developmental trajectory for the emergence of EF deficits. These externaling disorders are all highly comorbid, but ADHD is the first to develop in childhood. In this study, ADHD was also the disorder with the strongest and broadest relationship to EF deficits, which remained even after controlling for IQ. Symptoms of ADHD may contribute to and mediate the EF effects associated with other disorders. For instance, alcoholism and ASPD, which develop later in life, were associated with weaker EF deficits. Finally, drug dependence generally has the latest onset and usually occurs within the context of other disorders, perhaps accounting for the failure of this disorder to demonstrate unique EF effects. Thus, the developmental sequence of the externalizing disorders may be contributing to the relationships with EF seen in this study.

Additional Hypotheses

The present study provided information about other questions that further elucidate the association between EF and psychiatric disorders.

Specificity of EF deficits. One of the goals in the present study was to determine whether EF represented a nonspecific marker of disturbance or a potentially causal factor in the development or maintenance of these disorders. Processing speed tasks were included as non-executive indicators of general cognitive functioning. Processing speed was consistently related to the same disorders that demonstrated EF effects. Therefore, specificity was seen in the types of disorders related to cognitive deficits (i.e., ADHD, alcoholism, ASPD, externalizing), and in the EF processes/tests involved (i.e., Trails set-shifting, Stop Signal response inhibition and variability), but domain-specific cognitive deficits were not supported. A more general neurocognitive weakness appears to be associated with these disorders, rather than a specific or primary EF deficit.

The relationship between speed and psychiatric disorders remained significant even after controlling for age, gender, and FSIQ. This indicates that this general neurocognitive weakness was more robust than the EF impairment. It may be that the extensive literature that links EF deficits with psychiatric disorders stems in part from the use of measures that did not isolate EF or control for component processes such as processing speed. In this study, the prominent effects of speed were removed from two very commonly used EF tasks, Stroop and Trail Making Test, and perhaps the fact that this was almost never done in past studies contributed to wider support for EF deficits than is warranted. For instance, as mentioned previously, the large effect size for Stroop Color-Word in individuals with ADHD has at times been presented as support for deficits

in response inhibition or interference control (e.g., Boonstra et al., 2005); however, when the effects of speed are controlled, ADHD subjects do not demonstrate deficits in interference control (Boonstra et al., 2005; Hervey et al., 2004). Studies of executive functions also tend to rely upon the Trails B trial and fail to control for motor speed assessed through Trails A; however, doing so would provide a more pure measure of executive set-shifting abilities (Arbuthnott & Frank, 2000). The residual variables that were included in this study better isolated EF processes.

Concerns have been raised about whether or not EF processes are differentiable from other cognitive processes such as perceptual speed or the general intelligence factor (*g*), which appears to underlie performance on IQ tests (Salthouse et al., 2003; 2005). The EF effects that were found in this study withstood controls for processing speed despite a high correlation between EF and processing speed. Both cognitive processes were uniquely associated with psychopathology. The use of residual scores likely reduced the correlation between EF and processing speed in this study, and helped to differentiate these constructs to some degree. On the other hand, EF effects could not withstand controls for FSIQ (although speed continued to be a significant factor). This suggests that there is divergent validity between EF and speed processes, at least as related to psychopathology, but EF and *g* may be more difficult to differentiate. Some researchers have argued that components of EF underlie IQ (Conway et al., 2003; Friedman et al., 2006; Kane & Engle, 2002). However, direction of effects cannot be determined in the present study, and IQ remained the significant predictor herein. It is also possible that controlling for IQ inadvertently resulted in controlling for sample-based

differences in distributions of disorders. However, speed effects did withstand controls for IQ although these effects were vulnerable to the same issues.

Thus, although externalizing disorders (ADHD, alcoholism, and ASPD) were associated with EF weaknesses in this study, neuropsychological deficits crossed cognitive domains. Processing speed may be inflating the EF effects found in previous studies when not adequately controlled. Finally, EF effects may be mediated by IQ.

Direction of effects. The cross-sectional nature of the present study makes it difficult to determine causality between disorders and cognition. Directional effects were analyzed in this study from disorder (i.e., symptoms) to cognitive functioning. As mentioned previously, affect may impact cognition (Ashby et al., 1999). However, effects may also occur in the opposite direction. Top-down cognitive information-processing may interact with personality factors and contribute to psychopathology (Vasey et al., 2003). Such cognitive models have been proposed for both ADHD and alcoholism, wherein EF deficits precede and contribute to the development of disordered symptoms (Giancola et al., 2001; Nigg et al., 2006; Pennington & Ozonoff, 1996). Another possibility is that neither behavioral symptoms nor cognitive functions are "causal" in the etiology of these disorders, but that both are manifestations of other aberrant processes.

It should be noted that when the direction of causality was reversed in the structural models, fit did not change for either lifetime or current analyses (results not shown). In the lifetime model, only speed significantly predicted externalizing disorders in this model. In the current model, there were no significant predictive pathways. Conclusions on directionality cannot be derived from these results given model

equivalence and the cross-sectional nature of the study. However, questions about direction of effects are important and should continue to be examined. Prospective longitudinal studies will ultimately be required to better understand the developmental course of these disorders. Understanding etiological relationships will aid in prevention and treatment of these conditions.

Current versus lifetime disorders. Across analyses, EF effects were stronger for current versus lifetime disorders. Only lifetime ADHD contributed to EF weaknesses, and this group did not perform significantly more poorly from controls, suggesting that differences did not represent clinical deficits. More current disorders were associated with EF deficits, and these performances did differ from controls. Some literature has suggested that deficits may be seen even following symptom remittance in depression (Kessing, 1998; Paradiso et al., 1997) and abstinence in alcoholism (Munro et al., 2000). However, factors such as subclinical symptoms and disorder severity may contribute to these longer-term effects (Kessing, 1998), and effects generally remit over time (Selby & Azrin, 1998). Therefore, the exacerbation of EF effects during the active disorder states in the present study is consistent with past findings.

As mentioned, ADHD was the only lifetime disorder to demonstrate EF effects. Many participants with ADHD were specifically recruited because they continued to demonstrate symptoms of the disorder into adulthood. The high rates of ADHD at the time of testing likely enhanced the lifetime association to EF. On the other hand, cognitive effects associated with other current disorders may have been attenuated by the fact that, as previously mentioned, some "current" disorders may not have been present at

the time of testing. Despite these issues a strong "current" or recency effect was evident across the study.

Sensitivity of tasks. As covered in the literature review in the introduction, wide variability exists in the relationships between psychopathology and performance on specific EF tasks and processes. In the present study, the graphical depictions in Figures 7 through 10 highlight the generally wider dispersion of means for Trails Residual, Response Inhibition, and RT Variability. These variables were also associated with ADHD, alcoholism, and ASPD. Thus, it appears as though the Trail Making Test and Stop Signal Task were most sensitive to the negative effects of psychopathology in this study. It may be that these tasks and the processes that they assess are most likely to reveal the sometimes subtle neurocognitive changes that may be associated with psychiatric disorders. The Stop Signal Task in particular assesses very specific processes and is thus quite sensitive to differences in performance. As a result, both response inhibition and variability were variables that consistently demonstrated sensitivity to cognitive effects throughout analyses. The Trails Residual score, with its emphasis upon set-shifting, may have helped to make this task more "process pure." Thus, purer tasks may be more sensitive to the subtle effects of psychopathology.

The WCST, on the other hand, is a task that became popular after it was noted that individuals with brain damage (particularly to the frontal lobe) performed poorly upon it. It is a fairly simple task for "intact" individuals, and may be best suited to distinguish normal from abnormal brain function. The cognitive effects associated with the types of psychopathology included in this study are generally subtle and not necessarily considered "abnormal." As mentioned, the lack of sensitivity of the Stroop

Residual variable to psychopathology may be due to removal of speed effects. It was also the weakest indicator on the latent EF factor, suggesting that it shares less variance with other EF measures. Finally, individual EF tasks are notorious for poor reliability, and this may have affected sensitivity to effects and significance testing in the present study. Thus, multiple factors may have contributed to the sensitivity of certain tasks and processes to psychopathology. Set-shifting, as assessed by Trails Residual, and response inhibition and RT variability from the Stop Signal Task revealed consistent relationships with externalizing psychopathology and may be sensitive markers of psychopathology.

Limitations

A number of factors may limit the generalizability of the present results. First and foremost is the fact that this study relied upon combining two separate samples that differed in a number of respects, from the methods of recruitment and inclusion/exclusion criteria, to the specific diagnostic procedures (i.e., DIS versus SCID/KSADS, retrospective diagnosis of DSM-IV disorders in the alcoholism sample), to the resultant demographic characteristics of the samples. Further, different but similar measures were used to assess FSIQ and WCST between the two samples. The two-sample issue has been frequently referred to throughout this manuscript as potentially limiting the interpretation of the results in both general and specific ways. All issues will not be repeated here, but a few deserve further highlighting.

Different procedures were used to establish diagnoses in the two combined samples, which may have affected the reliability and validity of diagnoses. Different diagnostic interviews were used, as covered previously. Moreover, the extra attention given to diagnosing externalizing disorders (i.e., ADHD, ASPD, and alcoholism) may

have improved and led to better fit and appropriate representation for these disorders. In other words, the increased attention to these disorders may have overridden the potentially negative effects of using different diagnostic methods to some degree. On the other hand, the latent factor for internalizing disorders had poorer fit. It is possible that this factor was less stable and reliable a marker of true internalizing pathology than was the externalizing factor for externalizing disorders. Perhaps the increased attention to ensuring the reliability and validity of ADHD, alcoholism, and ASPD in the two samples included in this study created better measures for these disorders, resulting in a more consistent relationship with cognitive deficits.

Also, the diagnosis of "current" disorders in the present study was based upon disorders present at the time of testing in one sample (i.e., ADHD sample), and disorders present within approximately the three years prior to testing in the other sample (i.e., alcoholism sample). This may have weakened the effects associated with current disorders, but current disorders were still more strongly related to cognitive performance. Current MDD was excluded from the ADHD-based study, so its definition was based solely on the idea that the disorder was present within the past three years. Cognitive effects for MDD are most apparent during the acute phase of the disorder, and thus the definition of current in the present study likely weakened the ability to detect any cognitive effects associated with this disorder.

Other sample-related differences, such as FSIQ and age, were controlled in order to eliminate their influence upon the results. It is possible that differences in FSIQ and the distributions of disorders varied together between the samples, and that in controlling for FSIQ the effects of disorder were also inadvertently controlled. This could potentially

account for the removal or reduction of many effects after FSIQ was included in analyses. On the other hand, as mentioned previously, the effects of speed did remain even after controlling for FSIQ. As well, note that there were significant differences in IQ even between the "controls" in the two samples (alcoholism $M = 107.13$, $SD=12.45$; ADHD $M = 114.20$, $SD=9.50$), suggesting that the IQ discrepancies were not simply due to distributions of disorders but related to the different sample populations. Other differences such as SES could not be directly controlled, but may have contributed to or been related to the discrepancies in FSIQ and other variables. Taken together, the difficulty disentangling sample-dependent effects from true variation in the variables of interest complicates interpretation to some degree.

Another limit to generalizability is the fact that this was not a population-based study. Recruitment for the two samples that were combined in this study was focused on ADHD and alcoholism/ASPD. It is possible that the associations amongst disorders, and between disorders and cognitive performance, were somewhat different than would occur in the general population. For instance, there may be a greater preponderance of depressive and anxious disorders that are secondary to other pathology in the present sample. This may have affected the relationships amongst internalizing disorders and between internalizing disorders and cognitive effects. Despite this, a large number of people still met criteria for only a depressive or anxious disorder. Assortative mating may have affected the relationships amongst disorders and cognitive effects in the alcoholism study as well. Finally, the sample was predominantly Caucasian, which reduced generalizability. Thus, the fact that this was not a population-based study may limit the generalizability of the results.

The use of categorical disorders rather than dimensional symptoms in this study limited power to some degree. As well, individuals often present with quite heterogeneous manifestations of a particular diagnosis. It is possible that particular symptom constellations within individual disorders may be related to cognitive effects, and that these associations were removed by the use of categorical diagnoses in the present study. Future studies would benefit from examining how symptom counts and constellations contribute to cognitive performance. Given that shared underlying features of disorders appeared to be contributing to EF effects, this would help to elucidate the specific pathological processes that are most strongly related to cognitive effects.

It should also be noted that certain aspects of EF were not included in the present study. The present study used Pennington & Ozonoff's (1996) model of EF, although other models exist and could have been used (Moscovitch & Winocur, 1996; West, 1996) and some have questioned even the notion of the executive construct (Parkin, 1998). It may also be that working memory, initiation/generativity (i.e., verbal fluency), or planning are key processes that are associated with the disorders included in the present study. Other tasks such as the Halstead Category Test could have also provided useful information. The low factor loadings on the EF latent factor also suggest that the tasks included in this study did not have a lot of common variance. The use of tasks with strong psychometric properties, such as those included in recent studies (i.e., Miyake et al., 2000; Friedman et al., 2006), may improve reliability and specificity and, thus, strengthen the measurement of the EF construct. Therefore, additional EF processes and tasks should be included in future studies to more fully assess the relationship between EF and psychopathology.

In sum, some limitations associated with the present study may affect the generalizability of these results. However, a number of significant strengths help to offset these effects and highlight the ways in which the present study adds to the extant literature on EF and psychopathology.

Strengths

This study had numerous distinctive features. The high density of many different types of disorders in these at-risk samples provided a unique opportunity to simultaneously evaluate the cognitive effects associated with individual and classes of disorders. This is perhaps the first study to directly examine EF in this manner with so many different disorders. Thus, it provides the best evidence for EF effects in psychopathology, against which future studies may be evaluated.

The samples themselves were large, well-defined, and community-based. The integration of different sampling methods and a wide range of risk groups improved generalizability (e.g., range of SES, high risk alcoholics and other disorders, controls that are functioning well across a number of domains). Thus, although this was not a population-based study, and disorder rates were higher than those in the general population, this study included large and rather diverse samples from a socioeconomic perspective.

Both EF and psychopathology were measured from multiple perspectives. EF was considered as both a global factor as well as multiple distinct component processes. Psychopathology was examined at the level of individual disorders, comorbid conditions, and shared underlying dimensions. This broad approach allowed for an extensive examination of the relationship between EF and psychopathology.

Along with including multiple theoretical orientations, both traditional and more advanced statistical methods were used to examine associations. Of particular significance were latent modeling techniques, which were intended to reduce error and increase reliability. By maximizing construct-relevant variance and excluding variance unique to any single measure, latent modeling improved reliability of the single, global EF variable used in SEM analyses. This technique allowed for examination of a "purer" composite index of the EF, along with speed, internalizing, and externalizing constructs, than would be possible working at the individual variable level. The improved reliability associated with latent modeling helped to strengthen the results of the structural models. Other statistical techniques to help isolate the effects of interest in EF included removing component effects and creating residual scores, and controlling the effects of processing speed and FSIQ. Together, these methods helped to create purer measures to ensure to the extent possible that we were focusing on the constructs of interest.

Therefore, the unique nature of this study and its many strengths provided information that can advance the field towards new methods of study. This is a useful starting point for future examinations that should study large and diverse population-based samples longitudinally to further evaluate the effects of psychopathology on EF.

Conclusions

Many conclusions about the association between psychopathology and cognitive functioning may be drawn from this extensive examination. Firstly, nonspecific comorbidity and internalizing psychopathology were ruled out as being associated with EF. Externalizing disorders were related to EF weaknesses in what may be a developmentally-mediated manner. ADHD, a childhood-onset externalizing disorder that

continued into adulthood in this study, had the strongest relationship with EF. Shared features between early- and later-onset externalizing disorders may mediate and contribute to EF effects. While adult-onset disorders such as alcoholism and ASPD demonstrated weaker and more specific EF effects than ADHD, the overlap in affected processes between these externalizing disorders points to shared disturbances. Thus, common underlying pathways to EF deficits in psychopathology may be developmentally-mediated through early-onset externalizing disorders such as ADHD.

Importantly, cognitive effects in psychopathology were not isolated to the EF domain. Processing speed was also related to externalizing disorders, with more robust effects. Many effects disappeared after controlling for IQ, suggesting that IQ may mediate EF effects in some cases. Task impurity is a major concern in the measurement of EF, and these findings further highlight the possibility that other cognitive processes may underlie or account for apparent EF deficits.

In conclusion, these results show that the relationship between EF and psychopathology involves specific externalizing pathological processes, comorbidity among disorders, specific components of EF, and multiple cognitive domains. All of these factors have contributed to the seemingly wide-ranging relationship between psychiatric disorders and EF throughout the literature. These results highlight important issues that need to be accounted for in future studies to clarify the complex interplay between behavioral and cognitive aspects of psychopathology.

Table 1

Summary of Major Findings in the Literature Regarding EF Component Deficits

	Working Memory	Planning	Response Inhibition	Interference Control	Set-shifting & maintenance
Attention-Deficit /Hyperactivity Disorder	X	X	X		X
Antisocial Personality Disorder			X		
Alcohol Dependence	X		X	X	X
Substance Dependence	X		X	X	X
Obsessive-Compulsive Disorder	X	X	X	X	X
Other Anxiety Disorders	?			?	?
Depression	X	X	X	X	X

Notes to Table 1. An 'X' marks component processes with which a disorder has frequently been associated. Note that even though some disorders have similar deficits, there are often differences in the level of deficits, if not in the components affected (i.e., alcohol and substance dependence).

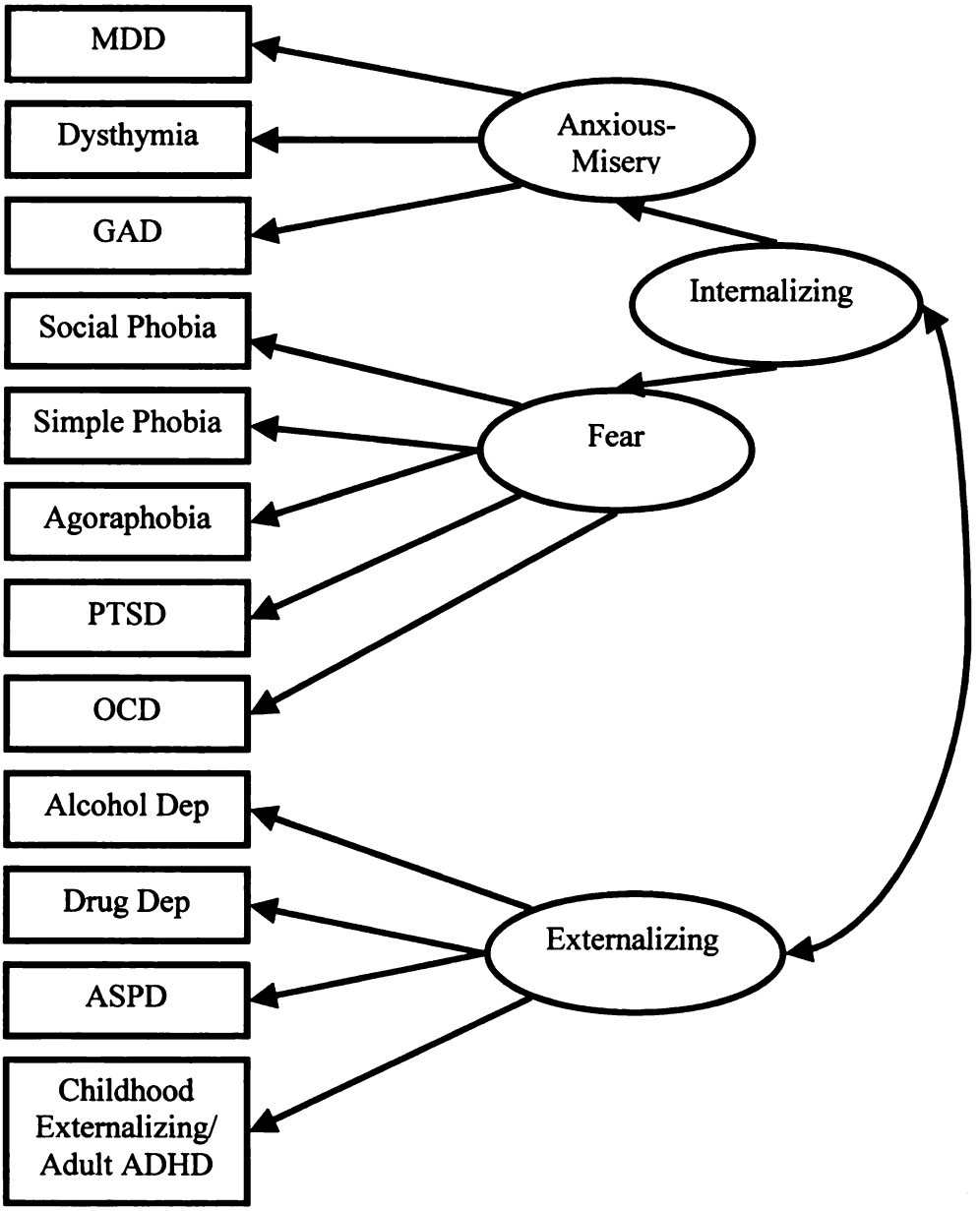

Figure 1. Initial proposed model representing the relationships between DSM-IV disorders based on Krueger's (1999) findings.

Note to Figure 1. Panic disorder could not be included although present in Krueger's model. Disorders that were added in the present analyses were childhood externalizing disorders (ADHD, ODD, CD), PTSD, and OCD. Childhood externalizing disorders were included in lifetime diagnosis analyses, and adult ADHD in current diagnosis analyses. GAD=generalized anxiety disorder; PTSD=post-traumatic stress disorder; OCD=obsessive-compulsive disorder; Dep=dependence; ASPD=antisocial personality disorder; ADHD=attention-deficit/hyperactivity disorder.

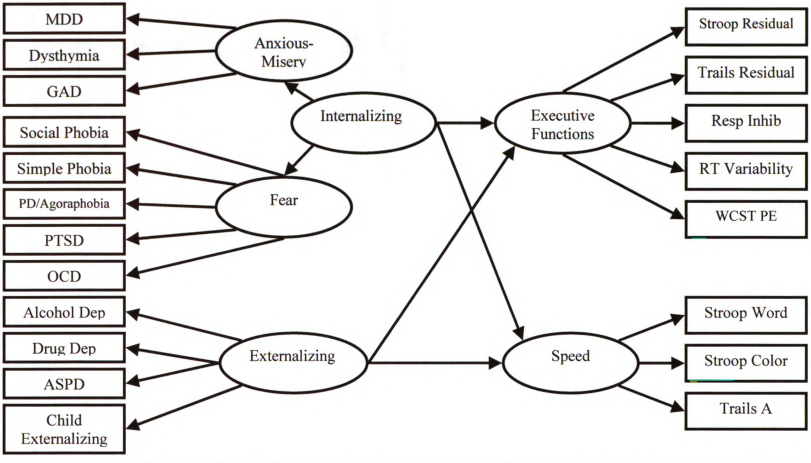

Figure 2. Proposed model to examine the relationships between underlying core psychopathology domains and neuropsychological test performance.

Note to Figure 2. GAD=generalized anxiety disorder; PTSD=post-traumatic stress disorder; ADHD=attention-deficit/hyperactivity disorder; ASPD=antisocial personality disorder; Dep=dependence; MDD=major depressive disorder; PD=panic disorder; WCST PE=Wisconsin Card Sorting Test perseverative errors; Resp Inhib=Response Inhibition as measured by Stop Signal Response Time; RT Variability=variability of go response from Stop Task.

Table 2

Demographic Information for the Combined, Alcoholism, and ADHD samples at the time of neuropsychological testing

Variable	Combined (*n*=641)	Alcoholism (*n*=448)	ADHD (*n*=193)	*p*
# and % male	336 (52.4%)	233 (52.0%)	103 (53.4%)	.75
# and % white	615 (95.9%)	448 (100.0%)	167 (86.5%)	<.01
# and % married	405 (69.5%)	361 (83.8%)	44 (28.9%)	<.01
Age in years	38.12 (10.39)	44.14 (5.00) (range=26.41 – 66.70)	24.15 (4.53) (range=18.19 – 37.59)	<.01
Education	14.07 (2.13)	13.97 (2.23)	14.30 (1.87)	.07
FSIQ	106.29 (12.85)	103.85 (12.83)	111.98 (10.97)	<.01

Notes to Table 2. Alcoholism=alcoholism sample; ADHD=attention-deficit/hyperactivity disorder sample; FSIQ=full scale intelligence quotient; SES=socioeconomic status. *t*-tests and chi-square were used for analyses.

Table 3

Numbers of Lifetime Disorders in the Combined, Alcoholism, and ADHD Samples

Task	Combined (*n*=641)	Alcoholism (*n*=448)	ADHD (*n*=193)	χ^2	*p*
No disorders	170 (26.5%)	106 (23.7%)	64 (33.2%)	6.25	.01
MDD	212 (33.1%)	169 (37.7%)	43 (22.3%)	14.53	<.001
Dysthymia	63 (9.8%)	52 (11.6%)	11 (5.7%)	5.31	.02
Depressive Disorders	234 (36.5%)	183 (40.8%)	51 (26.4%)	12.10	.001
GAD	39 (6.1%)	22 (4.9%)	17 (8.8%)	3.59	.06
Agoraphobia without PD	8 (1.2%)	8 (1.8%)	0 (0%)	3.49	.06
Social Phobia	50 (7.8%)	34 (7.6%)	16 (8.3%)	0.09	.76
Specific Phobia	89 (13.9%)	83 (18.5%)	6 (3.1%)	26.82	<.001
PTSD	26 (4.1%)	22 (4.9%)	4 (2.1%)	2.79	.13
OCD	11 (1.7%)	9 (2.0%)	2 (1.0%)	0.76	.52
Anxiety Disorders	174 (27.1%)	139 (31.0%)	35 (18.1%)	11.34	.001
ADHD	112 (17.5%)	9 (2.0%)	103 (53.4%)	246.75	<.001
Conduct Disorder	58 (9.0%)	51 (11.4%)	7 (3.6%)	9.86	.002
ODD	18 (2.8%)	2 (0.4%)	16 (8.3%)	30.41	<.001
Child Externalizing	166 (25.9%)	59 (13.2%)	107 (55.4%)	125.60	<.001
ASPD	72 (11.2%)	67 (15.0%)	5 (2.6%)	8.30	.004
Alcohol Dependence	208 (34.0%)	196 (43.8%)	22 (11.4%)	62.90	<.001
Drug Dependence	44 (6.9%)	30 (6.7%)	14 (7.3%)	0.07	.80

Notes to Table 3. MDD=major depressive disorder; GAD=generalized anxiety disorder; PD=panic disorder; PTSD=post-traumatic stress disorder; OCD=obsessive compulsive disorder; ADHD=attention-deficit/hyperactivity disorder; ODD=oppositional defiant disorder; ASPD=antisocial personality disorder.

Table 4

Numbers of Current Disorders in the Combined, Alcoholism, and ADHD Samples

Task	Combined (*n*=641)	Alcoholism (*n*=448)	ADHD (*n*=193)	χ^2	*p*
No disorder	360 (56.2%)	262 (58.5%)	98 (50.8%)	3.25	.07
MDD	100 (15.6%)	100 (22.3%)	0 (0.0%)	51.04	<.001
Dysthymia	14 (2.2%)	4 (0.9%)	10 (5.2%)	11.61	.002
Depressive Disorders	113 (17.6%)	103 (23.0%)	10 (5.2%)	29.46	<.001
GAD	30 (4.7%)	13 (2.9%)	17 (8.8%)	10.55	.001
Agoraphobia without PD	0 (0%)	0 (0.0%)	0 (0.0%)	--	--
Social Phobia	24 (3.7%)	13 (2.9%)	11 (5.7%)	2.93	.09
Specific Phobia	27 (4.2%)	21 (4.7%)	6 (3.1%)	0.83	.36
PTSD	14 (2.2%)	13 (2.9%)	1 (0.5%)	3.59	.08
OCD	3 (0.5%)	1 (0.2%)	2 (1.0%)	1.91	.22
Anxiety Disorders	78 (12.2%)	48 (10.7%)	30 (15.5%)	2.94	.09
ADHD	78 (12.2%)	--	78 (40.4%)	--	--
ASPD	72 (11.2%)	67 (15.0%)	5 (2.6%)	20.68	.000
Alcohol Dependence	42 (6.6%)	35 (7.8%)	7 (3.6%)	3.86	.05
Drug Dependence	8 (1.2%)	7 (1.6%)	1 (0.5%)	1.19	.45

Notes to Table 4. MDD=major depressive disorder; GAD=generalized anxiety disorder; PD=panic disorder; PTSD=post-traumatic stress disorder; OCD=obsessive compulsive disorder; ADHD=attention-deficit/hyperactivity disorder; ODD=oppositional defiant disorder; ASPD=antisocial personality disorder.

Table 5

Means and Standard Deviations of Cognitive Tasks for the Combined, Alcoholism, and ADHD Samples

Task	Combined (*n*=641)	Alcoholism (*n*=448)	ADHD (*n*=193)	*t*	*p*
Resp Inhib	248.05 (72.03)	250.95 (76.05)	241.32 (61.34)	1.56	.12
RT Variability	176.03 (77.87)	198.44 (79.71)	124.03 (39.14)	12.34	<.001
Stroop Residual	0.00 (8.39)	0.00 (8.27)	0.00 (8.68)	.00	1.00
Trails Residual	0.00 (18.19)	0.00 (19.73)	0.00 (14.04)	.00	1.00
WCST PE	97.12 (13.04)	96.06 (12.98)	99.57 (12.89)	-3.15	.002
Trails A	27.37 (9.17)	28.39 (9.55)	24.98 (7.72)	4.38	<.001
Stroop Word	100.18 (16.76)	99.74 (17.15)	101.21 (15.83)	-1.02	.31
Stroop Color	74.89 (13.72)	73.46 (13.53)	78.21 (13.62)	-4.07	<.001
Stroop Color-Word	44.44 (12.44)	40.52 (10.53)	53.53 (11.77)	-13.85	<.001
Trails B	60.51 (23.62)	63.48 (25.64)	53.62 (16.17)	5.87	<.001
FSIQ	106.29 (12.85)	103.85 (12.83)	111.98 (10.97)	-8.17	<.001

Notes to Table 5. SSRT=stop signal reaction time; SDX=variability of Go response time; Stroop Residual=unstandardized residual of Stroop Color-Word regressed on Stroop Color and Stroop Word; Trails Residual=unstandardized residual of Trails B regressed on Trails A; WCST PE=standardized score for Wisconsin Card Sorting Task perseverative errors; FSIQ=full scale intelligence quotient; Resp Inhib=Response Inhibition as measured by Stop Signal Response Time; RT Variability=variability of go response from Stop Task.

Table 6

Mean Scores for Cognitive Tasks for Lifetime Disorders in the Combined Sample

Disorder	Stroop Res	Trails Res	Resp Inhib	RT Var	WCST	Stroop word	Stroop color	Trails A	Stroop C-W	Trails B
No disorders	0.39 (7.17)	-1.62 (15.32)	239.44 (65.39)	168.42 (80.87)	97.69 (13.77)	103.91 (16.33)	78.98 (13.43)	25.93 (8.87)	47.73 (12.54)	56.32 (23.02)
MDD	-0.47 (8.65)	-0.15 (18.08)	246.78 (70.57)	171.74 (70.65)	96.94 (11.61)	100.39 (16.22)	73.49 (13.54)	27.78 (9.17)	42.36 (11.71)	61.44 (24.10)
Dysthymia	0.97 (9.07)	4.07 (22.25)	262.82 (88.40)	189.71 (86.83)	97.20 (12.79)	98.19 (18.27)	69.78 (14.53)	29.63 (7.82)	41.78 (12.52)	68.77 (28.67)
Depressive Disorders	-0.46 (8.51)	0.34 (18.07)	250.21 (74.07)	176.03 (74.29)	96.94 (12.07)	99.93 (16.07)	73.33 (13.33)	27.98 (9.03)	42.41 (11.53)	62.09 (24.03)
GAD	0.21 (8.91)	1.15 (21.56)	240/78 (71.08)	150.39 (64.13)	97.41 (13.81)	99.10 (13.98)	75.72 (15.29)	26.98 (8.73)	46.78 (14.74)	60.61 (30.00)
Agoraphobia	0.08 (7.63)	-13.55 (19.90)	282.01 (52.42)	174.65 (81.74)	95.63 (14.26)	104.13 (8.83)	71.13 (10.89)	28.48 (9.76)	40.25 (9.63)	53.45 (17.08)
Social Phobia	-0.32 (8.54)	3.04 (23.41)	231.65 (60.97)	153.29 (57.55)	96.36 (12.17)	98.86 (16.55)	74.06 (14.43)	28.11 (8.45)	44.17 (14.15)	64.40 (26.58)
Specific Phobia	-0.42 (7.74)	0.84 (22.95)	238.43 (71.66)	185.25 (70.80)	97.03 (13.17)	99.01 (17.04)	73.40 (13.44)	26.36 (9.13)	41.16 (10.93)	60.64 (29.22)
PTSD	0.56 (10.25)	3.63 (25.93)	232.87 (57.28)	171.48 (65.65)	95.69 (14.24)	99.15 (14.77)	72.62 (10.38)	25.68 (7.62)	42.23 (11.99)	61.70 (28.73)

Table 6 (con'd).

Disorder	Stroop Res	Trails Res	Resp Inhib	RT Var	WCST	Stroop word	Stroop color	Trails A	Stroop C-W	Trails B
OCD	0.30 (11.04)	9.84 (22.32)	238.28 (69.15)	184.39 (65.13)	93.18 (13.55)	98.09 (19.41)	70.36 (18.86)	27.54 (8.46)	42.18 (20.66)	71.48 (28.62)
Anxiety Disorders	0.03 (8.68)	1.17 (22.80)	237.94 (68.46)	171.20 (67.81)	95.99 (13.04)	99.08 (16.61)	73.91 (13.77)	26.58 (8.30)	43.00 (12.89)	60.88 (26.85)
ADHD	-0.48 (9.53)	2.75 (16.96)	250.35 (68.56)	136.82 (56.06)	99.33 (12.34)	98.16 (16.75)	75.14 (14.50)	25.77 (8.39)	50.49 (12.88)	58.01 (20.64)
Conduct Disorder	-0.26 (7.39)	3.38 (23.52)	240.85 (81.05)	197.60 (79.86)	96.11 (12.58)	97.09 (17.69)	70.44 (12.93)	29.35 (10.28)	40.28 (9.28)	68.42 (29.12)
ODD	-1.24 (9.70)	0.21 (13.22)	240.36 (87.37)	118.39 (33.76)	100.95 (10.14)	99.24 (20.64)	78.08 (15.40)	22.48 (7.57)	50.89 (11.45)	51.75 (16.24)
Child External	-0.06 (8.88)	3.32 (19.50)	246.98 (73.80)	157.76 (70.06)	98.09 (12.55)	97.41 (16.88)	73.12 (13.97)	27.16 (9.23)	47.09 (13.04)	62.14 (24.32)
ASPD	-0.21 (8.39)	3.96 (20.74)	261.38 (88.75)	207.33 (80.84)	97.32 (13.74)	94.64 (16.13)	69.33 (13.89)	30.15 (9.58)	38.88 (9.78)	70.21 (27.16)
Alcohol Dep	0.61 (9.17)	0.45 (18.85)	258.32 (82.75)	197.19 (80.70)	96.66 (12.58)	97.87 (17.38)	71.43 (14.21)	29.66 (9.77)	41.25 (11.78)	65.61 (23.82)
Drug Dep	1.79 (11.62)	1.54 (19.68)	263.80 (68.69)	170.19 (67.27)	95.68 (15.78)	93.86 (16.18)	68.86 (15.24)	28.68 (8.44)	43.25 (14.36)	64.21 (25.70)

Notes to Table 6. Stroop Res=unstandardized residual of Stroop Color-Word regressed on Stroop Color and Stroop Word; Trails Res=unstandardized residual of Trails B regressed on Trails A; Resp Inhib=Response Inhibition from Stop task; RT Var=variability of Go response; WCST=Wisconsin Card Sorting Task perseverative errors; Stroop C-W=Stroop Color-Word; MDD=major depressive disorder; GAD=generalized anxiety disorder; PTSD=post-traumatic stress disorder; OCD=obsessive compulsive disorder; ADHD=attention-deficit/hyperactivity disorder; ODD=oppositional defiant disorder; ASPD=antisocial personality disorder; Dep=dependence.

Table 7

Mean Scores forCognitve Tasks for Current Disorders in the Combined Sample

Disorder	Stroop Res	Trails Res	Resp Inhib	RT Var	WCST	Stroop word	Stroop color	Trails A	Stroop C-W	Trails B
No disorders	0.30 (8.16)	-0.80 (17.46)	241.37 (68.34)	174.44 (78.35)	96.55 (12.88)	101.13 (17.06)	76.12 (13.73)	27.17 (9.31)	45.02 (12.33)	59.51 (22.66)
MDD	-1.25 (8.98)	0.58 (20.84)	248.63 (63.95)	185.97 (72.09)	96.27 (12.20)	100.58 (17.40)	71.90 (15.01)	29.04 (10.23)	38.80 (10.92)	65.17 (28.57)
Dysthymia	1.83 (5.39)	-3.15 (12.81)	260.38 (49.11)	175.24 (82.60)	102.62 (12.93)	108.64 (17.51)	77.87 (11.37)	27.20 (7.62)	52.45 (9.38)	54.51 (15.88)
Depressive Disorders	-0.88 (8.70)	0.13 (20.11)	250.49 (62.37)	184.24 (73.34)	96.96 (12.43)	101.26 (17.29)	72.59 (14.76)	28.82 (9.98)	40.42 (11.65)	63.86 (27.63)
GAD	-1.27 (8.90)	2.71 (23.31)	248.98 (59.00)	150.86 (62.54)	96.82 (13.72)	101.20 (14.68)	77.57 (16.36)	27.42 (9.05)	47.81 (16.00)	62.45 (33.61)
Social Phobia	0.85 (8.94)	7.88 (28.67)	227.20 (44.03)	152.35 (54.77)	94.79 (14.68)	97.29 (14.29)	73.51 (16.35)	28.14 (9.25)	46.64 (17.26)	69.24 (34.01)
Specific Phobia	-1.62 (6.56)	0.39 (25.67)	239.03 (71.13)	172.95 (73.77)	95.85 (14.44)	100.00 (16.46)	74.44 (11.65)	26.25 (8.29)	41.89 (11.33)	59.52 (33.20)
PTSD	-3.10 (9.41)	5.60 (15.28)	228.31 (62.21)	188.35 (79.99)	99.71 (15.09)	99.14 (15.98)	70.71 (11.63)	27.36 (8.58)	37.07 (9.25)	66.44 (18.34)

Table 7 (con'd).

Disorder	Stroop Res	Trails Res	Resp Inhib	RT Var	WCST	Stroop word	Stroop color	Trails A	Stroop C-W	Trails B
OCD	4.31 (9.57)	1.58 (18.99)	236.28 (50.23)	131.72 (36.18)	86.00 (21.17)	96.00 (15.39)	86.33 (22.30)	27.67 (9.68)	59.00 (25.63)	62.44 (13.23)
Anxiety Disorders	-1.00 (8.86)	1.86 (21.94)	237.38 (60.79)	162.40 (69.13)	96.10 (14.51)	99.23 (15.62)	74.78 (13.92)	26.53 (7.86)	44.50 (14.73)	60.64 (27.33)
ADHD	-0.52 (8.86)	2.88 (13.94)	251.97 (68.12)	134.02 (42.13)	99.93 (12.60)	99.57 (15.43)	76.47 (13.61)	22.93 (6.75)	51.99 (11.94)	55.41 (16.09)
ASPD	-0.21 (8.39)	3.96 (20.74)	261.38 (88.75)	207.33 (80.84)	97.32 (13.74)	94.64 (16.13)	69.33 (13.89)	30.15 (9.58)	38.88 (9.78)	70.21 (27.16)
Alcohol Dep	-1.57 (10.91)	-0.65 (16.76)	276.53 (81.30)	211.47 (73.07)	97.38 (14.24)	99.40 (15.75)	68.71 (12.76)	30.28 (9.04)	38.79 (11.96)	64.97 (21.54)
Drug Dep	-1.25 (10.22)	0.62 (18.28)	279.62 (48.39)	181.28 (64.38)	95.88 (13.93)	89.63 (14.56)	67.63 (10.39)	26.44 (7.37)	37.13 (10.12)	60.11 (20.50)

Notes to Table 7. Stroop Res=unstandardized residual of Stroop Color-Word regressed on Stroop Color and Stroop Word; Trails Res=unstandardized residual of Trails B regressed on Trails A; Resp Inhib=Response Inhibition as measured by Stop Signal Response Time; RT Var=variability of go response from Stop Task; WCST=Wisconsin Card Sorting Task perseverative errors; Stroop C-W=Stroop Color-Word; MDD=major depressive disorder; GAD=generalized anxiety disorder; PTSD=post-traumatic stress disorder; OCD=obsessive compulsive disorder; ADHD=attention-deficity/hyperactivity disorder; ODD=oppositional defiant disorder; ASPD=antisocial personality disorder; Dep=dependence.

Table 8

Correlations Amongst Cognitive Tasks in the Combined Sample (n=641)

Task	RT Var	Stroop Residual	Trails Residual	WCST Pers. Errors	Trails A time	Stroop Word	Stroop Color	Stroop Color-Word	Trails B	FSIQ
Resp Inhibition	.51**	-.09*	.08*	-.08*	.24**	-.25**	-.22**	-.22**	.22**	-.17**
RT Var	--	-.09*	.10*	-.12**	.26**	-.15**	-.19**	-.35**	.28**	-.32**
Stroop Residual	--	--	-.12**	.11**	-.12**	.00	.00	.68**	-.17**	.20**
Trails Residual	--	--	--	-.20**	.00	-.25**	-.25**	-.23**	.77**	-.31**
WCST Pers. Errors	--	--	--	--	-.10**	.09*	.13**	.20**	-.22**	.17**
Trails A time	--	--	--	--	--	-.38**	-.41**	-.39**	.62**	-.34**
Stroop Word	--	--	--	--	--	--	.68**	.46**	-.43**	.26**
Stroop Color	--	--	--	--	--	--	--	.62**	-.45**	.29**
Stroop Color-Word	--	--	--	--	--	--	--	--	-.45**	.41**
Trails B	--	--	--	--	--	--	--	--	--	-.48**

Notes to Table 8. Resp Inhibition=Response Inhibition as measured by Stop Signal Response Time; RT Var=variability of go response from Stop Task; Stroop Residual=unstandardized residual of Stroop Color-Word regressed on Stroop Color and Stroop Word; Trails Residual=unstandardized residual of Trails B regressed on Trails A; WCST=Wisconsin Card Sorting Task perseverative errors; FSIQ=full scale intelligence quotient.

Table 9

Correlations Amongst Cognitive Tasks in the Alcoholism Sample (n=448)

Task	RT Var	Stroop Residual	Trails Residual	WCST Pers. Errors	Trails A time	Stroop Word	Stroop Color	Stroop Color-Word	Trails B	FSIQ
Resp Inhibition	.55**	-.04	.08	-.06	.25**	-.27**	-.22**	-.18*	.23**	-.15**
RT Var	--	-.12*	.09	-.04	.23**	-.13**	-.11*	-.17*	.22**	-.22
Stroop Residual	--	--	-.15**	.09	-.13	.00	-.00	.79**	-.20**	.22**
Trails Residual	--	--	--	-.18**	.00	-.26**	-.25**	-.28**	.77**	-.34**
WCST	--	--	--	--	-.08	.06	.11*	.13*	-.18**	.07
Trails A time	--	--	--	--	--	-.39**	-.41**	-.37**	.64**	-.34**
Stroop Word	--	--	--	--	--	--	.69**	.51**	-.45**	.27**
Stroop Color	--	--	--	--	--	--	--	.60**	-.46**	.29**
Stroop Color-Word	--	--	--	--	--	--	--	--	-.46**	.36**
Trails B	--	--	--	--	--	--	--	--	--	-.48**

Notes to Table 9. Resp Inhibition=Response Inhibition as measured by Stop Signal Response Time; RT Var=variability of go response from Stop Task; Stroop Residual=unstandardized residual of Stroop Color-Word regressed on Stroop Color and Stroop Word; Trails Residual=unstandardized residual of Trails B regressed on Trails A; WCST=Wisconsin Card Sorting Task perseverative errors; FSIQ=full scale intelligence quotient.

Table 10

Correlations Amongst Cognitive Tasks in the ADHD Sample (n=193)

Task	RT Var	Stroop Residual	Trails Residual	WCST Pers. Errors	Trails A time	Stroop Word	Stroop Color	Stroop Color-Word	Trails B	FSIQ
Resp Inhibition	.21**	-.25**	.08	-.12	.16*	-.22	-.17*	-.31**	.15*	-.21**
RT Var	--	-.07	.24**	-.23**	.09	-.24**	-.29**	-.24**	.26**	-.28**
Stroop Residual	--	--	-.05	.16*	-.09	.00	.00	.74**	-.09	.16*
Trails Residual	--	--	--	-.28**	.00	-.22**	-.25**	-.21**	.87**	-.25**
WCST Pers. Errors	--	--	--	--	-.11	.16*	.13	.21**	-.30**	.32**
Trails A time	--	--	--	--	--	-.35**	-.36**	-.32**	.50**	.-.18*
Stroop Word	--	--	--	--	--	--	.67**	.47**	-.37**	.25**
Stroop Color	--	--	--	--	--	--	--	.67**	-.40**	.19**
Stroop Color-Word	--	--	--	--	--	--	--	--	-.34**	.25**
Trails B	--	--	--	--	--	--	--	--	--	-.31**

Notes to Table 10. Resp Inhibition=Response Inhibition as measured by Stop Signal Response Time; RT Var=variability of go response from Stop Task; Stroop Residual=unstandardized residual of Stroop Color-Word regressed on Stroop Color and Stroop Word; Trails Residual=unstandardized residual of Trails B regressed on Trails A; WCST=Wisconsin Card Sorting Task perseverative errors; FSIQ=full scale intelligence quotient.

Table 11

Correlations Amongst Lifetime Disorders in the Combined Sample (n=641)

Disorder	Dys	Dep	GAD	Agora	Social	Spec	OCD	PTSD	Anx	AD/ HD	CD	ODD	Child	ASP	Alc	Drug
MDD	.25	.92	.20	.04	.17	.15	.14	.18	.28	.01	-.05	.04	-.01	.09	.01	.06
Dys	--	.43	.11	-.04	.10	.05	.08	.15	.14	.03	.12	.10	.08	.08	.11	.06
Depress	--	--	.19	.03	.17	.13	.12	.19	.26	.03	-.003	.07	.02	.10	.04	.08
GAD	--	--	--	.15	.19	.05	.12	.05	.42	.14	-.01	.12	.10	-.01	-.09	.06
Agora	--	--	--	--	.02	-.01	-.02	.05	.18	-.05	.01	-.02	-.03	.01	.01	.08
Social	--	--	--	--	--	.05	.19	.03	.48	.02	.05	-.05	.05	.01	-.01	.06
Specific	--	--	--	--	--	--	.09	.06	.66	-.11	-.001	-.01	-.09	.03	.03	-.002
OCD	--	--	--	--	--	--	--	-.03	.22	.002	.000	-.02	.004	.07	.01	.11
PTSD	--	--	--	--	--	--	--	--	.34	-.03	-.01	-.04	-.03	.05	.02	.07
Anxiety	--	--	--	--	--	--	--	--	--	-.02	.03	.02	.00	.01	.02	.09
ADHD	--	--	--	--	--	--	--	--	--	--	-.06	.27	.78	-.09	-.13	.05
CD	--	--	--	--	--	--	--	--	--	--	--	.14	.53	.40	.27	.13
ODD	--	--	--	--	--	--	--	--	--	--	--	--	.29	-.03	-.04	-.01
Child	--	--	--	--	--	--	--	--	--	--	--	--	--	.18	.06	.12
ASPD	--	--	--	--	--	--	--	--	--	--	--	--	--	--	.32	.16
Alcohol	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	.18

Notes to Table 11. Correlations ≥.08 significant at $p<.05$; correlations ≥.11 significant at $p<.01$.
MDD=major depressive disorder; Dys=dysthymia; Dep/Depress=depressive disorders; GAD=generalized anxiety disorder; Agora=agoraphobia; Social=social phobia; Spec/Specific=specific phobia; OCD=obsessive compulsive disorder; PTSD=post-traumatic stress disorder; Anx/Anxiety=anxiety disorders; ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder; Child=childhood externalizing disorders; ASP/ASPD=antisocial personality disorder; Alc/Alcohol=alcohol dependence; Drug=drug dependence.

Table 12

Correlations Amongst Lifetime Disorders in the Alcoholism Sample (n=448)

Disorder	Dys	Dep	GAD	Agora	Social	Spec	OCD	PTSD	Anx	AD/ HD	CD	ODD	Child	ASP	Alc	Drug
MDD	.26	.94	.19	.03	.19	.15	.15	.21	.29	.09	-.06	.09	-.02	.07	-.09	.09
Dys	--	.44	.14	-.05	.10	.03	.10	.11	.12	.20	.11	.19	.17	.08	.10	.04
Depress	--	--	.17	.03	.17	.13	.14	.21	.27	.14	-.01	.08	.04	.10	-.05	.09
GAD	--	--	--	.20	.13	.10	.12	.09	.34	.04	-.02	.30	.00	.02	-.12	.10
Agora	--	--	--	--	.03	-.02	-.02	.05	.20	-.02	.01	-.01	-.00	-.01	-.02	.10
Social	--	--	--	--	--	.06	.14	.05	.43	.08	.08	-.02	.11	.02	.02	.02
Specific	--	--	--	--	--	--	.10	.03	.71	.01	-.03	-.03	-.02	-.01	-.04	.01
OCD	--	--	--	--	--	--	--	-.03	.21	-.02	-.001	-.01	-.01	.07	.002	.09
PTSD	--	--	--	--	--	--	--	--	.34	.04	-.02	-.02	.003	.05	-.01	.10
Anxiety	--	--	--	--	--	--	--	--	--	.04	.02	.10	.04	-.01	-.03	.11
ADHD	--	--	--	--	--	--	--	--	--	--	-.001	.23	.37	-.02	.03	-.04
CD	--	--	--	--	--	--	--	--	--	--	--	.08	.92	.42	.28	.16
ODD	--	--	--	--	--	--	--	--	--	--	--	--	.17	.07	-.06	-.02
Child	--	--	--	--	--	--	--	--	--	--	--	--	--	.39	.27	.13
ASPD	--	--	--	--	--	--	--	--	--	--	--	--	--	--	.29	.16
Alcohol	--	--	-	--	--	--	--	--	--	--	--	--	--	--	--	.21

Notes to Table 12. Correlations ≥.10 significant at $p<.05$; correlations ≥.13 significant at $p<.01$.
MDD=major depressive disorder; Dys=dysthymia; Dep/Depress=depressive disorders; GAD=generalized anxiety disorder; Agora=agoraphobia; Social=social phobia; Spec/Specific=specific phobia; OCD=obsessive compulsive disorder; PTSD=post-traumatic stress disorder; Anx/Anxiety=anxiety disorders; ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder; Child=childhood externalizing disorders; ASP/ASPD=antisocial personality disorder; Alc/Alcohol=alcohol dependence; Drug=drug dependence.

Table 13

Correlations Amongst Lifetime Disorders in the ADHD Sample (n=193)

Disorder	Dys	Dep	GAD	Agora	Social	Spec	OCD	PTSD	Anx	AD/HD	CD	ODD	Child	ASP	Alc	Drug
MDD	.14	.88	.27	--	.11	-.02	.07	.01	.17	.23	-.10	.11	.23	-.01	.16	-.01
Dys	--	.41	.08	--	.09	.09	-.03	.28	.17	.10	.07	.17	.09	-.04	-.02	.10
Depress	--	--	.27	--	.16	-.04	.05	.08	.20	.19	-.06	.16	.19	-.03	.15	.06
GAD	--	--	--	--	.30	-.06	.15	-.05	.66	.18	.04	.04	.17	-.05	.06	-.02
Agora	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Social	--	--	--	--	--	.05	.34	-.04	.64	-.02	-.06	-.09	-.03	-.05	-.11	.13
Specific	--	--	--	--	--	--	-.02	.18	.38	.05	-.04	.16	.04	-.03	-.06	-.05
OCD	--	--	--	--	--	--	--	-.02	.22	.10	-.02	-.03	.09	-.02	-.04	.17
PTSD	--	--	--	--	--	--	--	--	.31	-.01	-.03	-.04	-.02	-.02	.06	-.04
Anxiety	--	--	--	--	--	--	--	--	--	.14	-.02	.05	.12	-.08	.000	.02
ADHD	--	--	--	--	--	--	--	--	--	--	.07	.17	.96	.15	.21	.14
CD	--	--	--	--	--	--	--	--	--	--	--	.44	.17	.14	.02	.05
ODD	--	--	--	--	--	--	--	--	--	--	--	--	.27	-.05	.13	-.01
Child	--	--	--	--	--	--	--	--	--	--	--	--	--	.15	.22	.13
ASPD	--	--	--	--	--	--	--	--	--	--	--	--	--	--	.25	.21
Alcohol	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	.15

Notes to Table 13. Correlations ≥.14 significant at $p<.05$; correlations ≥.19 significant at $p<.01$.
MDD=major depressive disorder; Dys=dysthymia; Dep/Depress=depressive disorders; GAD=generalized anxiety disorder; Agora=agoraphobia; Social=social phobia; Spec/Specific=specific phobia; OCD=obsessive compulsive disorder; PTSD=post-traumatic stress disorder; Anx/Anxiety=anxiety disorders; ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder; Child=childhood externalizing disorders; ASP/ASPD=antisocial personality disorder; Alc/Alcohol=alcohol dependence; Drug=drug dependence.

Table 14

Correlations Amongst Current Disorders in the Combined Sample (n=641)

Disorder	Dys	Dep	GAD	Agora	Social	Spec	OCD	PTSD	Anx	AD/ HD	ASP	Alc	Drug
MDD	-.04	.93	.05	--	.10	.08	.03	.17	.14	-.16	.12	.11	.03
Dys	--	.32	.07	--	.03	.02	-.01	-.02	.04	.14	-.05	.05	.08
Depress	--	--	.07	--	.10	.09	.03	.16	.15	-.10	.10	.11	.06
GAD	--	--	--	--	.19	.14	.20	.02	.60	.19	-.06	-.03	.04
Agora	--	--	--	--	--	--	--	--	--	--	--	--	--
Social	--	--	--	--	--	.16	.23	-.03	.53	.05	.03	-.05	-.02
Specific	--	--	--	--	--	--	.10	.02	.56	.02	.07	-.02	.12
OCD	--	--	--	--	--	--	--	-.01	.18	.11	-.02	-.02	-.01
PTSD	--	--	--	--	--	--	--	--	.40	-.06	.05	.05	.08
Anxiety	--	--	--	--	--	--	--	--	--	.12	.05	-.02	.13
ADHD	--	--	--	--	--	--	--	--	--	--	-.06	.00	.00
ASPD	--	--	--	--	--	--	--	--	--	--	--	.11	.09
Alcohol	--	--	--	--	--	--	--	--	--	--	--	--	.14

Notes to Table 14. Correlations $\geq$.08 significant at $p<.05$; correlations $\geq$.11 significant at $p<.01$.
MDD=major depressive disorder; Dys=dysthymia; Dep/Depress=depressive disorders; GAD=generalized anxiety disorder; Agora=agoraphobia; Social=social phobia; Spec/Specific=specific phobia; OCD=obsessive compulsive disorder; PTSD=post-traumatic stress disorder; Anx/Anxiety=anxiety disorders; ADHD=attention-deficit/hyperactivity disorder; ASP/ASPD=antisocial personality disorder; Alc/Alcohol=alcohol dependence; Drug=drug dependence.

Table 15

Correlations Amongst Current Disorders in the Alcoholism Sample (n=448)

Disorder	Dys	Dep	GAD	Agora	Social	Spec	OCD	PTSD	Anx	AD/ HD	ASP	Alc	Drug
MDD	.00	.98	.13	--	.16	.08	.09	.16	.21	--	.08	.10	.02
Dys	--	.17	-.02	--	-.02	-.02	.00	-.02	-.03	--	-.04	.06	-.01
Depress	--	--	.13	--	.16	.08	.09	.16	.21	--	.07	.10	.02
GAD	--	--	--	--	.13	.28	.27	.05	.50	--	-.04	.00	.09
Agora	--	--	--	--	--	--	--	--	--	--	--	--	--
Social	--	--	--	--	--	.21	-.01	-.03	.50	--	.08	-.05	-.02
Specific	--	--	--	--	--	--	.21	.03	.64	--	.09	-.03	.14
OCD	--	--	--	--	--	--	--	-.01	.14	--	-.02	-.01	-.01
PTSD	--	--	--	--	--	--	--	--	.50	--	.04	.05	.09
Anxiety	--	--	--	--	--	--	--	--	--	--	.10	.01	.19
ADHD	--	--	--	--	--	--	--	--	--	--	--	--	--
ASPD	--	--	--	--	--	--	--	--	--	--	--	.07	.10
Alcohol	--	--	--	--	--	--	--	--	--	--	--	--	.17

Notes to Table 15. Correlations ≥.10 significant at $p<.05$; correlations ≥.13 significant at $p<.01$.
MDD=major depressive disorder; Dys=dysthymia; Dep/Depress=depressive disorders; GAD=generalized anxiety disorder; Agora=agoraphobia; Social=social phobia; Spec/Specific=specific phobia; OCD=obsessive compulsive disorder; PTSD=post-traumatic stress disorder; Anx/Anxiety=anxiety disorders; ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder; Child=childhood externalizing disorders; ASP/ASPD=antisocial personality disorder; Alc/Alcohol=alcohol dependence; Drug=drug dependence.

Table 16

Correlations Amongst Current Disorders in the ADHD Sample (n=193)

Disorder	Dys	Dep	GAD	Agora	Social	Spec	OCD	PTSD	Anx	AD/ HD	ASP	Alc	Drug
MDD	--	--	--	--	--	--	--	--	--	--	--	--	--
Dys	--	1.0	.09	--	.04	.09	-.02	-.02	.09	.09	-.04	.08	.31
Depress	--	--	.09	--	.04	.09	-.02	-.02	.09	.09	-.04	.08	.31
GAD	--	--	--	--	.24	-.06	.15	-.02	.72	.19	-.05	-.06	-.02
Agora	--	--	--	--	--	--	--	--	--	--	--	--	--
Social	--	--	--	--	--	.09	.42	-.02	.57	.03	-.04	-.05	-.02
Specific	--	--	--	--	--	--	-.02	-.01	.42	.10	-.03	-.04	-.01
OCD	--	--	--	--	--	--	--	-.01	.24	.12	-.02	-.02	-.01
PTSD	--	--	--	--	--	--	--	--	.17	-.06	-.01	-.01	-.01
Anxiety	--	--	--	--	--	--	--	--	--	.17	-.07	-.08	-.03
ADHD	--	--	--	--	--	--	--	--	--	--	.20	.12	.09
ASPD	--	--	--	--	--	--	--	--	--	--	--	.32	-.01
Alcohol	--	--	--	--	--	--	--	--	--	--	--	--	-.01

Notes to Table 16. Correlations $\geq$.14 significant at $p<.05$; correlations $\geq$.19 significant at $p<.01$.
MDD=major depressive disorder; Dys=dysthymia; Dep/Depress=depressive disorders; GAD=generalized anxiety disorder; Agora=agoraphobia; Social=social phobia; Spec/Specific=specific phobia; OCD=obsessive compulsive disorder; PTSD=post-traumatic stress disorder; Anx/Anxiety=anxiety disorders; ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder; Child=childhood externalizing disorders; ASP/ASPD=antisocial personality disorder; Alc/Alcohol=alcohol dependence; Drug=drug dependence.

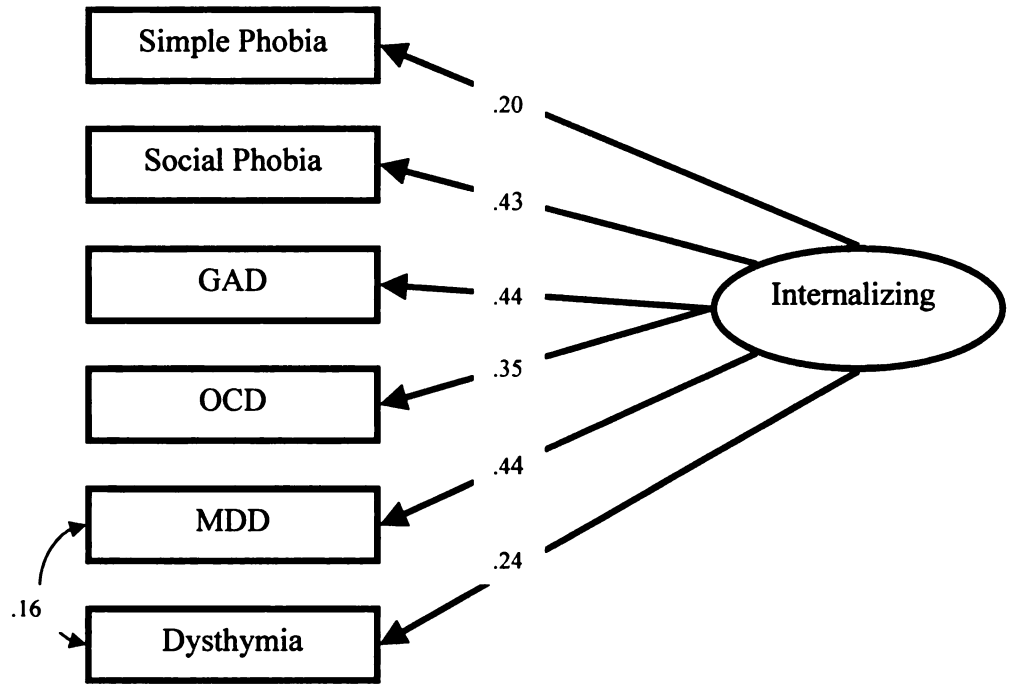

Figure 3. Final accepted latent model for internalizing disorders.

Notes to Figure 3. Fit statistics: χ^2 (8) = 8.30, $p > .05$, GFI = .996, CFI = .998, RMSEA = .008. All factor loadings were significant (p<.01). GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; MDD = major depressive disorder.

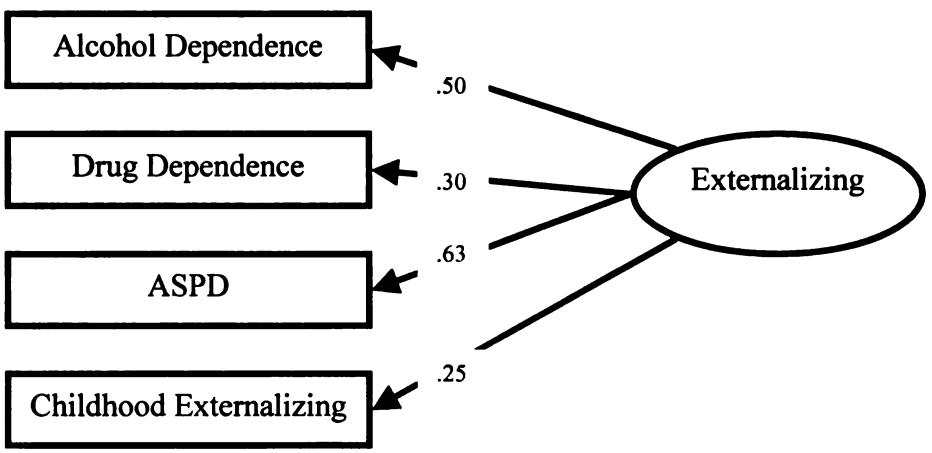

Figure 4. Final accepted latent model for externalizing disorders.

Notes to Figure 4. Fit statistics: χ^2 (2) = 8.32, $p < .05$; GFI = .99, CFI = .95, RMSEA = .07. All factor loadings were significant (p<.01). ASPD=antisocial personality disorder; Childhood Externalizing=ADHD, ODD, and CD.

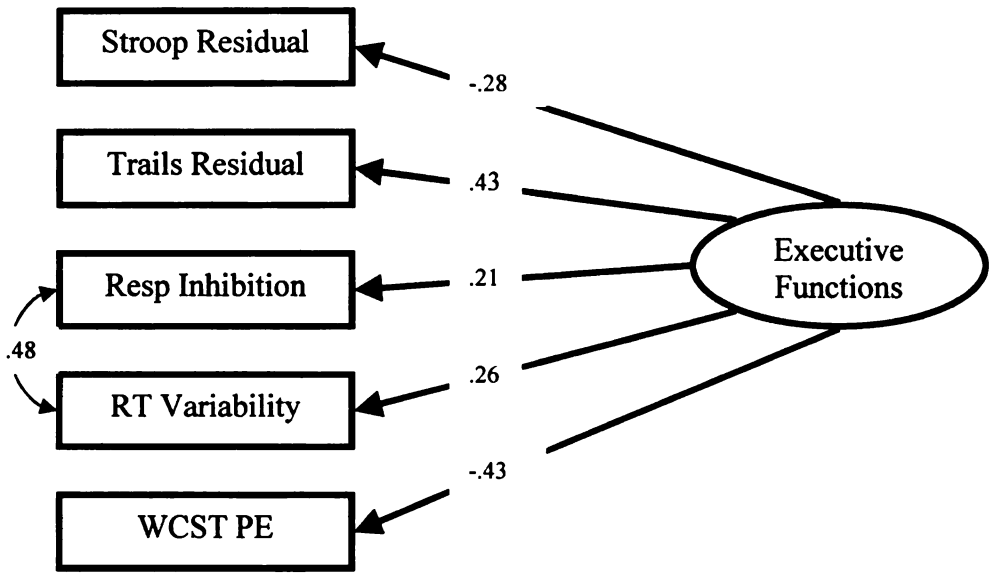

Figure 5. Final accepted latent model for executive function tests.

Notes to Figure 5. Fit statistics: $\chi^2(4) = 1.50, p > .05$; GFI = .999, CFI = 1.00, RMSEA = 0.00. All factor loadings were significant (p<.01). Stroop Residual=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; Trails Residual=nonstandardized residual of Trails B regressed on Trails A; Resp Inhibition=Response Inhibition as measured by Stop Signal Response Time; RT Variability=variability of go response from Stop Task; WCST PE = Wisconsin Card Sorting Test perseverative errors standard score.

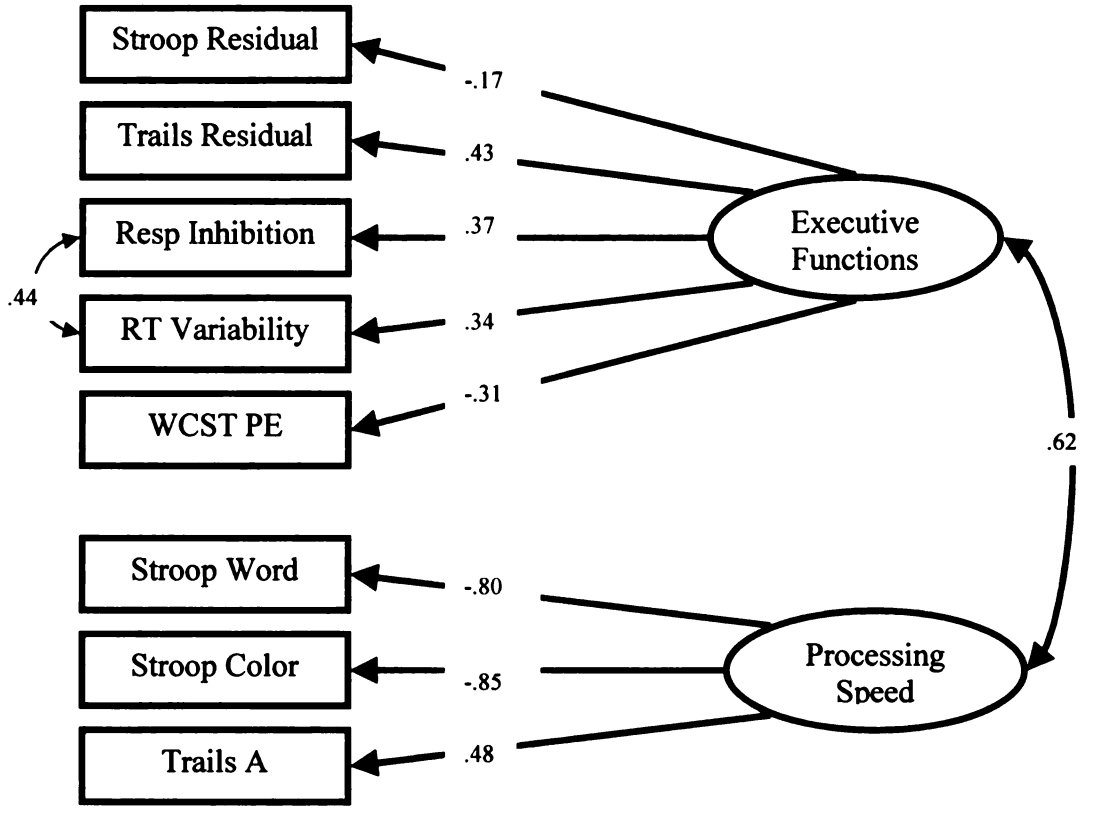

Figure 6. Latent measurement model for cognitive test performance.

Notes to Figure 6. Fit statistics: χ^2 (18) = 93.21, $p < .05$; GFI=.97, CFI=.92, RMSEA=0.08. All factor loadings were significant (p<.01). Stroop Residual=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; Trails Residual=nonstandardized residual of Trails B regressed on Trails A; Resp Inhibition=Response Inhibition as measured by Stop Signal Response Time; RT Variability=variability of go response from Stop Task; WCST PE=Wisconsin Card Sorting Test perseverative errors standard score.

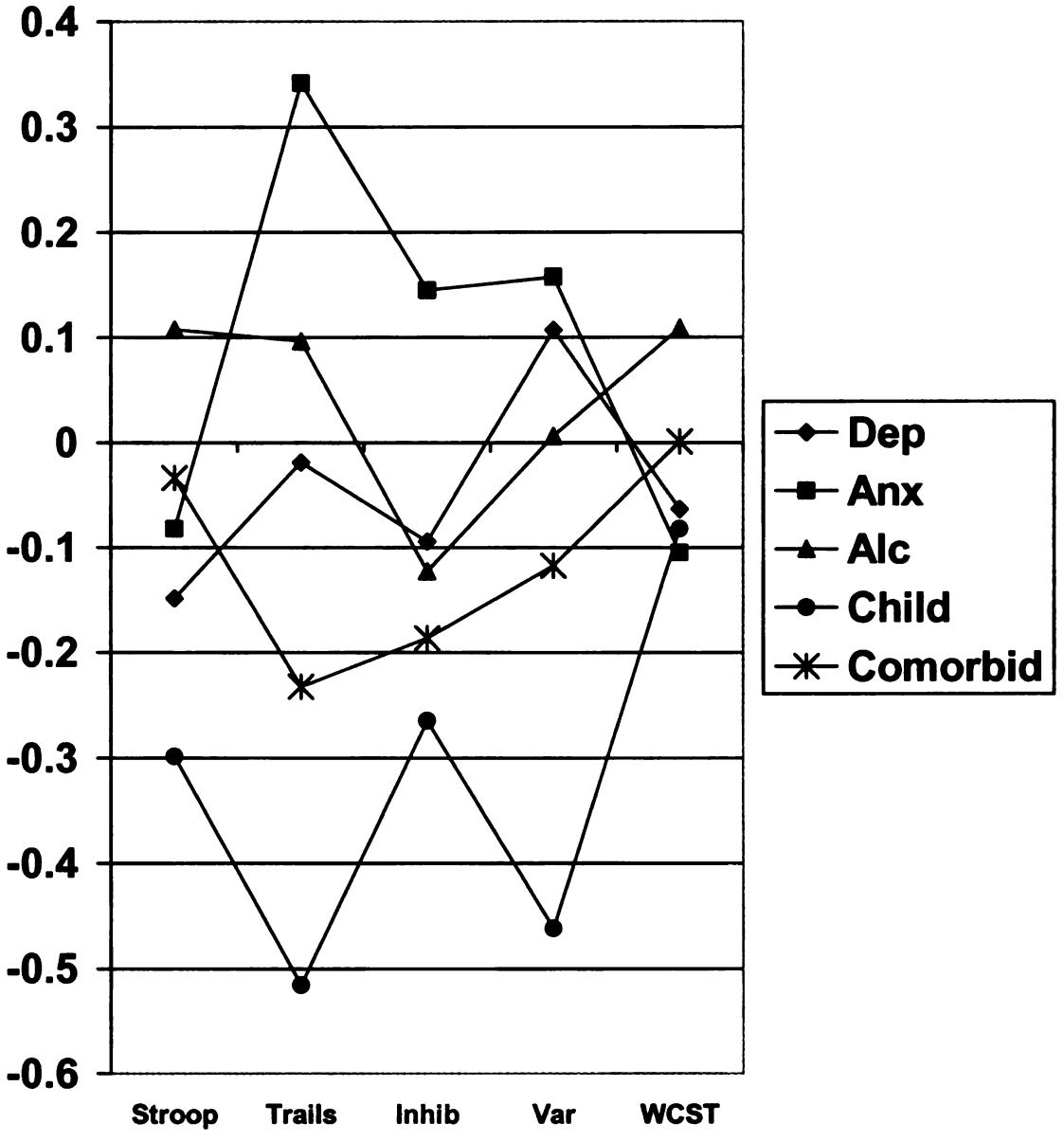

Figure 7. Mean z-scores for performance on executive function tests for lifetime disorders with nonoverlapping diagnostic groups.

Notes to Figure 7. Stroop=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; Trails=nonstandardized residual of Trails B regressed on Trails A; Inhib=Response Inhibition as measured by Stop Signal Response Time; Var=variability of go response from Stop Task; WCST=Wisconsin Card Sorting Test perseverative errors standard score; Dep=depressive disorders; Anx=anxiety disorders; Alc=alcohol dependence; Child=childhood externalizing disorders; Comorbid=multiple disorders. Note that *z*-scores for Trails, SSRT, and SDX were reverse scored so that lower scores reflected poorer performance.

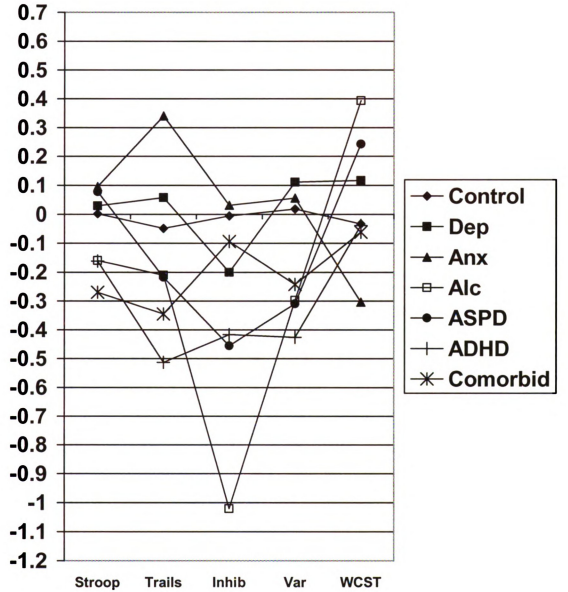

Figure 8. Mean z-scores for performance on executive function tests for current disorders with nonoverlapping diagnostic groups.

Notes to Figure 8. Stroop=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; Trails=nonstandardized residual of Trails B regressed on Trails A; Inhib=Response Inhibition as measured by Stop Signal Response Time; Var=variability of go response from Stop Task; WCST=Wisconsin Card Sorting Test perseverative errors standard score; Dep=depressive disorders; Anx=anxiety disorders; Alc=alcohol dependence; ASPD=antisocial personality disorder; ADHD=attention-deficit/hyperactivity disorder; Child=childhood externalizing disorders; Comorbid=multiple disorders. Note that *z*-scores for Trails, SSRT, and SDX were reverse scored so that lower scores reflected poorer performance.

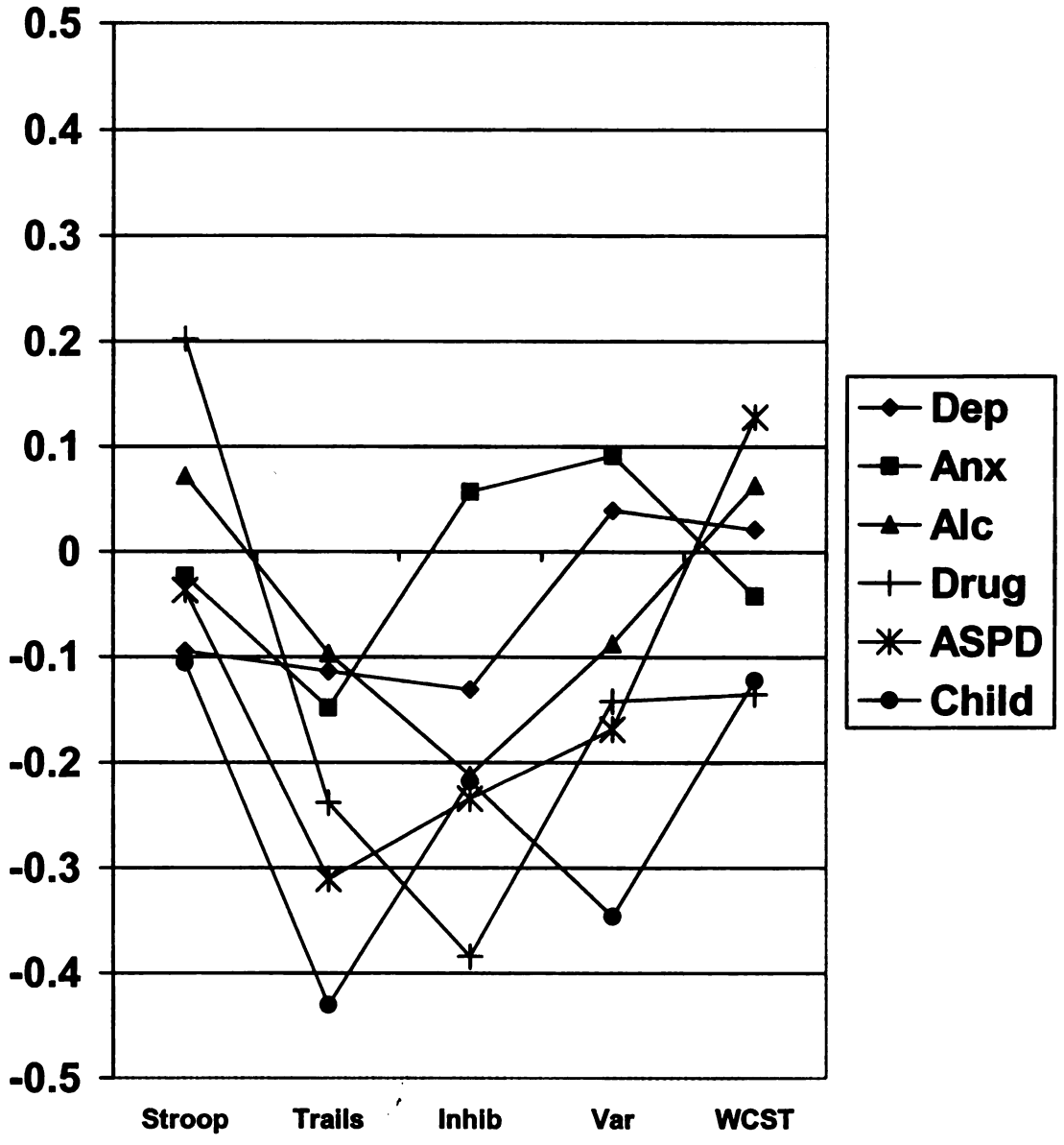

Figure 9. Mean z-scores for performance on executive function tests for lifetime disorders with overlapping diagnostic groups.

Notes to Figure 9. Stroop=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; Trails=nonstandardized residual of Trails B regressed on Trails A; Inhib=Response Inhibition as measured by Stop Signal Response Time; Var=variability of go response from Stop Task; WCST=Wisconsin Card Sorting Test perseverative errors standard score; Dep=depressive disorders; Anx=anxiety disorders; Alc=alcohol dependence; Drug=drug dependence; ASPD=antisocial personality disorder; Child=childhood externalizing disorders. Note that *z*-scores for Trails, SSRT, and SDX were reverse scored so that lower scores reflected poorer performance.

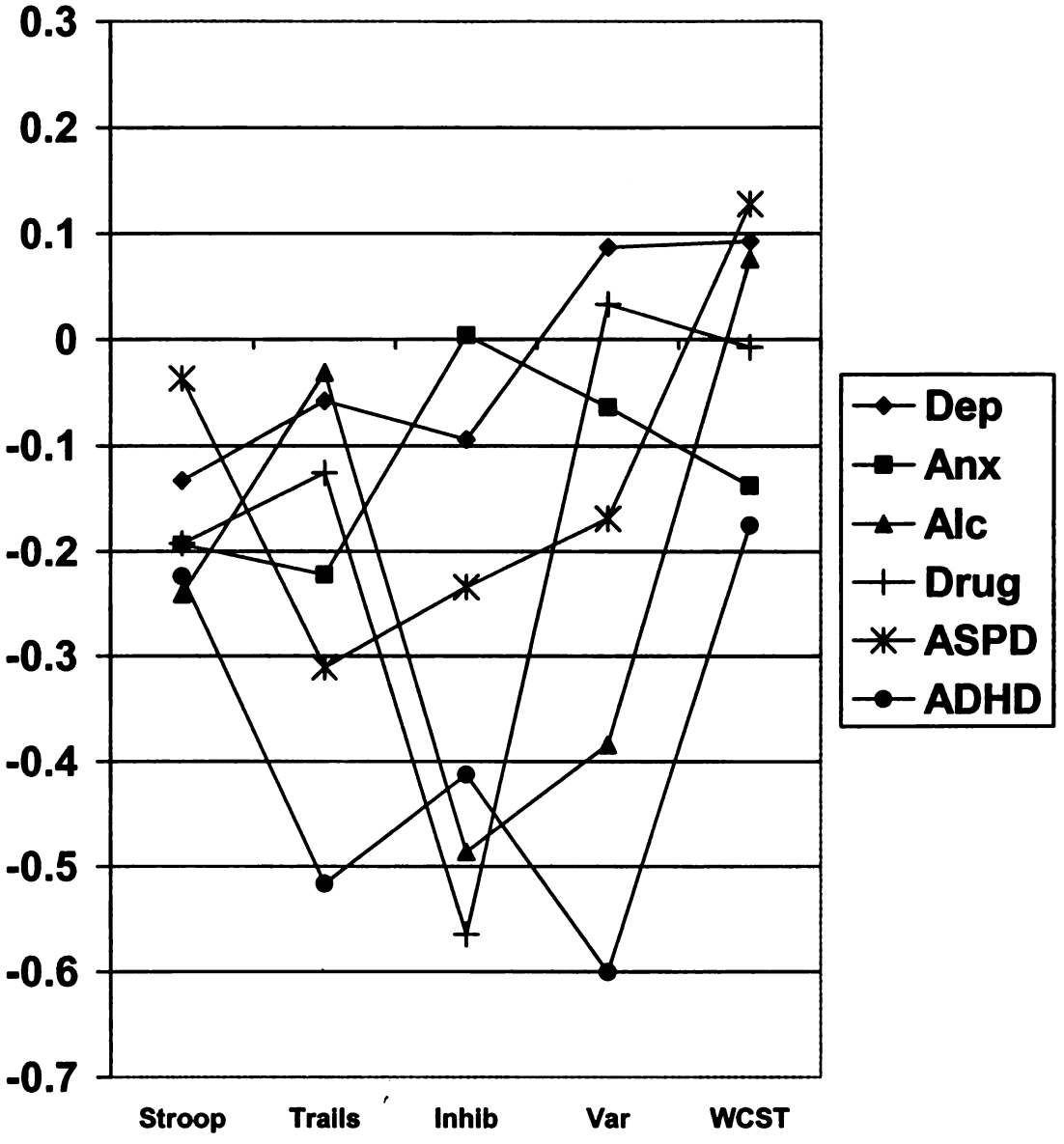

Figure 10. Mean z-scores for performance on executive function tests for current disorders with overlapping diagnostic groups.

Notes to Figure 10. Stroop=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; Trails=nonstandardized residual of Trails B regressed on Trails A; Inhib=Response Inhibition as measured by Stop Signal Response Time; Var=variability of go response from Stop Task; WCST=Wisconsin Card Sorting Test perseverative errors standard score; Dep=depressive disorders; Anx=anxiety disorders; Alc=alcohol dependence; Drug=drug dependence; ASPD=antisocial personality disorder; Child=childhood externalizing disorders. Note that *z*-scores for Trails, SSRT, and SDX were reverse scored so that lower scores reflected poorer performance.

Table 17

Summary of Regression Analysis for Lifetime Disorders Predicting Performance on Executive Function Composite Score

Disorders	*B*	SE *B*	β	*p*
Depressive	0.05	0.26	0.01	.8
Anxiety	0.38	0.28	0.05	.19
Alcohol Dependence	0.23	0.27	0.04	.40
Drug Dependence	-0.26	0.50	-0.02	.61
ASPD	-0.10	0.42	-0.01	.81
Child	-1.17	0.28	-0.17	<.001

Notes to Table 17. $R^2 = .032$. ASPD=antisocial personality disorder; Child=childhood externalizing diorders (attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder). Results remain after controlling for age, gender, and FSIQ.

Table 18

Summary of Regression Analysis for Current Disorders Predicting Performance on Executive Function Composite Score

Disorders	*B*	SE *B*	β	*p*
Depressive	0.24	0.33	0.03	.46
Anxiety	-0.12	0.38	-0.01	.76
Alcohol Dependence	-0.76	0.50	-0.06	.13
Drug Dependence	-0.18	1.11	-0.01	.87
ASPD	-0.37	0.39	-0.04	.34
Adult ADHD	-1.18	0.38	-0.19	<.001

Notes to Table 18. $R^2 = .042$. ASPD=antisocial personality disorder; ADHD=attention-deficit/hyperactivity disorder. Results remain after controlling for age, gender, and FSIQ.

Table 19

Summary of Regression Analysis for Lifetime Disorders Predicting Performance on Processing Speed Composite Score

Disorders	*B*	SE *B*	B	*p*
Depression	-0.16	0.21	-0.03	.44
Anxiety	0.11	0.23	0.02	.63
Alcohol Dependence	-0.57	0.22	-0.11	<.01
Drug Dependence	-0.67	0.39	-0.07	.09
ASPD	-0.49	0.33	-0.06	.14
Childhood Externalizing	-0.55	0.23	-0.10	.02

Notes to Table 19. $R^2 = .045$. ASPD=antisocial personality disorder; Childhood Externalizing=attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder. When controlling for age, gender, and FSIQ, only child externalizing disorders were significantly related to speed ($B = -.15$, $p < .01$), and drug dependence approached significance ($B = -.07$, $p = .05$).

Table 20

Summary of Regression Analysis for Current Disorders Predicting Performance on Processing Speed Composite Score

Disorders	*B*	SE *B*	β	*p*
Depression	-0.02	0.26	-0.003	.93
Anxiety	0.03	0.31	0.004	.93
Alcohol Dependence	-0.64	0.40	-0.06	.11
Drug Dependence	-0.54	0.90	-0.02	.55
ASPD	-0.95	0.31	-0.12	<.01
Adult ADHD	-0.08	0.30	-0.01	.79

Notes to Table 20. $R^2 = .042$. ASPD=antisocial personality disorder; ADHD=attention-deficit/hyperactivity disorder. When controlling for age, gender, and FSIQ, ASPD was no longer significant and ADHD became significant ($B = -.11$, $p < .05$).

Table 21

Frequencies of Numbers of Individual Lifetime Disorders in the Combined, Alcoholism, and ADHD Samples

Number of Disorders	Combined (*n*=641)	Alcoholism (*n*=448)	ADHD (*n*=193)
0	170 (26.5%)	106 (23.7%)	64 (33.1%)
1	187 (29.2%)	133 (29.7%)	54 (28.0%)
2	127 (19.8%)	91 (20.3%)	36 (18.7%)
3	90 (14.0%)	70 (15.6%)	20 (10.4%)
4	43 (6.7%)	28 (6.3%)	15 (7.8%)
5	13 (2.0%)	9 (2.0%)	4 (2.1%)
6	7 (1.1%)	7 (1.6%)	0 (0%)
7	3 (0.5%)	3 (0.6%)	0 (0%)
8	0 (0%)	0 (0%)	0 (0%)
9	1 (0.2%)	1 (0.2%)	0 (0%)

Notes to Table 21. Disorders included were lifetime major depressive disorder, dysthymia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder, agoraphobia, alcohol dependence, drug dependence, ASPD, conduct disorder, attention-deficit/hyperactivity disorder, and oppositional defiant disorder.

Table 22

Frequencies of Numbers of Individual Current Disorders in the Combined, Alcoholism, and ADHD Samples

Number of Disorders	Combined (*n*=641)	Alcoholism (*n*=448)	ADHD (*n*=193)
0	360 (56.2%)	262 (58.5%)	98 (50.8%)
1	188 (29.3%)	125 (27.9%)	63 (32.6%)
2	62 (9.7%)	39 (8.7%)	23 (11.9%)
3	24 (3.7%)	17 (3.8%)	7 (3.6%)
4	7 (1.1%)	5 (1.1%)	2 (1.0%)

Notes to Table 22. Disorders included were current major depressive disorder, dysthymia, social phobia, specific phobia, obsessive compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder, agoraphobia, alcohol dependence, drug dependence, antisocial personality disorder, and attention-deficit/hyperactivity disorder.

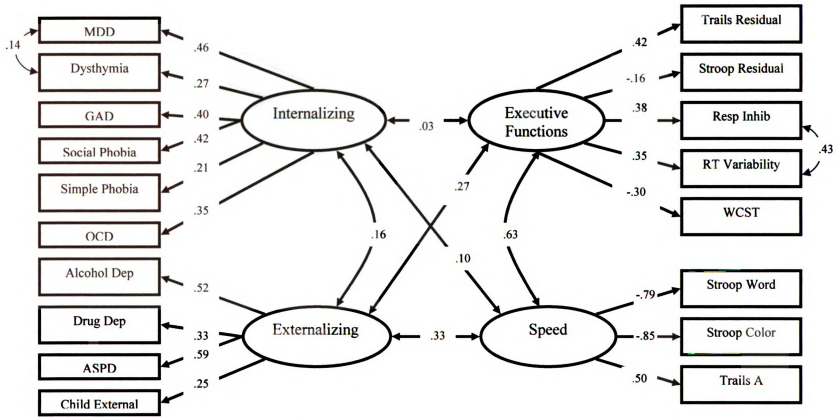

Figure 11. Measurement model for the relationships between lifetime internalizing and externalizing disorders on cognitive task performance for executive functions and speed.

Notes to Figure 11. Fit statistics: χ^2 (127) = 287.37, $p < .01$; GFI = .95, CFI = .88, RMSEA = 0.04. Squares represent manifest variables; Circles represent latent variables; D = disturbance; GAD=generalized anxiety disorder; ASPD=antisocial personality disorder; Dep=dependence; MDD=major depressive disorder; OCD = obsessive-compulsive disorder; Child External = Childhood Externalizing Disorders (ADHD, ODD, or CD); Trails Residual=nonstandardized residual of Trails B regressed on Trails A; Stroop Residual=nonstandardized residual of Stroop Color-Word regressed on Stroop Word and Stroop Color; WCST=Wisconsin Card Sorting Test perseverative errors; Resp Inhib=Response Inhibition as measured by Stop Signal Response Time; RT Variability=response variability from Stop Task.

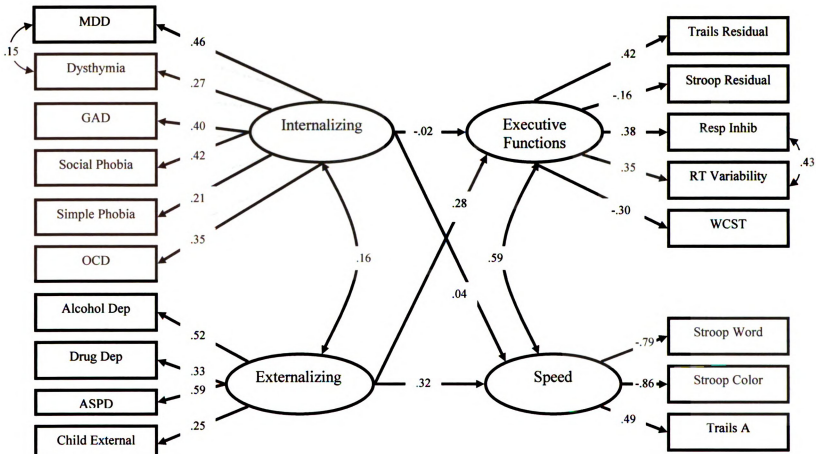

Figure 12. Model representing the predictive relationships between lifetime internalizing and externalizing disorders on cognitive task performance for executive functions and speed.

Notes to Figure 12. Fit statistics: $\chi^2(127) = 287.37$, $p < .01$; GFI = .95, CFI = .88, RMSEA = 0.04. Squares represent manifest variables; Circles represent latent variables; D = disturbance; GAD=generalized anxiety disorder; ASPD=antisocial personality disorder; Dep=dependence; MDD=major depressive disorder; OCD = obsessive-compulsive disorder; Child External = Childhood Externalizing Disorders (ADHD, ODD, or CD); Trails Residual=residual of Trails B regressed on Trails A; Stroop Residual=residual of Stroop Color-Word regressed on Stroop Word and Stroop Color; WCST=Wisconsin Card Sorting Test perseverative errors; Resp Inhib=Response Inhibition as measured by Stop Signal Response Time; RT Variability=response variability from Stop Task.

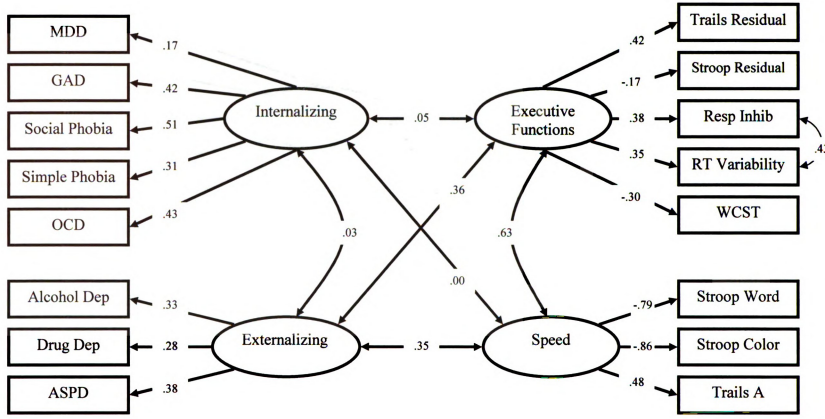

Figure 13. Measurement model representing the relationships between current internalizing and externalizing disorders on cognitive task performance for executive functions and speed.

Notes to Figure 13. Fit statistics: $\chi 2$ (97) = 213.07, $p < .001$, GFI = .96, CFI = .89, RMSEA = .04. Squares represent manifest variables; Circles represent latent variables; D = disturbance; GAD=generalized anxiety disorder; ADHD=attention-deficit/hyperactivity disorder; ASPD=antisocial personality disorder; Dep=dependence; MDD=major depressive disorder; OCD = obsessive-compulsive disorder; Trails Residual=nonstandardized residual of Trails B regressed on Trails A; Stroop Residual=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; WCST=Wisconsin Card Sorting Test perseverative errors; Resp Inhib=Response Inhibition as measured by Stop Signal Response Time; RT Variability=response variability from Stop Task.

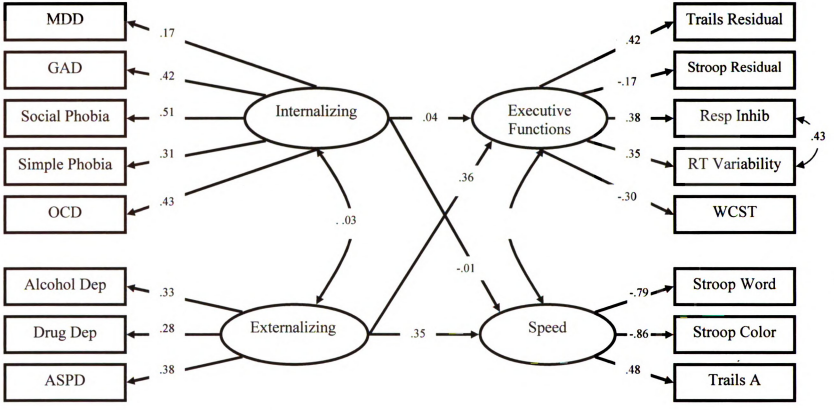

Figure 14. Model representing the predictive relationships between current internalizing and externalizing disorders on cognitive task performance for executive functions and speed.

Notes to Figure 14. Fit statistics: $\chi 2\ (97) = 213.07$, $p < .001$, GFI = .96, CFI = .89, RMSEA = .04. Squares represent manifest variables; Circles represent latent variables; D = disturbance; GAD=generalized anxiety disorder; ADHD=attention-deficit/hyperactivity disorder; ASPD=antisocial personality disorder; Dep=dependence; MDD=major depressive disorder; OCD = obsessive-compulsive disorder; Trails Residual=nonstandardized residual of Trails B regressed on Trails A; Stroop Residual=nonstandardized residual of Strop Color-Word regressed on Stroop Color and Stroop Word; WCST=Wisconsin Card Sorting Test perseverative errors; Resp Inhib=Response Inhibition as measured by Stop Signal Response Time; RT Variability=response variability from Stop Task.

APPENDIX

Anatomy of the Frontal Lobes and Frontal Subcortical Circuits

EF have historically been associated with activity in the prefrontal or frontal cortex. The historical underpinnings for the connection between EF and the frontal lobes come from early observations of seemingly disparate effects following frontal lobe damage (Pennington & Ozonoff, 1996). Therefore, the localization of these cognitive functions preceded their conceptualization. Although the disrupted processes appeared to be quite different from one another, they could all be understood as involving dysregulation in goal-directed activity that could not be attributed to deficits in more basic cognitive processes; as a result it was thought that the frontal lobes were involved in "executive" or "supervisory" functions (Pennington & Ozonoff, 1996; quotes appeared in original article).

The functional integrity of the frontal lobes (specifically prefrontal cortex) is required to engage in "any series of purposive actions that deviates from rehearsed automatic routing" (Fuster, 1997, p. 3), but an emphasis has also been on the vast circuitry that connects the frontal lobes with cortical and subcortical regions (Alexander, DeLong, & Strick, 1986; Lichter & Cummings, 2001; Stuss, Knight, & Ed, 2002). All components of these networks are important for task performance, and lesions at any point in the system may cause deficits that look like 'frontal' damage, whether the lesion site is cortical or subcortical (Lichter & Cummings, 2001; Mesulam, 2002). The importance of other regions to EF abilities is a key reason why the frontal metaphor is inadequate for EF.

The frontal lobes are the area of the brain anterior to the central sulcus. Directly in front of the central sulcus is the primary motor and premotor cortex, and anterior to those areas are the prefrontal cortices, areas of the brain which are larger and most highly developed in the human brain (Petrides & Pandya, 2002). This is the region of most interest for cognitive control processes.

The prefrontal cortex appears to have several architectonically distinct regions (Petrides & Pandya, 2002). In particular, the connections from the prefrontal cortex to other cortical and subcortical regions are important, as they were observed to involve two functionally and anatomically distinct systems (Pandya & Barnes, 1987). The first system mediates the sequential processing of sensory, spatially-related, and motivational information through a dorsal stream, which involves the *dorsolateral* and *medial* areas of the frontal lobes as well as interconnections with the posterior parietal lobe and cingulate gyrus. The second system, which mediates emotional tone, is ventrally located and involves the *orbital* surface of the frontal lobes as well as paralimbic regions. Thus, the frontal lobes are the site where these partially overlapping systems involving external sensory information and internal cognitive and emotional/limbic responses are integrated and processed to modulate motivation and facilitate motor responses (Lichter & Cummings, 2001). The functional significance of these circuits will be elaborated upon shortly.

A pattern of anatomical and functional duality has also emerged when examining connections between the prefrontal cortex and subcortical structures, particularly the basal ganglia. The basal ganglia is a subcortical system that is important in the regulation and coordination of cortically-originated movement. It consists of the striatum (i.e.,

caudate nucleus, putamen, and nucleus accumbens), globus pallidus, substantia nigra, and subthalamic nucleus. Efferent projections from functionally-related areas of the prefrontal lobe converge upon discrete areas of the striatum, which also appear to share functional properties (Lichter & Cummings, 2001). Specifically, the dorsal system of the frontal lobes connects to the dorsal caudate nucleus, while the ventral system maps onto the ventromedial portion of the caudate and adjacent portions of the nucleus accumbens. Thus, information processed by the cortex is received and processed by the striatum in a manner that apparently maintains partial separation and specialization of functional domains (Lichter & Cummings, 2001). Thus, the structure of the prefrontal cortex and underlying circuitry provides the anatomical framework for differential processing.

The neuroanatomy of frontostriatal circuits was recently extended by Middleton and Strick (2002) to include seven hypothesized "categories" of circuits based upon findings in primates. These circuits arise from extensive closed loop connections (i.e., both efferent and afferent connections) between the basal ganglia, frontal cortex, and thalamus, thus supporting distinct anatomical and functional regions within the frontal cortex. The term "categories" is used to denote the multiple parallel segregated circuits that are contained within each category. Three of these categories of circuits are less relevant to the present discussion because they involve the motor areas of the frontal lobes and posterior cortex. The main circuits of interest here are those that involve projections between the basal ganglia and the following regions of the prefrontal cortex: (1) dorsolateral; (2) lateral orbitofrontal; (3) medial orbitofrontal; and (4) anterior cingulate (note that (3) and (4) are often combined in other conceptions). The circuits traverse from these prefrontal regions to areas of the striatum ((1) dorsolateral caudate

head; (2) ventromedial caudate head; (3) ventromedial caudate and ventral striatum; and (4) ventromedial caudate head, respectively). These striatal regions project to regions of the globus pallidus and pars reticulata of the substantia nigra, which send efferents to specific nuclei of the thalamus, which then project back to the prefrontal region, forming a closed loop (Middleton & Strick, 2002). Middleton and Strick (2002) note that while these projections mean that the basal ganglia can influence many cortical regions and thus involve many functions, the "highly topographic and closed-loop nature" (p. 56) of these circuits means that very specific functional impairment can result from damage to the structures in basal ganglia.

The cerebellum also appears to be involved in prefrontal circuitry. Cerebrocerebellar circuits are heavily connected to the dorsolateral and dorsomedial regions of the prefrontal cortex (Middleton & Strick, 2001; Schmahmann & Pandya, 1995). Medial regions appear to be less heavily connected with the cerebellum, while no connections have been observed from the ventral prefrontal and orbitofrontal cortices (Schmahmann & Pandya, 1995). In conjunction with its role in motor activity, the cerebellum appears to be important to the same cognitive functions as the dorsolateral prefrontal cortex. The cerebellum and this region of the prefrontal cortex appear to interact with and modulate each other throughout development and during cognitive task performance (Diamond, 2000). As such, the cerebellum is another important subcortical structure that contributes to prefrontal cortex activity.

Along with the vast subcortical input into the prefrontal cortex, the frontal lobes also receive reciprocal connections from posterior cortical areas (i.e., areas posterior to the central sulcus). Afferent connections from posterior association cortices provide

highly processed sensory-specific or multimodal information to areas of the prefrontal cortex, whose reciprocal efferent connections allow the prefrontal cortex to regulate information processing in these posterior cortical areas (Petrides & Pandya, 2002). Thus the prefrontal cortex exchanges information with other cortical regions.

Therefore, the frontal lobes serve to integrate and modulate sensory and perceptual information from distributed networks to aid in motor output. Reciprocal circuits connect regions of the prefrontal cortex to posterior cortical association areas and subcortical regions such as the limbic lobe, basal ganglia, and cerebellum. The prefrontal cortex thus appears to be a site of convergence for information from overlapping yet distinct circuits that are involved in emotion, motivation, cognitive processes, and motor output. Recent advances in the study of frontostriatal circuits have supported the existence of four (or, more commonly, three) distinct circuits connecting the prefrontal cortex to subcortical regions. It is important to view these circuits as forming a "frontal network system" (Mesulam, 2002) in order to recognize that problems at any stage in processing may cause deficits that look similar to those typically associated with the frontal lobes. Further, due to the segregated and closed-loop nature of these circuits, damage may result in the loss of very specific abilities.

Functional Significance of Prefrontal Regions: Prefrontal Behavioral Syndromes

Three prototypical behavioral neurological syndromes have been observed following injury to certain areas of the prefrontal cortex. Damage to the dorsolateral region may result in a "frontal abulic syndrome" (Mesulam, 2002), which is characterized by a loss of initiative and creativity, reduced ability to concentrate, and a tendency towards emotional apathy and flat affect. Fuster (1997) noted that a disruption of

"intensive and selective" attention is at the forefront of this syndrome (p. 172), which impairs the ability to direct or focus general arousal upon a particular sensory or internal experience. Some patients suffer from depression, but it is difficult to determine whether it is primary or secondary to the cognitive disorder. Cognitively, these symptoms manifest as the traditional "dysexecutive syndrome," which involves problems with perseveration, planning, working memory, verbal fluency, and temporal organization of behavior (Fuster, 1997).

Damage to the orbitofrontal region may result in a "frontal disinhibition syndrome" (Mesulam, 2002), which is characterized by deficits in the "exclusionary" aspect of attention (Fuster, 1997, p. 174). Individuals with this disorder have difficulty suppressing interference from external or internal stimuli. The result is behavioral excesses and too much drive, but these behaviors are characterized by impulsivity with little judgment, insight, foresight, or ability to learn from experience. These patients may disregard social conventions and show impaired moral judgment. Their affect is generally euphoric, with irritability, contentiousness, and paranoia. Cognitively, they have problems with focused attention (Fuster, 1997).

A third, less common syndrome, whose behavioral presentation is similar to frontal abulia has been called "akinetic mutism" (Pennington & Ozonoff, 1996) and may result from damage to the medial/cingulate cortex (Fuster, 1997). This disorder is poorly defined, but it involves apathy and deficits in the ability to initiate speech and other spontaneous behavior. Too much anterior cingulate activity may be associated with obsessive-compulsive and tic-like symptoms, while too little activity has been related to diminished self-awareness and depression (Devinsky et al., 1995). Cognitively, the

anterior cingulate is important for response selection, motivation, and initiation (Devinsky et al., 1995).

This summary greatly simplifies the processes of the prefrontal cortex, as certain regions are consistently activated during diverse EF processes (Duncan & Owen, 2000). However, damage to different regions of the prefrontal cortex may result in distinct behavioral/cognitive syndromes. Many of the functional changes that are observed following frontal lobe damage parallel the behavioral sequelae of psychiatric disorders, providing a conceptual connection between frontal lobe circuits and psychopathology. The dual realms of the prefrontal cortex, which integrate cognitive as well as motivational and emotional information (Lichter & Cummings, 2001), highlight the means by which EF deficits may be associated with both behavioral and emotional symptomatology. Damage to or dysfunction in these regions of the brain may result not only in cognitive changes, which would primarily involve EF, but also directly affect emotional and behavioral functioning (Fuster, 1997; Lichter & Cummings, 2001).

Clinical parallels to psychological disorders may be drawn for each of these neurological prefrontal syndromes. The dorsolateral-frontal abulic syndrome resembles the symptomatology of ADHD, as well as depression to some degree. The orbitofrontal-disinhibition syndrome resembles mania, antisocial personality disorder (ASPD), and the hyperactive symptomatology sometimes associated with ADHD. Finally, the cingulate-akinetic mutism syndrome resembles the symptoms of major depressive disorder (MDD), while excessive cingulate activity is analogous to symptoms of anxiety disorders. Therefore, the surface similarities between these frontal syndromes and symptom presentations in key psychiatric disorders suggest some hypotheses for how

psychopathology may be related to components of EF dysfunction. Imaging research has also provided varying degrees of support for dysfunctions in frontal regions of the brain in ADHD, ASPD, alcoholism, substance dependence, depression, and anxiety (see section on *EF in Key Psychopathologies*), and it is therefore unsurprising that EF deficits have also been associated with each of these disorders.

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