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# Reaction time variability in ADHD: A meta-analytic review of 319 studies

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## Highlights

- Children & adults with ADHD exhibit increased RT variability (RTV) relative to nonclinical groups.
- This RTV was attenuated by stimulants, but unaffected by psychosocial & other medical treatments.
- Individuals with ADHD did not evince slower processing speed (mean RT) after accounting for RTV.
- Comparison with clinical control groups reveals that RT variability is not specific to ADHD.
- RTV is a stable feature of ADHD & other clinical disorders observed

## Abstract

Individuals with ADHD are characterized as ubiquitously slower and more variable than their unaffected peers, and increased reaction time (RT) variability is considered by many to reflect an etiologically important characteristic of ADHD. The present review critically evaluates these claims through meta-analysis of 319 studies of RT variability in children, adolescents, and adults with ADHD relative to typically developing (TD) groups, clinical control groups, and themselves (subtype comparisons, treatment and motivation effects). Random effects models corrected for measurement unreliability and publication bias revealed that children/adolescents (Hedges'  $g = 0.76$ ) and adults ( $g = 0.46$ ) with ADHD demonstrated greater RT variability relative to TD groups. This increased variability was attenuated by psychostimulant treatment ( $g = -0.74$ ), but unaffected by non-stimulant medical and psychosocial interventions. Individuals with ADHD did not evince slower processing speed (mean RT) after accounting for RT variability, whereas large magnitude RT variability deficits remained after accounting for mean RT. Adolescents and adults with ADHD were indistinguishable from clinical control groups, and children with ADHD were only minimally more variable than clinical control children ( $g = 0.25$ ). Collectively, results of the meta-analysis indicate that RT variability reflects a stable feature of ADHD and other clinical disorders that is robust to systematic differences across studies.

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## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a complex, chronic, and potentially debilitating disorder of brain, behavior, and development that affects approximately 2.8 to 3.9 million U.S. school children at an annual cost of illness of over \$14,000 per child (American Psychiatric Association, 2000, Pelham et al., 2007, U.S. Census Bureau, 2010). Longitudinal studies reveal that functionally impairing ADHD symptoms continue into adolescence and adulthood for most individuals, and are associated with a host of adverse outcomes. These include scholastic underachievement and school failure, increased high school/college dropout rates, earlier/riskier sexual activity, dysfunctional interpersonal relationships, negative driving-related outcomes, lower overall

socioeconomic status, poor work histories, and less secure employment (Barkley et al., 2006, Mannuzza et al., 1993).

Anecdotal and controlled observations suggest that individuals with ADHD are *consistently inconsistent* (Rapport, Chung, Shore, & Isaacs, 2001) both behaviorally and in their performance on neurocognitive tests (Klein et al., 2006, Kofler et al., 2008, Russell et al., 2006, Willcutt et al., 2008). Although long treated as a nuisance variable in the search for underlying neurocognitive deficits in ADHD (for an exception, see Cohen & Douglas, 1972), *intraindividual variability* is currently considered by many to be a core and stable feature of the disorder, and referred to frequently as a ubiquitous and etiologically important characteristic of ADHD (Table 1). Intraindividual variability refers to moment-to-moment (within-subject) fluctuations in behavior and task performance occurring over a period of seconds or milliseconds rather than hours or days (Castellanos et al., 2005, Russell et al., 2006, Tamm et al., 2012). It is distinguished from systematic changes in behavior or performance related to practice, learning, development, treatment, or variations in the clinical condition (Buzy et al., 2009, Russell et al., 2006). Neurological correlates of intraindividual variability include regions implicated consistently in ADHD, including dorsolateral prefrontal, orbital frontal, and anterior cingulate cortices (Bellgrove et al., 2004, MacDonald et al., 2006). In addition, dysfunctional dopaminergic and noradrenergic neurotransmission, as well as reduced myelination and inadequate lactate transport, have been hypothesized as neurobiological mechanisms responsible for increased intraindividual variability in ADHD (Biederman and Spencer, 1999, Castellanos et al., 2005, Russell et al., 2006).

Intraindividual (i.e., within-subject) variability is indexed conventionally by reaction time (RT) dispersion during laboratory tasks. RT variability refers to inconsistency in an individual's speed of responding, measured in seconds or milliseconds, and has been argued to reflect a subset of abnormally slow responses during laboratory tasks (Klein et al., 2006, Leth-Steensen et al., 2000, Russell et al., 2006, Schmiedek et al., 2007, Tamm et al., 2012). A large body of research indicates that individuals with ADHD exhibit increased RT variability across a wide range of tasks, including tasks measuring reaction time on motor speed, choice decision, vigilance, behavioral inhibition, cognitive interference, working memory, visual saccade, and visual discrimination (e.g., Alderson et al., 2007, Buzy et al., 2009, Klein et al., 2006, Willcutt et al., 2008). In addition, RT variability has been proposed as an underlying trait (Hicks et al., 1989, Russell et al., 2006) or potential endophenotype of the disorder (Castellanos et al., 2005, Sonuga-Barke

and Castellanos, 2007).

The heightened interest in RT variability as a potential core and etiologically important feature of ADHD is reflected by the growing number of narrative summary and meta-analytic reviews on the topic within the past 8 years. These reviews focus primarily on examining two issues—the extent to which children and adults with ADHD differ from typically developing control groups in RT variability, and whether the magnitude of between-group differences is greater for this measure relative to traditional test metrics such as mean reaction time. An initial narrative review of 42 child and adult studies indicated that ADHD and control groups differed significantly in intraindividual variability in the vast majority of published studies, and that these differences were of greater magnitude relative to conventional metrics such as mean reaction time, stop signal reaction time, and errors (Klein et al., 2006). These findings, however, were based on comparing the significance levels reported between and among studies as opposed to quantifying the different outcome measures in comparable metrics (effect sizes) while controlling for study power (cf. Howard, Maxwell, & Fleming, 2000).

An initial meta-analytic review of 39 RT variability studies of children with ADHD updated the Klein et al. (2006) review, and indicated moderate-to-large magnitude ( $d = 0.71$ ) ADHD-related intraindividual variability relative to typically developing children (Willcutt et al., 2008). Four additional meta-analytic reviews examined RT variability on specific tasks or with specific subgroups. Hervey, Epstein, and Curry (2004) examined seven adult studies reporting RT variability during continuous performance tasks, and three additional meta-analyses focused exclusively on the stop signal task: Alderson et al. (2007) reviewed 12 child studies; Lijffijt, Kenemans, Verbaten, and van Engeland (2005) examined 29 child and adult studies; and Lipszyc and Schachar (2010) evaluated 38 child and adult studies reporting RT variability during stop-signal tasks. Collectively, these four meta-analytic reviews reported moderate RT variability effect sizes of 0.61, 0.73, 0.65, and 0.71, respectively; however, their interpretations and conclusions may be premature due to the limited variety of tasks and/or age groups and resultant small percentage of available studies included in the reviews (i.e., between 3% and 12% of the 319 studies included in the current meta-analytic review). In addition, none of the studies examined differences among ADHD subtypes or corrected for measurement unreliability (Hunter & Schmidt, 2004), and only Lipszyc and Schachar (2010) corrected for publication bias.

The current meta-analytic review includes 319 studies of RT variability in children, adolescents, and adults with ADHD relative to typically developing (TD) and clinical control groups across a wide range of laboratory tasks (Tables S1–S8), and corrects for measurement unreliability and publication bias (Hunter and Schmidt, 2004, Lipsey and Wilson, 2001) to address the primary limitations of previous meta-analytic reviews. A series of fundamental questions concerning the measurement and specificity of RT variability, and the degree to which it is modifiable by pharmacological or motivational interventions are also addressed in the review.

Three fundamental issues regarding specificity are addressed in our review to determine the extent to which RT variability (a) is unique to one or more of the three ADHD subtypes, (b) differs between individuals with ADHD relative to typically developing groups, and (c) represents a performance pattern characteristic of other clinical disorders rather than being unique to ADHD. The specificity of RT variability for the three ADHD subtypes (Inattentive, Hyperactive/Impulsive, and Combined subtypes) is addressed initially to determine whether its occurrence is limited to one or more of the three ADHD subtypes. The results of these analyses also have potential implications for interpreting studies that collapse data across ADHD subtypes when comparing them with typically developing and clinical control groups (e.g., between-group effect size differences may be deflated if RT variability is limited to a single ADHD subtype).

Studies comparing ADHD to typically developing and other clinical disorder groups are analyzed subsequently to address issues related to the potential specificity of RT variability (Zakzanis, 2001). The specificity of RT variability to ADHD is key, given the myriad disorders that feature clinically impairing attention problems and/or impulsive behavior (cf. Youngstrom, Arnold, & Frazier, 2010). An initial, selective meta-analytic review indicated that RT variability was not specific to ADHD, but rather a common feature of many different childhood disorders (Willcutt et al., 2008). This review, however, included only a small subset of currently available studies (12%), and did not directly compare ADHD to clinical control groups. Recent studies comparing children with ADHD to children with other clinical disorders are equivocal, with studies reporting decreased (Geurts et al., 2008), similar (Oosterlaan & Sergeant, 1995), or increased (O'Brien et al., 1992) RT variability in children with ADHD. Substantive differences exist across studies (e.g., comparison groups, diagnostic methods), however, and these differences must be investigated systematically via meta-analysis to determine the specificity of increased RT variability in ADHD.

Early studies relied primarily on global measures of RT variability such as standard deviation (SD) and standard error (SE), and these metrics remain the most common indices of RT variability despite their well-documented conceptual and statistical limitations (Castellanos et al., 2005, Geurts et al., 2008, Leth-Steensen et al., 2000, Schmiedek et al., 2007). For example, global measures of RT dispersion such as SD correlate highly with measures of overall mean reaction time (MRT;  $r = .92$ ; Wagenmakers & Brown, 2007). In ADHD studies, correlations between MRT and SD of RT (SDRT) range from .70 to .90 (Epstein et al., 2003, Spencer et al., 2009), and medication-related improvements in these metrics are also highly correlated ( $r = .80$ ; Spencer et al., 2009). These correlations imply multicollinearity in measurement (Tabachnick & Fidell, 2007), and question the extent to which the MRT and SD variables are measures of the same underlying construct (Klein et al., 2006).

Several authors have calculated dispersion around mode RT, or computed the coefficient of variability (CV) to address this issue. CV is a metric that reflects global variability after accounting for overall reaction time ( $CV = SDRT/MRT$ ). The resultant metric is uncorrelated with mean reaction time, and has been argued to be a more appropriate index of RT variability (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005). The CV metric (like SD and SE) rests on the assumption that reaction times are normally distributed, however, which does not appear to be the case (Castellanos et al., 2006, Schmiedek et al., 2007). Specifically, reaction time distributions tend to be positively skewed, especially for individuals with ADHD, as a result of a subset of abnormally slow responses (Castellanos et al., 2006, Schmiedek et al., 2007). In addition, critics of this approach argue that it removes variance attributable to SDRT from SDRT (Klein et al., 2006). To address this issue, some researchers have used ex-Gaussian or spectral power-based/signal processing methods, which attempt to dissect global variability based on disparate assumptions.

Ex-Gaussian methods are preferable when RT variability results from a randomly occurring subset of abnormally slow responses. This method separates each child's RT distribution into exponential ("Ex-") and normal (Gaussian) components. Within the normal component, this approach provides estimates of mu ( $\mu$ ) and sigma ( $\sigma$ ). Mu reflects the mean reaction time of the normal distribution, and sigma reflects the variability of this normal component. If a child's RTs are normally distributed, then mu and sigma will equal MRT and SDRT, respectively, and tau ( $\tau$ ) will equal zero. Tau reflects the exponential component of the RT distribution, and reflects the subset of extremely slow responses that otherwise have a strong influence on MRT and SDRT calculation. Tau

is similar conceptually to a distribution's skewness, but is considered a more reliable metric (Schmiedek et al., 2007).

In contrast, signal processing methods are preferred when RT variability results from nonrandom, periodic fluctuations whose rhythmicity will be reflected in increased power to specific spectral bands. Conceptually, signal processing methods examine the temporal pattern of a RT series to determine if the abnormally long RTs identified by other methods occur in a predictable, temporal sequence (Castellanos et al., 2005, Geurts et al., 2008). Recent studies, however, have questioned the veracity of conclusions based on power in specific frequency bands. For example, task characteristics (e.g., interstimulus intervals, stimulus predictability) and the choice of task appear to influence the peak frequency band that will be obtained (Johnson et al., 2007). In addition, Geurts et al. (2008) demonstrated that small changes in data preparation, method of spectral estimation, and subset of trials analyzed can significantly impact the peak frequency band obtained.

In summary, although many studies have utilized multiple RT variability indices, the relative sensitivity of these correlated but theoretically dissimilar methods for detecting ADHD-related variability remains unknown. The current meta-analysis addresses this issue by examining the extent to which the metric used to estimate RT variability moderates the magnitude of between-group effect sizes. This analysis will allow us to determine whether specific metrics are better able to differentiate individuals with ADHD from other groups, or whether the additional complexity of ex-Gaussian and spectral-based analyses fails to result in larger effect sizes (Spencer et al., 2009).

Researchers disagree regarding whether ADHD-related RT variability occurs randomly, or coincides temporally with periodic fluctuations in underlying physiological or neuronal processes (Castellanos et al., 2005, Geurts et al., 2008). The answer to this question has potentially important implications for ADHD treatment and etiological models. For example, discovering that RT variability results from predictable fluctuations in performance over time and is unique to ADHD could inform the development of novel interventions and important targets for outcome assessment. Periodic performance fluctuations would have direct implications for etiological models of ADHD to the extent that these fluctuations could be linked with coinstantaneous physiological and neuronal processes. Although this link remains hypothetical in humans, preliminary evidence of neuronal and behavioral synchronization in rats makes this a compelling possibility

(Castellanos et al., 2005).

The current meta-analysis synthesizes extant studies employing spectral power-based analyses of RT data and compares findings for specific power spectrums relative to global spectral power (power across all measured bands) across studies. Convergent findings of increased RT variability in specific spectral bands would provide compelling support for etiological models such as the default mode network model (Sonuga-Barke & Castellanos, 2007). In contrast, equivocal results across studies and peak frequency band effect sizes approximating effect size magnitude of other RT variability indices would contradict hypotheses regarding predictable, periodic fluctuations in performance (Geurts et al., 2008).

If intraindividual variability is a ubiquitous characteristic of ADHD (Klein et al., 2006, Russell et al., 2006) it should be observable across tasks, contexts, and states. Initial reviews suggest that children with ADHD demonstrate increased intraindividual variability across a wide range of tasks (Lipszyc and Schachar, 2010, Tamm et al., 2012, Willcutt et al., 2008). In addition, a factor analysis of laboratory tasks indicated that RT variability appears to be best characterized as a single factor in children with ADHD, suggesting that it could reflect a stable characteristic despite considerable differences in task demands (Klein et al., 2006). Studies manipulating task characteristics such as working memory demands and inter-stimulus intervals (Buzy et al., 2009, Epstein et al., 2006) report conflicting results and limit conclusions that RT variability represents a stable neurocognitive deficit in ADHD. For example, Klein et al. (2006) reported that RT variability across a wide variety of tasks loaded on a single factor for children with ADHD, whereas Tillman, Thorell, Brocki, and Bohlin (2008) reported a nonsignificant relation between RT variability metrics on two commonly used laboratory tasks ( $r = .03$ , *ns*). These conflicting findings suggest that environmental factors (e.g., task demands) may significantly moderate the magnitude, if not the appearance, of increased intraindividual variability in ADHD. The current meta-analysis examines whether intraindividual variability is a ubiquitous feature of ADHD by analyzing between-study heterogeneity and potential moderators to examine the extent to which task factors and internal physiologic and/or cognitive states (e.g., treatment, motivation/incentive effects) may impact the association between ADHD and RT variability.

*RT variability and ADHD symptoms.* If RT variability reflects a core neuropsychological deficit in ADHD, it should predict ADHD behavioral symptoms and functional



impairments. In this regard, the results to date are equivocal. For example, divergent results indicate that RT variability is related to both inattention and hyperactivity/impulsivity (Epstein et al., 2003), inattention only (Wåhlstedt, Thorell, & Bohlin, 2009), hyperactivity only (Buzy et al., 2009), or the interaction between inattention and hyperactivity (Clarke et al., 2007). In addition, RT variability is frequently attributed to periodic lapses in attention (e.g., Hervey et al., 2006); however, Schmiedek et al. (2007) investigated this claim and concluded that attentional lapse models could not account for RT variability. Similarly, Epstein et al. (2010) found that temporal performance-based indices of inattention (omission errors) and behavioral inhibition (commission errors, successful inhibitions) could not account for ADHD-related impairments in RT variability (Cohen's  $d$  changed minimally, from .78 to .70). The present meta-analytic review addresses this issue by examining heterogeneity among ADHD subtypes and comparing obtained effect sizes to estimate the extent to which RT variability is related to inattentive, hyperactive/impulsive, or both symptom clusters.

Studies examining the relation among neurocognitive impairments have direct implications for etiological models of ADHD. Extant models make specific, divergent predictions regarding the role of RT variability in ADHD (Table 1). The evidence to date, however, is incomplete and equivocal. For example, Schmiedek et al. (2007) found that RT variability was strongly related to working memory and higher-order reasoning ( $r = -.71$  to  $-.72$ ), as well as processing speed ( $r = -.58$ ). There is contradictory evidence, however, regarding whether RT variability is affected by manipulating working memory demands in children with ADHD (Buzy et al., 2009, Klein et al., 2006). For example, Finke et al. (2011) concluded that their findings supported working memory model (Rapport et al., 2001) predictions regarding the role of working memory deficits, rather than perceptual processing or energetic factors, as etiological factors underlying increased RT variability in ADHD. In contrast, Verté, Geurts, Roeyers, Oosterlaan, and Sergeant (2006) indicated that working memory, response inhibition, and RT variability are distinct but related cognitive domains. In another study, RT variability was influenced by a host of cognitive processes, including visual processing, working memory, response selection and preparation, and response execution/motor response, whereas RT variability did not predict ADHD-related impairments in processing speed (Jacobson et al., 2011). In contrast, motivational/volitional control factors have been found to be related (Andreou et al., 2007, Kuntsi et al., 2009) and unrelated (Aase et al., 2006, Epstein et al., 2011) to RT variability, and findings regarding behavioral inhibition are similarly equivocal (Buzy et

al., 2009, Epstein et al., 2010, Lipszyc and Schachar, 2010). The current meta-analysis addresses this issue by examining heterogeneity in RT variability effect sizes, and testing the extent to which any between-study heterogeneity is attributable to several model-implied moderators (e.g., behavioral inhibition task demands, effects of incentives).

The clinical model of psychopathology hypothesizes that interventions aimed at improving suspected underlying neurological substrate(s) and core psychological/cognitive features of ADHD should produce the greatest level and breadth of therapeutic change (National Advisory Mental Health Council's Workgroup, 2010, Rapport et al., 2001). Interventions aimed at peripheral behaviors, on the other hand, should show limited generalization upward to core features, and minimally affect other peripheral symptoms. For this reason, a key test of RT variability's role as an ADHD core deficit will be the extent to which pharmacological and psychosocial treatments known to improve ADHD behavioral symptoms also decrease RT variability. Studies of medication effects on RT variability in ADHD are equivocal to date, with studies reporting significant (Heiser et al., 2004, Teicher et al., 2004) and nonsignificant (Aggarwal and Lillystone, 2000, van der Meere et al., 1999) treatment-related changes. The current meta-analysis addresses this issue by examining the magnitude of treatment-related changes in RT variability relative to baseline and placebo conditions, and the extent to which treatment type is a significant moderator of this relationship.

The performance of individuals with ADHD across a wide range of laboratory tasks has long been characterized as *slower* and more variable. Several previous meta-analytic reviews have examined mean reaction time (MRT), and consistently reported small-to-moderate effect sizes ranging from 0.29 to 0.66 (Alderson et al., 2007, Frazier et al., 2004, Lijffijt et al., 2005, Lipszyc and Schachar, 2010, Oosterlaan et al., 1998). However, MRT is influenced heavily by RT variability (Schmiedek et al., 2007, Wagenmakers and Brown, 2007), and several studies suggest that the MRT of children with ADHD is not slower than their peers after accounting for RT variability using ex-Gaussian methods (e.g., Buzy et al., 2009, Epstein et al., 2003). These findings could be related to study power, however, and a meta-analytic approach is needed to determine the magnitude of MRT differences after accounting for RT variability. Specifically, the current meta-analysis can test the extent to which children with ADHD demonstrate slower MRT after accounting for RT variability by examining studies using ex-Gaussian estimation (i.e.,  $\mu$ , which reflects MRT after accounting for variability in both the normal and exponential components of the RT distribution) and/or reporting MRT after accounting for RT variability (e.g.,

ANCOVA). Obtained effect sizes can be compared to studies examining the opposite relationship—RT variability after controlling for MRT (i.e., tau and CV metrics)—to draw conclusions regarding the presence of ADHD-related impairments in one or both of these neurocognitive indices (processing speed, variability).

In summary, the current meta-analysis is a comprehensive review of 319 studies reporting on reaction time variability in children, adolescents, and adults with ADHD relative to (a) typically developing groups, (b) clinical control groups, and (c) themselves (i.e., subtype comparisons, treatment and motivation effects). Through meta-analytic synthesis, analysis, adequately powered moderator investigation, and best case analysis, the current review seeks to inform current debate regarding the veracity of RT variability as an ADHD core deficit, with implications for the evaluation of etiological models and treatment interventions for children and adults with ADHD.

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## Section snippets

### Literature searches

A three-phase literature search was conducted using Medline, PubMed, PsycInfo, PsycArticles, PsycBooks, ERIC, Dissertation Abstracts International, and Social Science Citation Index. Search terms included permutations of the ADHD diagnostic label (ADHD, ADD, attention deficit, attention problems, inattent\*, hyperact\*, hyperkinesis, minimal brain dysfunction/damage, MBD), variability, reaction time (RT), variability metrics (SDRT, coefficient of variation, CV, sigma, tau, RT of SE, Slow-\*,...

### Overview

Five datasets (Tiers) were created to address the primary questions raised in the Introduction. In Tier I, ADHD subtypes are compared to inform inclusion criteria for subsequent analyses. Tier II examines questions related to comparisons of individuals with ADHD to typically developing individuals, whereas Tier III addresses specificity questions involving comparison of ADHD groups to groups with other forms of psychopathology (clinical control groups). Tier IV addresses treatment and...

## Discussion

Individuals with ADHD are described frequently as ubiquitously *slower and more variable* than their unaffected peers, and ADHD-related reaction time (RT) variability is considered by many to reflect a unique, stable, and etiologically important characteristic of the disorder. The present review critically evaluated these claims through meta-analytic synthesis and analysis of the 319 published and unpublished studies of RT variability in children, adolescents, and adults with ADHD relative to...

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Neuropsychologia (2005)

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# Mapping causal links between prefrontal cortical regions and intra-individual behavioral variability ↗

2024, Nature Communications



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- 7 Studies included in the meta-analysis but not cited in the text are listed in the Appendix and Tables S1-S8

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