



# Integrating genetic, psychopharmacological and neuroimaging studies: A converging methods approach to understanding the neurobiology of ADHD

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## Abstract

This paper aims to illustrate how combining multiple approaches can inform us about the neurobiology of ADHD. Converging evidence from genetic, psychopharmacological and functional neuroimaging studies has implicated dopaminergic fronto-striatal circuitry in ADHD. However, while the observation of converging evidence from multiple vantage points is convincing, it does not necessarily inform us on how these observations fit together. How does a polymorphism in a (dopamine) risk-gene for ADHD translate into a neurobiological substrate and result in behaviors that warrant a diagnosis of ADHD in a developing child? To illustrate how integrating multiple methods may help address this issue, we discuss studies combining genetics, neuropsychopharmacology and neuroimaging approaches. We show how investigators are using these approaches to map the effects of ADHD risk-genes, and common ADHD-treatments on neurobiological measures. Given its central role in both ADHD and in stimulant treatment, the dopamine transporter gene

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is frequently discussed as an example. The studies discussed here demonstrate that a converging methods approach is a potentially powerful tool in unraveling the neurobiology of ADHD. These approaches may suggest new avenues for research, as well as point out new directions for the development of targeted treatments for this disorder.

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## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a behaviorally defined neuropsychiatric disorder with onset by age 7 that is characterized by developmentally inappropriate levels of activity and impulsivity, as well as dis-organized and inattentive behaviors (APA, 2000; Kaplan, Sadock, & Grebb, 1994). Historically, ADHD has been viewed as a biological disorder of the control of behavior. While early accounts from the 1900s viewed the disorder as driven by morals and volitional inhibition, labels soon changed to “brain damage syndrome” and “organic drivenness” and later to “hyperkinetic impulse disorder” and “ADD” and finally ADHD. Although a greater appreciation for the modulating role of the environment on the expression of ADHD symptoms has gradually emerged, the view of biological factors as primary in the development of the disorder has never been displaced (see Schachar, 1986, for a historical review). While some years ago, it was assumed that ADHD was outgrown by puberty, recently the perspective has emerged that ADHD is a chronic developmental disorder persisting into adulthood in at least 30% of the patients (Wilens, Biederman, & Spencer, 2002).

In the current paper, we will focus on a developmental cognitive neuroscience perspective of ADHD. Based on theoretically driven models, this approach allows the integration of findings from multiple disciplines by investigating the relationship between brain and cognitive development. Thus, it may inform us on cognitive mechanisms at different points in the life cycle, and characterize precisely how these mechanisms subservise developmental changes in both typical and atypical development. In addition, developmental cognitive neuroscience research can inform a variety of practical applications, such as earlier diagnosis and more effective treatment of developmental disorders.

Theoretical accounts of ADHD all address aspects of self-regulation in some form. Self-regulation—or in contemporary terms, cognitive control—is characterized as the ability to suppress inappropriate behaviors in response to contextual and temporal cues and adjust behavior accordingly (Nigg & Casey, 2005). Diagnostic criteria for ADHD reflect these deficits, as they include inappropriate and disruptive behaviors in inappropriate contexts, such as blurting out (unintentionally hurtful) comments, disruptive behavior in the classroom, and potentially dangerous behaviors, such as running out into traffic. Although a significant amount of research has now addressed the neurobiological bases of ADHD, the etiological pathways are still not understood. In this paper, we discuss this issue from a converging methods approach. In Section I, we present a selective review of genetics, psychopharmacology and functional neuroimaging studies of ADHD. In Section II, we focus on how these approaches can be integrated to address the question of how ADHD is conceptualized from a neurobiological perspective. The overall aim is to illustrate how combining multiple approaches can inform us regarding complex neuropsychiatric disorders, such as ADHD.

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