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Reaction Time Variability in ADHD: A Review

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Abstract For the past decade, intra-individual variability in reaction times on computerized tasks has become a central focus of cognitive research on Attention-Deficit/Hyperactivity Disorder (ADHD). Numerous studies document increased reaction time variability among children and adults with ADHD, relative to typically developing controls. However, direct comparisons with other disorders with heightened reaction time variability are virtually nonexistent, despite their potential to inform our understanding of the phenomenon. A growing literature examines the sensitivity of reaction time variability to theoretically and clinically relevant manipulations. There is strong evidence that stimulus treatment reduces reaction time variability during a range of cognitive tasks, but the literature is mixed regarding the impact of motivational incentives and variation in stimulus event rate. Most studies of reaction time variability implicitly assume that heightened reaction time variability reflects occasional lapses in attention, and the dominant neurophysiological interpretation suggests this variability is linked to intrusions of task-negative brain network activity during task performance. Work examining the behavioral and neurophysiological correlates of reaction time variability provides some support for these hypotheses, but considerably more work is needed in this area. Finally, because conclusions from each of domains reviewed are limited by the wide range of measures used to measure reaction time variability, this review highlights the need for increased attention to the cognitive and motivational context in which variability is assessed and recommends that future work always supplement macro-level variability indices with metrics that isolate particular components of reaction time variability.

Keywords reaction time variability · response variability · intra-individual variability · ADHD · attentional processes · coefficient of variation

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders [1]. Children with ADHD show cognitive impairments in attention, inhibitory control, and working memory compared with typically-developing children [2–4] but no specific cognitive impairment is universal across patients with ADHD. One of the more consistent findings in the ADHD neuropsychology literature is increased reaction time variability (RTV), also known as intra-individual variability, on computerized tasks [5]. Elevated RTV among individuals with ADHD compared with typically-developing children has been documented across multiple studies using a wide variety of computerized tasks, including those assessing working memory [6–8], attention [9], inhibitory control [8, 10–13], and choice discrimination [14]. These ADHD between-group differences on RTV tend to be larger in magnitude than most other neuropsychological indicators [15]. In addition, increased RTV has been documented in both pediatric [16, 17] and adult ADHD samples [18, 19].

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Although there is clear evidence that, compared to healthy controls, ADHD is characterized by greater intra-individual RTV during cognitive tasks, ADHD is not alone in this respect. Elevated RTV has been observed in individuals with high functioning autism [20], schizophrenia [21], bipolar disorder with psychotic symptoms [22], traumatic brain injury [23–26], and early stage Alzheimer's dementia [27, 28]. One commonality among these various populations with increased RTV are problems with attention, although there seems to be considerable variability in the types of attentional difficulties across populations (e.g., selective [29, 30], sustained [29], and divided attention [31], and combinations of these).

This consideration of nuances in attentional processes across diagnostic groups raises the question of what specific aspect of attention RTV reflects. In ADHD research, RTV in ADHD is typically interpreted (at least implicitly) as reflecting occasional lapses in attention (i.e., failures of sustained attention that are not severe enough to result in an error of omission) [10, 32, 33]. However, the precise psychological and neurophysiological meaning of RTV in ADHD is continually being debated. Hypotheses emphasizing several factors have been proposed: a temporal processing deficit [34], a deficit in the ability to appropriately modulate very low-frequency fluctuations in neuronal activity [35], inefficiency in the deployment of attention by executive control processes [36], deficit of sustained attention [10, 32], and difficulties with the regulation of energetic state [14, 37–39]. Importantly, these are not mutually exclusive hypotheses. Work that pits alternative hypotheses against 1 another and/or integrates multiple perspectives is an important area for future work on RTV in ADHD. Work that includes a clinical control group would be particularly informative.

This brief consideration of fine-grained models of attention in psychopathology and hypotheses as to the meaning of RTV in ADHD raises the question of whether RTV itself reflects a single construct or process. The vast majority of studies documenting increased RTV in ADHD have used a reaction time standard deviation (RTSD), which is often used because it is easy to compute. Unfortunately, RTSD almost always correlates quite highly (e.g., $r=0.90$; [17]) with the mean reaction time [18, 40, 41] that 1 cannot distinguish speed and variability limiting the clarity of the psychological or neurophysiological interpretation. For this reason, some advocate using the coefficient of variation (CV), with CV = RTSD/mean reaction time) [40]. However, both RTSD and CV face a second obstacle. They are too molar to provide information regarding specific aspects of the RTV construct, particularly the asymmetrical positive skew that occasional lapses in attention, which would be expected to produce.

For the past decade, the field has slowly begun to move toward more sophisticated metrics of RTV, and that effort has brought new insights. In a seminal study, Leth-Steensen et al. [32] used ex-Gaussian modeling to generate separate measures of the mean (mu) and standard deviation (sigma) of the normal (Gaussian) component of the RT distribution and a measure of variability for the exponential component of the RT distribution (tau). Research using ex-Gaussian parameters has shown that ADHD-related RTV is largely the result of an elevation in tau [10, 13, 32]. Higher tau values are produced by RT distributions with a larger rightward skew or tail, consistent with a lapse of attention framework. Alternative metrics that do not require that ex-Gaussian assumptions have also been developed (for more detail, see Sabol et al. [42] and Spencer et al. [43]), and further work in this area will be critical for developing a consensus of RTV estimation. It should also be noted that 1 study, using ex-Gaussian parameters, reported significant differences, albeit with a small effect size (0.08) between ADHD and control groups in the fast portion of the RT distribution, which was interpreted as reflecting different causal mechanisms for the potentially multidimensional construct of RTV [44].

In addition to RT distribution models, there is good reason to consider the periodicity of long RTs in the frequency domain [9, 13, 35]. Such analysis may help bridge our understanding of the neurophysiological correlates of RTV in ADHD. In particular, the temporal patterns of long RTs may provide us with a better understanding of long RT manifestation. For example, an oscillating pattern of long RTs that manifest periodically at 20 seconds, as reported by Castellanos et al. [35], might indicate the length of attention before attention lapses. Such temporal patterns would be useful in the continued search for the underlying pathophysiology of ADHD-related attentional deficits (e.g., neuroenergetics; for more detail, see Russell et al. [45]). Unfortunately, there have been very few studies that have examined the periodicity of long RTs, and results from these studies have been mixed in regard to the frequency at which long RTs occur [9, 13, 35, 46].

Although the ideal metrics of RTV are not yet clear, it is becoming increasingly clear that relying solely on RTSD or CV is not advisable. However, because the vast majority of previous studies have done this, we include those studies in the remainder of the review, but wherever possible we emphasize studies that included more precise indicators.

Behavioral Correlates

The relationship between RTV and ADHD symptoms, as well as whether there are differences between the ADHD subtypes (typically ADHD-Combined Type *vs* ADHD-Inattentive Type) on RTV parameters, has been the subject of numerous studies. Determining whether there are indeed associations between RTV and specific ADHD-related behavior is important, especially because RTV has been purported to indicate mostly attention-related behavioral and cognitive states in the literature (e.g., attentional lapses, sustained attention). Regarding the differences between ADHD subtypes on RTV in the research conducted to date, there are few, if any, differences in RTV across the ADHD subtypes [13, 47–51]. Only a few exceptions exist, with some reporting greater RTV among children with ADHD-Combined Type compared with ADHD-Inattentive Type on certain tasks [41]. Where relations between RTV and the ADHD symptom domains have been examined, RTV has correlated with measures of behavioral inattention [48, 52, 53] but has also been found to correlate with hyperactivity-impulsivity in a minority of studies (for more detail, see Gomez-Guerrero et al. [54]). In a study examining whether RTV was specifically correlated with individual ADHD symptoms (e.g., short attention span), significant relations were observed between RTV and all 18 ADHD symptoms, suggesting no specificity between RTV and specific ADHD behaviors [55]. Research examining relations between RTV and the ADHD symptom domains or ADHD subtypes has not been convincingly associated with either ADHD symptom domain or any specific ADHD symptoms, although relations between RTV and inattention seem to be more consistent in the literature [48, 52, 53].

Finally, because it appears that RTV is the result of intermittent long RTs, examining behaviors that occur concomitantly or proximally with long RTs might give us some insight into behavioral correlates of RTV. Epstein et al. [33] conducted a study examining whether instances of long RT could be predicted by task events. Children with ADHD demonstrated pronounced slowing (i.e., long RTs) on the trial before an omission error, as well as slowing, although not nearly as pronounced, on trials following an omission error. Thus, long RTs seem to be part of a similar cognitive process that surrounds omission errors. Omission errors occur when a patient does not respond to a target stimulus and has been linked to attentional lapses [56], thus suggesting that long RTs, the primary cause of RTV, are due to inattention. Consistent with this interpretation, Spencer et al. [43] observed that the effect of acute methylphenidate on RTV in a simple choice discrimination task was moderately correlated with the effect of the same medication in being able to reduce omissions on a separate continuous performance task.

Research that would be helpful in investigating behavioral correlates of RTV are studies that examine actual behavior (e.g., visual gaze) during actual instances of long RTs or which relate patterns of observed behavioral attention to RTV (for more detail, see Rapport et al. [57]). For example, during instances of long RTs, are patients disengaged or distracted from the task at hand? Furthermore, rather than examining the 2 ADHD symptom domains, it would be interesting to examine whether sluggish cognitive tempo (SCT) accounts for significant variance in predicting RTV, because some of the core characteristics of SCT (e.g., slow movement, daydreamy) seem related to RT and RTV.

Neurophysiological Correlates of RTV

RTV-Related Neuroimaging Findings Using Typically Developing Controls

Morphometric neuroimaging studies have examined volumetric correlates of RTV. Among typically developing controls, an association between RTV and reduced white matter volume [58] has been reported. Moreover, several studies have also demonstrated that adults with lesions to the frontal lobes tend to have higher RTV than controls and adults with lesions to other brain areas [59, 60]. Finally, RTV has been associated with a higher proportion of white matter hyperintensities (i.e., small regions of high intensity observed on magnetic resonance imaging) across the frontal regions [61]. These structural studies clearly implicate a frontal lobe pathophysiology for RTV.

In regard to associations with functional activation, studies have examined correlations between RTV during cognitive performance and brain activation, as measured by functional magnetic resonance imaging (fMRI) [36, 62]. A consistent trend has emerged whereby higher RTV correlates with higher levels of frontal activation during tasks [36, 62, 63], specifically, in the middle frontal regions [36], the medial frontal cortex, frontal operculum, lateral and anterior prefrontal cortex [63], and rostral supplementary motor area [62]. It is interesting that individuals with lower RTV tend to display increased activation in motor areas [62], suggesting that reliance on more efficient networks, such as premotor circuitry rather than higher order cognitive networks, reduces RTV. Such correlational studies suggest an overall pattern of higher frontal lobe activation, particularly the rostral supplementary motor area, but do not specifically link instances of long RTs to increased frontal lobe activity. However, using an event-related design, Weissman et al. [64] did examine brain activation around long RTs and found that instances of intermittent long RTs were associated with decreased activity in the frontal cortex *prior* to stimulus presentation. It is not clear why correlational studies find increased frontal lobe activity correlated with RTV, whereas this event-related study found decreased frontal lobe activity during instances of long RT.

Another intriguing RTV-related functional imaging finding is increased activity in the posterior cingulate, precuneus, and middle temporal gyrus at the time of stimulus presentation during long RT trials [64]. These regions are part of the putative default mode network (DMN), a network of regions activated during rest. The DMN is considered a task negative network because it must be suppressed concomitant with activation in the task positive network (i.e., the neural network required to perform the cognitive task at hand). Brain activation in the DMN is negatively correlated with activation in task positive regions [65–67] and positively correlated with RT fluctuations [68]. Although this literature is still developing, preliminary findings suggest that the inability to sufficiently suppress the DMN leads to inconsistent performance (i.e., increased RTV).

To date, neuroimaging research has linked RTV to both abnormalities in frontal lobe volumes and brain activation, as well as what appears to be insufficient suppression of the DMN. Poor signal-to-noise ratios in neural transmission may explain RTV. Signal-to-noise ratios are affected by an inability to consistently suppress the DMN, which interferes with task positive activation if it remains activated during cognitive performance, [69]. To overcome an active DMN, individuals must allocate more effort to the task positive network, which in the case of executive functioning and/or attentional tasks, involves frontal regions. We therefore observe a correlation between increased activation in these frontal regions and increased RTV.

This signal-to-noise explanation converges with the actual RT patterns we observe in individuals with ADHD. That is, the majority of RTs for both ADHD and non-ADHD populations tend to be within the normal range. However, intermittently dispersed in the RT stream are instances of periodic long RTs. Using a signal-to-noise explanation, these periodic long RT instances may be brief periods of time when signal-to-noise ratios in the brain do not favor task positive networks. That is, either because task-negative networks are temporarily unable to be suppressed or because task-positive networks lose intensity, the signal-to-noise ratio decreases, and the behavioral manifestation of this loss in signal/increase in noise is a long RT.

ADHD Neuroimaging Literature

Because patients with ADHD consistently demonstrate higher levels of RTV than controls, predictions can be made regarding ADHD-related neurophysiological patterns. Specifically, we expect to see indications of neural inefficiencies among individuals with ADHD (i.e., lower signal-to-noise ratios). Such lower signal-to-noise ratios could be related to a lower intensity task-positive network (i.e., low signal) and/or a higher intensity DMN (i.e., high noise).

Regarding DMN, resting-state fMRI provides a measure of task-negative or DMN brain activity. In general, individuals with ADHD display significantly higher resting state activation [70, 71] and reduced DMN homogeneity [72–76]. Children with ADHD have also been shown to be less able to deactivate the DMN than controls, and this inability to deactivate the DMN has been directly related to RTV [77]. The task-negative network among individuals with ADHD is of higher intensity and likely dysfunctional in terms of connectivity. Hence, those with ADHD require additional cognitive effort to suppress the higher intensity, less coordinated DMN activity than those without ADHD.

In terms of task-positive activation among individuals with ADHD, there is a large and expanding ADHD functional imaging literature [78–81]. Although behavioral paradigms vary widely across studies, the vast majority of studies have demonstrated decreased activation during cognitive performance among patients with ADHD compared with controls, especially in the frontal lobes [81]. Also, 1 correlational fMRI study found that higher RTV was associated with decreased activation of the prefrontal cortex in those with ADHD [82]. This trend for decreased frontal task-positive activation is antithetical to what has been found in the RTV neuroscience literature, which was a positive relationship between frontal activation and RTV. One explanation for this set of results is that individuals with ADHD possess dual deficits such that not only do individuals with ADHD have more active task-negative activation at rest, but they also have less task-positive activation during cognitive performance. As a result, task-negative activation overcomes task-positive activation more frequently, which leads to intermittent long RTs and thus higher levels of RTV.

Reaction Time Variability Manipulations

In an effort to better understand increased RTV among patients with ADHD, investigators have varied task parameters to examine what the conditions were that the patients with ADHD evidenced increased RTV. For example, the event rate (ER) or speed at which stimuli appear on the screen has been varied within tasks. Generally, RTV decreases during faster ERs for all children [41, 83, 84]. Most studies report that ADHD-related increases in RTV disappear are attenuated, and often disappear, during faster ERs [39, 83, 85, 86]. Alternatively, long ERs, relative to what is optimal for the task, appear to exacerbate ADHD-related between-group differences [14, 85]. One explanation for this pattern of effects is provided by the state regulation dysfunction model, which suggests that short ERs may increase activation states, whereas long ERs may lead to underactivation (for more detail, see van der Meere et al. [86] and Sergeant [83]). Hence, quickening the pace of the task creates a raised energetic state among children with ADHD, thereby normalizing RTV. This set of results is corroborated by studies that have found that varying the ER on a trial-by-trial basis also seems to reduce ADHD-related increases in RTV [87, 88]. Similar to the argument that speeding the ER increases the energetic state, a variable ER is believed to create a higher state of vigilance, thereby keeping individuals, including those individuals with ADHD “on their toes” while performing the task [89]. Although an explanation using the state regulation dysfunction model is appealing, it is also possible that these effects of ER on RTV effects in ADHD can be explained methodologically (e.g., fast ERs limit RTs [15]) or using other models (e.g., delay aversion [85]).

Researchers have also examined the effects of task contingencies on RTV with mixed results. Some studies have found that ADHD-related increases in RTV are attenuated when rewards for performance are provided [12, 14, 90–92], whereas others have not found this effect of reward [49, 93]. Two studies in the literature have suggested that combining fast ER and reward can synergistically improve RTV [14, 91]. Still another study suggests the effects of reward may be task-specific because reward improved performance only on tasks require inhibition [41].

ERs and rewards are both task manipulations that target the energetic and motivational states of the individuals. Although it is well-documented that speeding the ERs attenuates ADHD-related RTV differences, research on the effects of the reward is quite mixed, possibly because the effects of incentives are not robust or because the magnitude, saliency, or targets of incentives applied has varied considerably across studies. Future studies examining the effects of the reward should pay particular attention to conditions of the reward and should attempt to provide immediate, as opposed to delayed, reinforcement [94]. In addition, it would be informative to tie incentives to the patient's performance on RTV (e.g., maintaining RTs within a specific RT range) rather than accuracy or RT speed. Indeed, preliminary evidence suggests that the strong, immediate rewards for task performance that improve spatial working memory to the same extent as stimulant medication [95] are similarly effective in reinforcing fast, consistent responses in children with ADHD [96].

Effects of Stimulant Medication on RTV in ADHD

The effects of stimulant medication (i.e., the most common and effective treatment for ADHD) on RTV has also been examined in multiple studies. In general, ADHD-related increases in RTV are attenuated, and may even normalize, with stimulant medication [35, 41, 43, 97–102]. In a recent investigation of medication effects on RTV, which included a range of cognitive tasks, Epstein et al. [41] found that stimulant medication reduced RTV on a range of cognitive tasks. In addition, results showed the effects of medication were of the largest magnitude and most consistent for RTV indicators, especially ex-Gaussian tau, compared to other performance indicators, such as RT speed and task accuracy. These results suggest that medication specifically reduces intermittent long RTs, which is consistent with other studies showing that medication reduces tau [100] and reduces the peak and skew of RT distributions [43]. Also, most studies using fast Fourier transform (FFT) analyses have demonstrated that stimulant medication attenuated [35] or normalized [103] long RT oscillations in individuals with ADHD compared with controls, although 1 study failed to replicate this effect [104].

In summary, findings from traditional measurements of RTV, as well as those using ex-Gaussian and FFT techniques, show that stimulant medication attenuates between group RTV differences. There is also converging evidence that medication has a more robust effect on RTV compared to other cognitive indicators. Medication effects on ex-Gaussian tau and FFT indicators suggest that medication specifically reduces positive distributional skew likely by decreasing the number, frequency, and/or magnitude of intermittent long RTs. A direction for future research is to examine and compare whether other evidence-based ADHD pharmacological interventions (e.g., atomoxetine, guanfacine) demonstrate a similar pattern of effects on RTV outcomes. Such research has the potential to illustrate possible differential mechanisms of action across ADHD medicines.

Summary and Future Directions

RTV is, at the group level, clearly greater among children with ADHD than among typically developing controls. Although RTV is characteristic of ADHD, it also appears to be characteristic of other populations, including autism spectrum disorders, schizophrenia, and traumatic brain injury, and has been commonly observed in the aging [105, 106] and dementia [27, 28] populations. Although we conclude that RTV is not necessarily unique to ADHD, future studies examining similarities and differences in patterns of RTV across populations need to retreat from using RTSD, which is potentially confounded by being a measure of central tendency, and use more in-depth and specific methods to characterize RTV. Ex-Gaussian analyses and FFT are 2 such approaches, but fractal analyses [107] or diffusion model approaches [108, 109] may also be useful. It is likely that although increased RTV is present across populations, the characteristics of RTV across populations is likely different. For example, in a study using ex-Gaussian indicators, McAuley et al. [110] demonstrated that older adults differed from young adults on both ex-Gaussian variance indicators, sigma, and tau, suggesting that RTV in older adults is due to both variable responding (sigma) and extreme responding (tau), as opposed to patients with ADHD for whom RTV is composed primarily of extreme responses, tau.

It remains to be seen whether RTV is a cause or a consequence of psychological or physiological processes. At the cognitive level, RTV likely reflects impairments in information processing and, more specifically, a dysfunction related with a failure to maintain attentional control [36]. Neurophysiological data suggest that the neurological basis for RTV is related to frontal lobe dysfunction, and RTV might be a sensitive marker for the efficiency of top-down attention control. Although there is some promising data regarding the neurophysiological basis for RTV in typically developing populations, there are many fewer neuroimaging studies specifically investigating the phenomenon of RTV in ADHD. Thus, additional studies investigating morphometry, structural and functional connectivity, and functional activation patterns in relation to RTV would be helpful. Studies using physiological measures, such as electroencephalograms, electrocardiograms, or electro-oculographic recordings, in conjunction with measuring RTV could also be useful in elucidating the construct it reflects.

It will also be critical to conduct studies that document the relationship between RTV and cognitive and behavioral characteristics that it is hypothesized to reflect in attempting to define what RTV is in relation to ADHD. For example, it would also be helpful to investigate relations between observable behavior and RTV, especially if the 2 could be measured simultaneously, thereby allowing linkages between actual behavior during instances of long RTs, which appears to be the primary cause of RTV for patients with ADHD.

Although there is still a very small literature in regard to treatment effects, the results of several studies are consistent in suggesting that stimulant medication reduces RTV, including narrow-band measures of RTV (i.e., ex-Gaussian tau), which focus on the skew of the RT distribution. Expanding this demonstration of medication effects on RTV to other evidence-based medications would help in understanding the mechanism by which different medications exert their effect in patients with ADHD. The findings for incentive manipulations, an analogue of behavioral treatment, suggest modest impact on RTV in ADHD; however, preliminary evidence suggests that stronger and more immediate incentives may have effects on RTV that are comparable to that of stimulant medication. Finally, there is a burgeoning literature on cognitive training in ADHD [111, 112], and it is possible that cognitive training can also target RTV [113]. Reducing RTV in the laboratory will be an exciting area of study for the next wave of research on variability in ADHD. It will be incumbent on those studies to also document that reductions in RTV on laboratory tasks are also associated with clinical improvement.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS. Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. Arch Pediatr Adolesc Med 2007;161:857–864.
2. Nigg JT, Casey BJ. An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. Dev Psychopathol 2005;17:785–806.
3. Solanto MV, Abikoff H, Sonuga-Barke E, et al. The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. J Abnorm Child Psychol 2001;29:215–228.
4. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry 2005;57:1336–1346.
5. Sonuga-Barke EJ, Sergeant JA, Nigg J, Willcutt E. Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: nosologic and diagnostic implications. Child Adolesc Psychiatr Clin N Am 2008;17:367–384, ix.
6. Buzy WM, Medoff DR, Schweitzer JB. Intra-individual variability among children with ADHD on a working memory task: an ex-Gaussian approach. Child Neuropsychol 2009;15:441–459.
7. Karatekin C. A test of the integrity of the components of Baddeley's model of working memory in attention-deficit/hyperactivity disorder (ADHD). J Child Psychol Psychiatry 2004;45:912–926.
8. Klein RM, Castel AD, Pratt J. The effects of memory load on the time course of inhibition of return. Psychon Bull Rev 2006;13:294–299.
9. Johnson KA, Kelly SP, Bellgrove MA, et al. Response variability in attention deficit hyperactivity disorder: evidence for neuropsychological heterogeneity. Neuropsychologia 2007;45:630–638.
10. Hervey AS, Epstein JN, Curry JF, et al. Reaction time distribution analysis of neuropsychological performance in an ADHD sample. Child Neuropsychol 2006;12:125–140.
11. Rubia K, Russell T, Overmeyer S, et al. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage 2001;13:250–261.
12. Uebel H, Albrecht B, Asherson P, et al. Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. J Child Psychol Psychiatry 2010;51:210–218.
13. Vaurio RG, Simmonds DJ, Mostofsky SH. Increased intra-individual reaction time variability in attention-deficit/hyperactivity disorder across response inhibition tasks with different cognitive demands. Neuropsychologia 2009;47:2389–2396.
14. Andreou P, Neale BM, Chen W, et al. Reaction time performance in ADHD: improvement under fast-incentive condition and familial effects. Psychol Med 2007:1–13.
15. Epstein JN, Langberg JM, Rosen PJ, et al. Evidence for higher reaction time variability for children with ADHD on a range of cognitive tasks including reward and event rate manipulations. Neuropsychology 2011;25:427–441.
16. Klotz JM, Johnson MD, Wu SW, Isaacs KM, Gilbert DL. Relationship between reaction time variability and motor skill development in ADHD. Child Neuropsychol 2011. doi:10.1080/09297049.2011.625356.
17. Desman C, Petermann F, Hampel P. Deficit in response inhibition in children with attention deficit/hyperactivity disorder (ADHD): impact of motivation? Child Neuropsychol 2008;14:483–503.
18. Adams ZW, Roberts WM, Milich R, Fillmore MT. Does response variability predict distractibility among adults with attention-deficit/hyperactivity disorder? Psychol Assess 2011;23:427–436.
19. Dhar M, Been PH, Minderaa RB, Althaus M. Information processing differences and similarities in adults with dyslexia and adults with Attention Deficit Hyperactivity Disorder during a Continuous Performance Test: a study of cortical potentials. Neuropsychologia 2010;48:3045–3056.
20. Verte S, Geurts HM, Roeyers H, Oosterlaan J, Sergeant JA. Executive functioning in children with autism and Tourette syndrome. Dev Psychopathol 2005;17:415–445.
21. Kaiser S, Roth A, Rentrop M, Friederich HC, Bender S, Weisbrod M. Intra-individual reaction time variability in schizophrenia, depression and borderline personality disorder. Brain Cogn 2008;66:73–82 [Epub 2007 Jul 2].
22. Bora E, Vahip S, Akdeniz F. Sustained attention deficits in manic and euthymic patients with bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1097–1102.
23. Segalowitz SJ, Dywan J, Unsal A. Attentional factors in response time variability after traumatic brain injury: an ERP study. J Int Neuropsychol Soc 1997;3:95–107.

24. Stuss D, Pogue D, Buckle L, Bondar J. Characterization of stability of performance in patients with traumatic brain injury: Variability and consistency on reaction time tests. Neuropsychology 1994;8:316–324.
25. Tinius TP. The intermediate visual and auditory continuous performance test as a neuropsychological measure. Arch Clin Neuropsychol 2003;18:199–214.
26. Whyte J, Polansky M, Fleming M, Coslett HB, Cavallucci C. Sustained arousal and attention after traumatic brain injury. Neuropsychologia 1995;33:797–813.
27. Duchek JM, Balota DA, Tse CS, Holtzman DM, Fagan AM, Goate AM. The utility of intraindividual variability in selective attention tasks as an early marker for Alzheimer's disease. Neuropsychology 2009;23:746–758.
28. Gorus E, De Raedt R, Lambert M, Lemper JC, Mets T. Reaction times and performance variability in normal aging, mild cognitive impairment, and Alzheimer's disease. J Geriatr Psychiatry Neurol 2008;21:204–218.
29. Egeland J. Frequency of attention deficit in first-episode schizophrenia compared to ADHD. Appl Neuropsychol 2010;17:125–134.
30. Thaler NS, Allen DN, Park BS, McMurray JC, Mayfield J. Attention processing abnormalities in children with traumatic brain injury and attention-deficit/hyperactivity disorder: differential impairment of component processes. J Clin Exp Neuropsychol 2010;32:929–936.
31. Parasuraman R, Nestor P. Attention and driving. Assessment in elderly individuals with dementia. Clin Geriatr Med 1993;9:377–387.
32. Leth-Steensen C, Elbaz ZK, Douglas VI. Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychol (Amst) 2000;104:167–190.
33. Epstein JN, Hwang ME, Antonini T, Langberg JM, Altaye M, Arnold LE. Examining predictors of reaction times in children with ADHD and normal controls. J Int Neuropsychol Soc 2010;16:138–147.
34. Toplak ME, Dockstader C, Tannock R, Toplak ME, Dockstader C, Tannock R. Temporal information processing in ADHD: findings to date and new methods. J Neurosci Methods 2006;151:15–29.
35. Castellanos FX, Sonuga-Barke EJ, Scheres A, Di Martino A, Hyde C, Walters JR. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol Psychiatry 2005;57:1416–1423.
36. Bellgrove MA, Hester R, Garavan H. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. Neuropsychologia 2004;42:1910–1916.
37. Kuntsi J, Oosterlaan J, Stevenson J. Psychological mechanisms in hyperactivity. I. Response inhibition deficit, working memory impairment, delay aversion, or something else? J Child Psychol Psychiatry 2001;42:199–210.
38. Scheres A, Oosterlaan J, Sergeant JA. Response execution and inhibition in children with AD/HD and other disruptive disorders: The role of behavioural activation. J Child Psychol Psychiatry Allied Discip 2001;42:347–357.
39. Sergeant JA, Geurts H, Huijbregts S, et al. The top and the bottom of ADHD: a neuropsychological perspective. Neurosci Biobehav Rev 2003;27:583–592.
40. Wagenmakers EJ, Brown S. On the linear relation between the mean and the standard deviation of a response time distribution. Psychol Rev 2007;114:830–841.
41. Epstein JN, Brinkman WB, Froehlich T, et al. Effects of stimulant medication, incentives, and event rate on reaction time variability in children with ADHD. Neuropsychopharmacology 2011;36:1060–1072.
42. Sabol KE, Richards JB, Broom SL, Roach JT, Hausknecht K. Effects of stimulus salience and methamphetamine on choice reaction time in the rat: central tendency versus distribution skew. Behav Pharmacol 2003;14:489–500.
43. Spencer SV, Hawk LW, Richards JB, Shiels K, Pelham WE, Waxmonsky JG. Stimulant treatment reduces lapses in attention among children with ADHD: the effects of methylphenidate on intra-individual response time distributions. J Abnorm Child Psychol 2009;37:805–816.
44. Williams BR, Strauss EH, Hultsch DF, Hunter MA, Tannock R. Reaction time performance in adolescents with attention deficit/hyperactivity disorder: evidence of inconsistency in the fast and slow portions of the RT distribution. J Clin Exp Neuropsychol 2007;29:277–289.
45. Russell VA, Oades RD, Tannock R, et al. Response variability in Attention-Deficit/Hyperactivity Disorder: A neuronal and glial energetics hypothesis. Behav Brain Funct 2006;2:30.
46. Di Martino A, Ghaffari M, Curchack J, et al. Decomposing intra-subject variability in children with attention-deficit/hyperactivity disorder. Biol Psychiatry 2008;64:607–614.
47. Huang-Pollock CL, Mikami AY, Pfiffner L, McBurnett K. ADHD subtype differences in motivational responsivity but not inhibitory control: evidence from a reward-based variation of the stop signal paradigm. J Clin Child Adolesc Psychol 2007;36:127–136.
48. Nigg JT. The ADHD response-inhibition deficit as measured by the stop task: replication with DSM-IV combined type, extension, and qualification. J Abnorm Child Psychol 1999;27:393–402.
49. Shanahan MA, Pennington BF, Willcutt EW. Do motivational incentives reduce the inhibition deficit in ADHD? Dev Neuropsychol 2008;33:137–159.
50. Pasini A, Paloscia C, Alessandrelli R, Porfirio MC, Curatolo P. Attention and executive functions profile in drug naive ADHD subtypes. Brain Dev 2007;29:400–408.
51. Solanto MV, Gilbert SN, Raj A, et al. Neurocognitive functioning in AD/HD, predominantly inattentive and combined subtypes. J Abnorm Child Psychol 2007;35:729–744.
52. Wahlstedt C. Neuropsychological deficits in relation to symptoms of ADHD: independent contributions and interactions. Child Neuropsychol 2009;15:262–279.
53. Wahlstedt C, Thorell LB, Bohlin G. Heterogeneity in ADHD: neuropsychological pathways, comorbidity and symptom domains. J Abnorm Child Psychol 2009;37:551–564.
54. Gomez-Guerrero L, Martin CD, Mairena MA, et al. Response-time variability is related to parent ratings of inattention, hyperactivity, and executive function. J Atten Disord 2011;15:572–582.
55. Epstein JN, Erkanli A, Conners CK, Klaric J, Costello JE, Angold A. Relations between Continuous Performance Test performance measures and ADHD behaviors. J Abnorm Child Psychol 2003;31:543–554.
56. Corkum PV, Siegel LS. Is the Continuous Performance Task a valuable research tool for use with children with Attention-Deficit-Hyperactivity Disorder? J Child Psychol Psychiatry 1993;34:1217–1239.
57. Rapport MD, Kofler MJ, Alderson RM, Timko TM, Jr., Dupaul GJ. Variability of attention processes in ADHD: observations from the classroom. J Atten Disord 2009;12:563–573.
58. Walhovd KB, Fjell AM. White matter volume predicts reaction time instability. Neuropsychologia 2007;45:2277–2284.
59. Murtha S, Cismaru R, Waechter R, Chertkow H. Increased variability accompanies frontal lobe damage in dementia. J Int Neuropsychol Soc 2002;8:360–372.
60. Stuss DT, Murphy KJ, Binns MA, Alexander MP. Staying on the job: the frontal lobes control individual performance variability. Brain 2003;126:2363–2380.
61. Bunce D, Anstey KJ, Christensen H, Dear K, Wen W, Sachdev P. White matter hyperintensities and within-person variability in

community-dwelling adults aged 60–64 years. Neuropsychologia 2007;45:2009–2015.
62. Simmonds DJ, Fotedar SG, Suskauer SJ, Pekar JJ, Denckla MB, Mostofsky SH. Functional brain correlates of response time variability in children. Neuropsychologia 2007;45:2147–2157.
63. Yarkoni T, Barch DM, Gray JR, Conturo TE, Braver TS. BOLD correlates of trial-by-trial reaction time variability in gray and white matter: a multi-study fMRI analysis. PLoS ONE 2009;4: e4257.
64. Weissman DH, Warner LM, Woldorff MG. Momentary reductions of attention permit greater processing of irrelevant stimuli. Neuroimage 2009;48:609–615.
65. Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. Neuroimage 2008;39:527–537.
66. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003;100:253–258.
67. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001;98:676–682.
68. Helps SK, Broyd SJ, James CJ, Carl A, Sonuga-Barke E. The attenuation of very low frequency brain oscillations in transitions from a rest state to active attention. J Psychophysiol 2009;23:191–198.
69. MacDonald SW, Li SC, Backman L. Neural underpinnings of within-person variability in cognitive functioning. Psychol Aging 2009;24:792–808.
70. Tian L, Jiang T, Liang M, et al. Enhanced resting-state brain activities in ADHD patients: a fMRI study. Brain Dev 2008;30:342–348.
71. Tian L, Jiang T, Wang Y, et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett 2006;400:39–43.
72. Uddin LQ, Kelly AM, Biswal BB, et al. Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 2008;169:249–254.
73. Castellanos FX, Kelly C, Milham MP. The restless brain: attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. Can J Psychiatry 2009;54:665–672.
74. Cao Q, Zang Y, Sun L, et al. Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study. Neuroreport 2006;17:1033–1036.
75. Castellanos FX, Margulies DS, Kelly C, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 2008;63:332–337.
76. Fair DA, Posner J, Nagel BJ, et al. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol Psychiatry 2010;68:1084–1091.
77. Fassbender C, Zhang H, Buzy WM, et al. A lack of default network suppression is linked to increased distractibility in ADHD. Brain Res 2009;1273:114–128.
78. Bush G, Valera EM, Seidman LJ. Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. Biol Psychiatry 2005;57:1273–1284.
79. Fassbender C, Schweitzer JB. Is there evidence for neural compensation in attention deficit hyperactivity disorder? A review of the functional neuroimaging literature. Clin Psychol Rev 2006;26:445–465.
80. Durston S, Mulder M, Casey BJ, Ziermans T, van Engeland H. Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. Biol Psychiatry 2006;60:1062–1070.
81. Epstein JN. A Pathophysiology of Attention Deficit Hyperactivity Disorder: Clues from Neuroimaging. In: Neuroimaging in Developmental Clinical Neuroscience. Rumsey J, Ernst M, eds. Cambridge: Cambridge University Press, 2009:113–139.
82. Suskauer SJ, Simmonds DJ, Caffo BS, Denckla MB, Pekar JJ, Mostofsky SH. fMRI of intrasubject variability in ADHD: anomalous premotor activity with prefrontal compensation. J Am Acad Child Adolesc Psychiatry 2008;47:1141–1150.
83. Sergeant JA. Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. Biol Psychiatry 2005;57:1248–1255.
84. Sanders A. Towards a model of stress and human performance. Acta Psychol 1983;53:61–97.
85. Sonuga-Barke EJ, Wiersema JR, van der Meere JJ, Roeyers H. Context-dependent dynamic processes in Attention Deficit/Hyperactivity Disorder: Differentiating commong and unique effects of state regualtion deficits and delay aversion. Neuropsychol Rev 2010;20:86–102.
86. van der Meere J, Marzocchi GM, De Meo T. Response inhibition and Attention Deficit Hyperactivity Disorder with and without Oppositional Defiant Disorder screened from a community sample. Dev Neuropsychol 2005;28:459–472.
87. Wiersema R, van der Meere J, Roeyers H, Van Coster R, Baeyens D. Event rate and event-related potentials in ADHD. J Child Psychol Psychiatry 2006;47:560–567.
88. Wiersema JR, van der Meere J, Antrop I, Roeyers H. State regulation in adult ADHD: An event-related potential study. J Clin Exp Neuropsychol 2006;7:1113–1126.
89. Ryan M, Martin R, Denckla MB, Mostofsky SH, Mahone EM. Interstimulus jitter facilitates response control in children with ADHD. J Int Neuropsychol Soc 2010;16:388–393.
90. Slusarek M, Velling S, Bunk D, Eggers C. Motivational effects on inhibitory control in children with ADHD. J Am Acad Child Adolesc Psychiatry 2001;40:355–363.
91. Kuntsi J, Wood AC, Van Der Meere J, Asherson P. Why cognitive performance in ADHD may not reveal true potential: findings from a large population-based sample. J Int Neuropsychol Soc 2009;15:570–579.
92. Gopin CB, Berwid O, Marks DJ, Mlodnicka A, Halperin JM. ADHD Preschoolers With and Without ODD: Do They Act Differently Depending On Degree of Task Engagement/Reward? J Atten Disord 2012. doi:10.1177/1087054711432140.
93. Luman M, Ooserlaan J, Sergeant J. Modulation of response timein in ADHD, effects of reinforcement valence and magnitude. J Abnorm Child Psychol 2008;36:445–456.
94. Sagvolden T, Johansen EB, Aase H, et al. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. Behav Brain Sci 2005;28:397–419.
95. Strand MT, Hawk LW, Jr., Bubnik M, Shiels K, Pelham WE, Jr., Waxmonsky JG. Improving Working Memory in Children with Attention-Deficit/Hyperactivity Disorder: The Separate and Combined Effects of Incentives and Stimulant Medication. J Abnorm Child Psychol 2012. doi:10.1007/s10802-012-9627-6.
96. Bubnik MG, Hawk LW, Jr., Strand MT, et al. eds. Intra-individual variability in children with ADHD: treatment effects and construct validity. International Society for Research on Child and Adolescent Psychopathology 2011; Chicago, IL.
97. Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK. Does methylphenidate improve inhibition and other cognitive abilities in adults with childhood-onset ADHD? J Clin Exp Neuropsychol 2005;27:278–298.
98. Rosa-Neto P, Lou HC, Cumming P, et al. Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. Neuroimage 2005;25:868–876.

99. Fitzpatrick PA, Klorman R, Brumaghim JT, Borgstedt AD. Effects of sustained-release and standard preparations of methylphenidate on attention deficit disorder. J Am Acad Child Adolesc Psychiatry 1992;31:226–234.
100. Teicher MH, Lowen SB, Polcari A, Foley M, McGreenery CE. Novel strategy for the analysis of CPT data provides new insight into the effects of methylphenidate on attentional states in children with ADHD. J Child Adolesc Psychopharm 2004;14:219–232.
101. Tannock R, Schachar R, Logan G. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. J Abnorm Child Psychol 1995;23:235–266.
102. Epstein JN, Conners CK, Hervey AS, et al. Assessing medication effects in the MTA study using neuropsychological outcomes. J Child Psychol Psychiatry 2006;47:446–456.
103. Johnson KA, Barry E, Bellgrove MA, et al. Dissociation in response to methylphenidate on response variability in a group of medication naive children with ADHD. Neuropsychologia 2008;46:1532–1541.
104. Tucha O, Prell S, Mecklinger L, et al. Effects of methylphenidate on multiple components of attention in children with attention deficit hyperactivity disorder. Psychopharmacol 2006;185:315–326.
105. Salthouse TA, Berish DE. Correlates of within-person (across-occasion) variability in reaction time. Neuropsychology 2005;19:77–87.
106. MacDonald SW, Nyberg L, Backman L. Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. Trends Neurosci. 2006;29:474–80. Epub 2006 Jul 3.
107. Holden JG. Gauging the fractal dimension of response times from cognitive tasks. In: Contemporary nonlinear methods for behavioral scientists: A webbook tutorial. Riley MA, Van Orden GC, eds. http://www.nsf.gov/sbe/bcs/pac/nmbs/nmbs.jsp: National Science Foundation; 2005:267–318.
108. Ratcliff R. Modeling response signal and response time data. Cogn Psychol 2006;53:195–237.
109. Ratcliff R, Van Zandt T, McKoon G. Connectionist and diffusion models of reaction time. Psychol Rev 1999;106:261–300.
110. McAuley T, Yap M, Christ SE, White DA. Revisiting inhibitory control across the life span: insights from the ex-Gaussian distribution. Dev Neuropsychol 2006;29:447–458.
111. Epstein JN, Tsal Y. Evidence for cognitive training as a treatment strategy for children with attention-deficit/hyperactivity disorder. J ADHD Relat Disord 2010;1:49–64.
112. Tamm L, McCandliss BD, Liang A, Wigal TL, Posner MI, Swanson JM. Can attention itself be trained? Attention training for children at risk for ADHD. Attention Deficit/Hyperactivity Disorder: Concepts, Controversies, New Directions. New York: Informa Healthcare; 2007:399–411.
113. Lutz A, Slagter HA, Rawlings NB, Francis AD, Greischar LL, Davidson RJ. Mental training enhances attentional stability: neural and behavioral evidence. Neurosci 2009;29:13418–13427.