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Annual Research Review: Reaction time variability in ADHD and autism spectrum disorders: measurement and mechanisms of a proposed trans-diagnostic phenotype

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Background: Intraindividual variability in reaction time (RT) has received extensive discussion as an indicator of cognitive performance, a putative intermediate phenotype of many clinical disorders, and a possible trans-diagnostic phenotype that may elucidate shared risk factors for mechanisms of psychiatric illnesses. **Scope and Methodology:** Using the examples of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), we discuss RT variability. We first present a new meta-analysis of RT variability in ASD with and without comorbid ADHD. We then discuss potential mechanisms that may account for RT variability and statistical models that disentangle the cognitive processes affecting RTs. We then report a second meta-analysis comparing ADHD and non-ADHD children on diffusion model parameters. We consider how findings inform the search for neural correlates of RT variability. **Findings:** Results suggest that RT variability is increased in ASD only when children with comorbid ADHD are included in the sample. Furthermore, RT variability in ADHD is explained by moderate to large increases (d = 0.63–0.99) in the ex-Gaussian parameter τ and the diffusion parameter drift rate, as well as by smaller differences (d = 0.32) in the diffusion parameter of nondecision time. The former may suggest problems in state regulation or arousal and difficulty detecting signal from noise, whereas the latter may reflect contributions from deficits in motor organization or output. The neuroimaging literature converges with this multicomponent interpretation and also highlights the role of top-down control circuits. **Conclusion:** We underscore the importance of considering the interactions between top-down control, state regulation (e.g. arousal), and motor preparation when interpreting RT variability and conclude that decomposition of the RT signal provides superior interpretive power and suggests mechanisms convergent with those implicated using other cognitive paradigms. We conclude with specific recommendations for the field for next steps in the study of RT variability in neurodevelopmental disorders. **Keywords:** Reaction time variability, intraindividual, ADHD, ASD, trans-diagnostic phenotype, biomarker.

Introduction

That phenotypic and genotypic heterogeneity within existing psychiatric diagnostic categories limits the field's ability to detect pathophysiology or predict clinical course for individual children is no longer much disputed. At the same time, many symptom dimensions are shared across existing diagnostic boundaries, and the extent to which this indicates shared liability or etiology across disorders remains a major question (Insel et al., 2010; Sanislow et al., 2010). To help resolve these twin issues, investigators have turned to intermediate phenotypes. As used here, an *intermediate phenotype* is a behavioral or biological measure that is presumed to mediate between etiological mechanisms of disorders and psychiatric symptoms. The related term *endophenotype* has also been used, often to connote processes that are heritable and thought to specifically mediate gene-disorder pathways (see Gottesman & Gould, 2003; Kendler & Neale, 2010; Nolen-Hoeksema & Watkins, 2011 for discussion of genes and endophenotypes; see Kendler & Neale for discussion of endophenotypes as mediating between environmental risk or gene x environment interactions and later disease). When they cut across existing diagnostic boundaries and/or relate to symptom dimensions expressed across multiple disorders they are referred to as *trans-diagnostic phenotypes* (Nolen-Hoeksema & Watkins, 2011).

In this review, we consider closely one such measure: *intra*individual (or within-person) variability in reaction time (RT). RT variability could serve as an intermediate, endo-, or trans-diagnostic phenotype depending on the context. Alternatively, it may

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be a *biomarker* that is associated with risk for a disorder (via shared environmental or genetic influence), but does not mediate symptoms (Kendler & Neale, 2010). While recognizing that any of these may be possible, for simplicity we use the broad term trans-diagnostic phenotype generically.

Computerized RT measures, long recognized as a valuable indicator of cognitive performance (Barrett, Eysenck, & Lucking, 1986; Berkson & Baumeister, 1967; Jensen, 1992), have recently gained renewed attention due to recognition that within-child RT variability may convey unique information. RT variability has been discussed in the literature as a potentially important index of the stability/instability of an individual's nervous system. However, it lacks specificity to a single psychiatric population and so has not been seen as useful as an intermediate phenotype for specific disorders. Indeed, increased RT variability characterizes populations ranging from those most commonly associated with childhood (e.g. ADHD, Castellanos & Tannock, 2002), to those associated with pathological aging (e.g. Alzheimer's and other dementias; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000), to acquired disorders, such as traumatic brain injury (e.g. Stuss, Pogue, Buckle, & Bondar, 1994).

One possibility is that increased RT variability may simply be a final common correlate of many disorders that reduce psychological or physical health, much like fever is a final common correlate of many infections. Alternatively, RT variability may be a trans-diagnostic phenotype that is associated with shared risk for several disorders or with symptom domains that cut across several disorder categories (Gottesman & Gould, 2003; Nolen-Hoeksema & Watkins, 2011). Finally, it may be that RT variability can be decomposed into distinct processes that differ among psychiatric conditions. We discuss these latter two possibilities in detail here, focusing on two major neurodevelopmental disorders of particular interest for the JCPP readership: attention deficit hyperactivity disorder (ADHD), for which the RT variability literature is voluminous, and autism spectrum disorder (ASD), for which the literature is more sparse.

We select these two for several reasons. ADHD is among the most heavily studied conditions with regard to RT variability (Castellanos, Kelly, & Milham, 2009; Castellanos et al., 2005; Epstein et al., 2011; Geurts et al., 2008; Karalunas, Huang-Pollock, & Nigg, 2012b; Kofler et al., 2011; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), and has been subjected to reviews and meta-analyses, on which we build. Also, there is preliminary evidence for shared genetic mechanisms for RT variability and ADHD (Andreou et al., 2007; Kuntsi et al., 2006; Rommelse et al., 2008; Uebel et al., 2010; Wood, Asherson, van der Meere, & Kuntsi, 2010); this line of thinking is not as explicitly developed in many other disorders. At the same time, ASD is a major overlapping condition with ADHD—particularly so in the new DSM-5 that puts both disorders in the camp of neurodevelopmental conditions.

Although core diagnostic criteria for ASD do not overlap with those of ADHD, children with ASD often show high levels of inattention and hyperactivity-impulsivity symptoms, and individuals with ADHD often show deficits in one or more of the two primary ASD symptom domains (social communication impairments or restricted/repetitive behavioral patterns). Furthermore, ADHD and ASD may share common genetic liability (Musser et al., 2014; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008), and RT variability has been explicitly proposed as a trans-diagnostic phenotype that indexes shared risk for these disorders (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). With this background in mind, the possibility that RT variability may serve as a trans-diagnostic phenotype is intriguing, but its potential to do so relies on the answers to several key subquestions that have, as of yet, not been well-addressed in the literature. It is the aim of this review to organize thinking on these questions to help the field forward.

First, most basically, are ADHD and ASD populations both characterized by increased RT variability? This is a question that has been only minimally addressed with the ASD literature, and thus it is the first that we address here. We review meta-analytic results for ADHD and report new meta-analytic data for ASD. Second, what mechanisms might account for RT variability? RT scores are complexly determined and not easily interpreted in terms of either cognitive or neural mechanisms. Which mechanisms account for RT variability in specific populations and whether these are the same or different across populations remains poorly understood. We describe statistical approaches that have been used to better characterize RT variability, and then discuss what findings imply in terms of potential cognitive and neural interpretations of RT variability. We also introduce new meta-analytic data for ADHD that complement the recent Kofler et al. (2013) meta-analysis. After considering these two basic questions, we conclude the review with specific recommendations for future studies that are needed.

Characterizing RT variability in ADHD and ASD

ADHD and ASD provide an intriguing case for potential shared genetic liability. Could RT variability index a shared liability in both disorders or does it distinguish the two conditions?

RT variability in ADHD

In ADHD, there is consistent meta-analytic evidence that measures of RT variability distinguish individuals with ADHD from typically developing

populations with medium to large effect sizes (ESs) for children/adolescents (0.72–0.85, Klein, Wendling, Huettner, Ruder, & Peper, 2006; Kofler et al., 2013; Lijffijt et al., 2005; Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012), and small to medium ESs for adults (Hedge's $g = 0.46$, Kofler et al., 2013).

The most recent and largest of these meta-analyses (Kofler et al., 2013) included 283 studies on 9,780 individuals with ADHD and 12,024 typically developing controls. Consistent with earlier meta-analyses, results indicated individuals with ADHD were more variable than their typically developing counterparts with an ES of $g = 0.71$. This effect was moderated by age with child/adolescent populations showing larger between-group effects ($g = 0.76$, 95% *CI*: 0.68–0.84) than adults (18+ years; $g = 0.46$, 95% *CI*: 0.31–0.61). This apparent decrease in the size of between group effects for RT variability with age is coincident with declines in ADHD symptoms (particularly hyperactive-impulsive symptoms) that occur with age (Biederman, Mick, & Faraone, 2000). Kofler et al. (2013) also found that RT variability effects were attenuated by stimulant treatments, but they were unaffected by nonstimulant and psychosocial treatments. Results suggest a possible parallel course for cognitive and symptom improvements (either developmentally or with specific treatment) that warrants more study (Buzy, Medoff, & Schweitzer, 2009; Epstein et al., 2003; Wåhlstedt, Thorell, & Bohlin, 2009). After accounting for participants' age, there was no significant unexplained between-study variance in effects, suggesting that other sample characteristics (e.g. gender) or task characteristics (e.g. duration, inhibitory control demands) were not required to explain between-study differences in the size of effects observed. This finding is important because it suggests that RT variation may be a quite robust measure with a clear signal related to ADHD.

In secondary analyses, Kofler et al. (2013) examined ADHD versus other disorders (71 studies comparing 6,486 individuals with ADHD to 10,176 individuals with other clinical disorders, such as other psychiatric conditions and learning disorders, physical health conditions, and subthreshold ADHD). As a group, children with ADHD (but not adolescents or adults with ADHD) were also significantly more variable than the combined clinical comparison groups, albeit with only a small ES ($g = 0.25$, 95% *CI*: 0.09–0.41). However, given the wide variety in the clinical comparison groups, it is difficult to draw conclusions about specific comparisons of interest, such as between ADHD and ASD. Overall, the literature on ADHD and RT variability is large, has been reduced by meta-analysis, and shows a reliable association of RT variability to ADHD that is to a small extent distinct from other conditions in aggregate.

RT variability in ASD

In ASD, although RT variability has received some theoretical attention as a putative trans-diagnostic phenotype and/or key feature of the disorder (e.g. Rommelse et al., 2011; Sinzig, Bruning, Morsch, & Lehmkuhl, 2008), the evidence for increased RT variability remains mixed. Some studies have found increased RT variability in ASD as compared to typically developing controls (e.g. Christakou et al., 2012; Dinstein et al., 2012; Geurts et al., 2008), while others have not (Geurts & Vissers, 2012; Johnson et al., 2007; Lundervold et al., 2012).

Similarly, evidence is mixed for whether individuals with ADHD and ASD can be differentiated on the basis of RT variability, with some studies finding that children with ADHD are more variable in their responding than children with ASD (e.g. Christakou et al., 2012; Johnson et al., 2007) and others unable to differentiate between the two clinical groups (e.g. Raymaekers, Antrop, Van der Meere, Wiersema, & Roeyers, 2007; Sinzig et al., 2008). In several studies, the ASD group was even less variable in their response pattern as compared to controls (Lundervold et al., 2012; Raymaekers, van der Meere, & Roeyers, 2006) or to children with ADHD (Lundervold et al., 2012). Together, the contradictory results for comparisons of children with ASD to typically developing children or children with ADHD raise the basic question: Is RT variation even abnormal in ASD? To answer this question we report a new meta-analysis.

Is increased RT variability present in ASD? A meta-analysis

Methods. A literature search was conducted in August 2013 using Medline, PubMed, and PsychInfo. Search terms included permutations of the ASD diagnostic label (Autism, autistic, pervasive developmental disorder, PPD-NOS, Asperger's, high functioning autism, HFA) with variability, reaction time (RT), or common variability metrics (SDRT, coefficient of variation, CV, sigma, tau, SE of RT, Slow-*, frequency, signal processing). See Figure 1 for PRISMA flow chart describing the number of articles found and excluded at each stage of search.

In total, 18 unique articles reporting between-group comparisons for either children or young adults (age <30 years) were identified. All 18 reported ASD-Control comparisons, and 10 studies additionally reported ASD-ADHD comparisons. One study was excluded (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004) because the sample overlapped substantially with a larger study on the list (Geurts et al., 2008). Thus, the final pooled results are based on 17 studies ($n = 1{,}520$) for the ASD-Control and 10 studies ($n = 881$) for the ASD-ADHD comparisons. Studies included in the

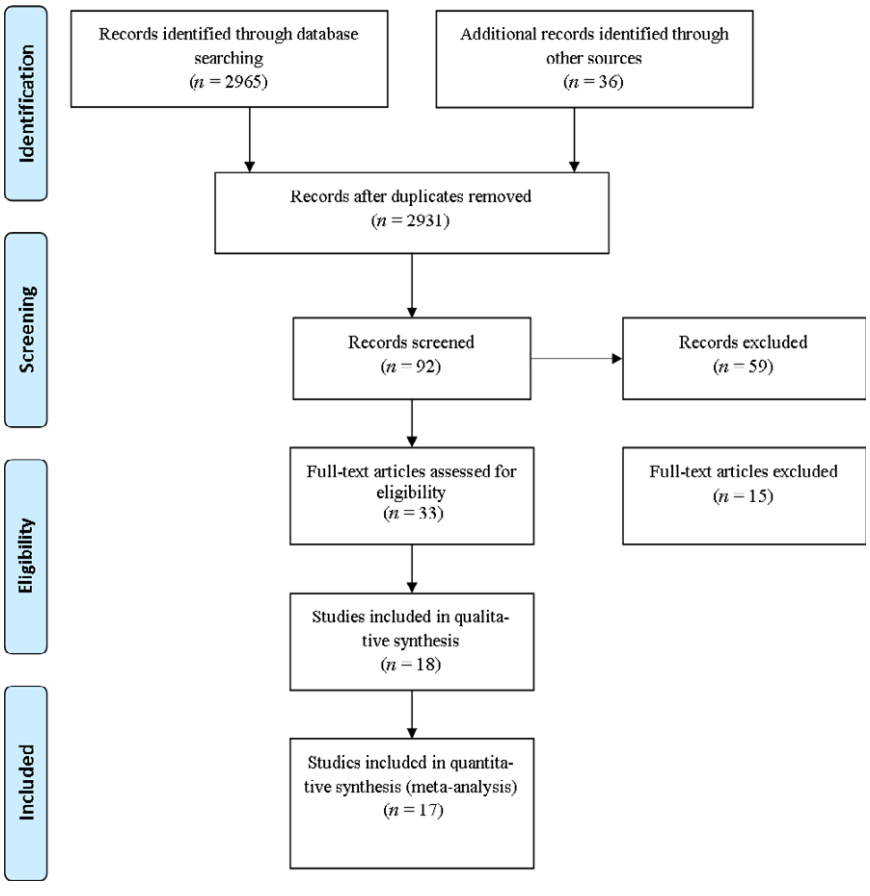

Figure 1 Autism spectrum disorder meta-analysis: PRISMA diagram

quantitative analyses are listed and summarized in Table 1.

A random effects model was used to compute pooled ESs for each between-group comparison. The bias corrected ES Hedges' *g* is reported (interpreted similarly to the familiar Cohen's *d*). Calculations were completed using the software Comprehensive Meta-analysis (Biostat Inc, Englewood, NJ). Although several studies reported non-Gaussian RT variability metrics (e.g. ex-Gaussian or frequency-domain measures), which are discussed in more detail in the next section, there were too few of these studies to pool here. Thus, results below are based on standard deviation and/or variance. For studies that included more than one task condition (Christakou et al., 2012; Dinstein et al., 2012; Geurts, Begeer, & Stockmann, 2009; Johnson et al., 2007; Pascualvaca, Fantie, Papageorgiou, & Mirsky, 1998; Sinzig et al., 2008), results were pooled across tasks using a synthetic effects model (Borenstein, Hedges, Higgins, & Rothstein, 2011). For cases in which data were reported for an ASD-only and a comorbid ASD+ADHD group (Adamo et al., 2013; Geurts et al., 2008; Lundervold et al., 2012; Sinzig et al., 2008; Tye et al., 2013), data from the comorbid group were excluded for analyses comparing ASD to typically developing controls; however, we report on potential effects of comorbid ADHD and ASD symptoms in more detail below.

ES heterogeneity is described using the *Q* statistic, which provides a statistical test to determine whether heterogeneity is present, and the I^2 statistic, which quantifies the amount of unexplained between-study variance (Huedo-Medina, Sanchez-Meca, Marin-Martinez, & Botella, 2006). A limited sensitivity analysis was conducted via a leave-one study-out procedure, in which ESs were recalculated with each study in turn removed. Potential publication bias was examined using funnel plots. In the case of statistically significant between-group heterogeneity for the ASD-Control comparisons, moderator analyses were conducted to examine effects of age, sample gender composition, IQ, diagnostic method, and exclusion of comorbid ADHD; however, given the small number of studies, these comparisons had low power. We do not report on type of task as a moderator because the number of studies reporting each type of task is too small. Meta-analyses in ADHD have found that neither task type nor task conditions (e.g. type of task, event rates, inter-stimulus interval, task length) moderated ES (Huang-Pollock, Karalunas, Tam, & Moore, 2012; Kofler et al., 2013; Metin et al., 2012). However, the effects of task variables, particularly in ASD, may be an important area for future research, particularly because task type or condition effects could cause the omnibus estimates to be too low or too high.

Table 1 Summary of articles included in autism spectrum disorders meta-analysis

Study	Task type	Groups	*N*	Age (years)	IQ	Gender (Male: Female)	Comparison	ES (*g*)	95% *CI*
Adamo et al. (2013)	SART	Control	36	10.0	112	19:17	ASD-Control	0.15	−0.26 to 0.54
		ASD	46	10.0	109	42:4	ASD-ADHD	0.14	−0.28 to 0.58
		ADHD	46	10.0	106	39:7	ADHD-Control	0.15	−0.28 to 0.58
Christ, Holt, White, and Green (2007)		Control	48	10.8	112.0	23:25	ASD-Control	1.45	0.83–2.06
		ASD	16	8.2	88.4	16:2[a]			
Christakou et al. (2012)	Sustained attention	Control	20	14.7	114.0	20:0	ASD-Control	0.27	−0.34 to 0.88
		ASD	20	14.7	112.9	20:0	ASD-ADHD	−0.55	−1.17 to 0.07
		ADHD	20	14.0	108.2	20:0	ADHD-Control	1.02	0.38–1.67
Dinstein et al. (2012)	1-back (Working Memory)	Control	14	26.0	114.0	10:4	ASD-Control	0.42	−0.31 to 1.15
		ASD	14	26.5	114.0	10:4			
Geurts et al. (2008)	Change task	Control	85	9.2	111.6	65:20	ASD-Control	0.73	0.27–1.18
		ASD	25	9.3	106.8	23:2	ASD-ADHD	0.42	−0.05 to 0.90
		ADHD	53	9.1	100.8	46:7	ADHD-Control	0.26	−0.08 to 0.60
Geurts et al. (2009)	Go/No-go (Social Stimuli)	Control	22	10.3	103.2	19:3	ASD-Control	0.59	−0.04 to 1.21
		ASD	18	10.3	108.0	16:2			
Johnson et al. (2007)	SART	Control	18	11.1	107.7	18:3	ASD-Control	0.24	−0.37 to 0.86
		ASD	21	12.2	98.7	21:1	ASD-ADHD	−0.87	−1.48 to 0.26
		ADHD	23	10.5	97.3	20:3	ADHD-Control	1.16	0.50–1.81
Lundervold et al. (2012)	Conners' CPT	Control	134	9.7	93.8	77:57	ASD-Control	−0.55	−1.23 to 0.12
		ASD	9	10.3	92.2	8:1	ASD-ADHD	−0.85	−1.58 to −0.11
		ADHD	38	10.0	78.1	32:6	ADHD-Control	0.43	0.07–0.79
Milne (2011)	CPT	Control	12	12.4	111.1	11:1	ASD-Control	0.32	−0.45 to 1.08
		ASD	13	11.8	105.9	12:1			
Pascualvaca et al. (1998)	CPT	Control	46	5.9	108.9	30:16	ASD-Control	0.23	−0.38 to 0.85
		ASD	23	8.7	77.6	15:8			
Raymaekers et al. (2004)	Go/No-go	Control	17	28.8	121.0	15:2	ASD-Control	0.52	−0.14 to 1.19
		ASD	17	28.4	111.7	15:2			
Raymaekers et al. (2006)	Response inhibition	Control	29	10.5	107.0	18:11	ASD-Control	0.64	0.16–1.13
		ASD	39	11.3	107.0	33:6			
Raymaekers et al. (2007)	Go/No-go	Control	28	10.5	107.0	20:8	ASD-Control	0.17	−0.33 to 0.68
		ASD	31	10.5	107.0	27:4	ASD-ADHD	0.18	−0.34 to 0.71
		ADHD	24	9.6	99.0	15:9	ADHD-Control	0.66	0.11–1.21
Sinzig et al. (2008)	Attention/ Inhibition	Control	30	12.8	109.0	23:7	ASD-Control	−0.05	−0.61 to 0.51
		ASD	20	14.5	112.0	16:4	ASD-ADHD	−0.53	−1.10 to 0.04
		ADHD	30	12.9	102.0	27:3	ADHD-Control	0.63	0.11–1.14
Tye et al. (2013)	CPT	Control	26	10.6	120.0	26:0	ASD-Control	0.37	−0.54 to 0.62
		ASD	19	11.7	115.7	19:0	ASD-ADHD	−0.48	−1.14 to 0.18
		ADHD	18	10.5	104.1	18:0	ADHD-Control	0.42	−0.19 to 1.04
van der Meer et al. (2012)	Simple RT	Control	418	9.5	106.2	227:191	ASD-Control	0.37	0.10–0.65
		ASD+ADHD	58	11.5	104.2	50:2	ASD-ADHD	0.11	−0.21 to 0.43
		ADHD	109	9.9	104.2	72:37	ADHD-Control	0.07	−0.14 to 0.28
Verté, Geurts, Roeyers, Oosterlaan, and Sergeant (2006)	Change Task	Control	82	9.2	112.2	67:15	ASD-Control	0.64	0.31–0.97
		ASD	66	8.7	101.5	61:5	ASD-ADHD	0.07	−0.27 to 0.41
		ADHD	65	9.1	99.8	54:11	ADHD-Control	−0.58	−0.91 to −0.25
Overall		Control	1065				ASD-Control	0.37	0.19–0.56
		ASD	455				ASD-ADHD	−0.17	−0.43–0.09
		ADHD	426				ADHD-Control	0.37	0.07–0.66

ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; SART, Sustained Attention to Response Task; CPT, continuous performance test; TOVA, Test of Variables of Attention.
[a]Gender ratio reported is for the full sample in the study. Gender ratio for the subset of individuals included in the RT variability comparison was not reported.

Results. The pooled ES for the ASD-Control group comparison (total $N_{ASD} = 455$, $N_{control} = 1065$) was $g = 0.37$ ($SE = 0.09$; 95% confidence interval [CI]: 0.19–0.55; $p < .001$), indicating that individuals with ASD were significantly more variable than typically developing controls but with a small to moderate ES. See Figure 2 for plot of ESs for each study. The *Q* statistic for the comparison of ASD and typically developing children indicated significant unexplained between-study heterogeneity ($Q = 32.0$, $p = .010$, $I^2 = 50.1$). Leave-one-out sensitivity analyses indicated the effect was not driven by any single outlier study (with each study in turn removed, *g* ranged from 0.33 to 0.42, all $p < .01$). Funnel plots showed no evidence of publication bias.

The ADHD-Control group ES for the 10 studies reporting this comparison was also computed to allow direct comparison to the ASD ES. This avoids the

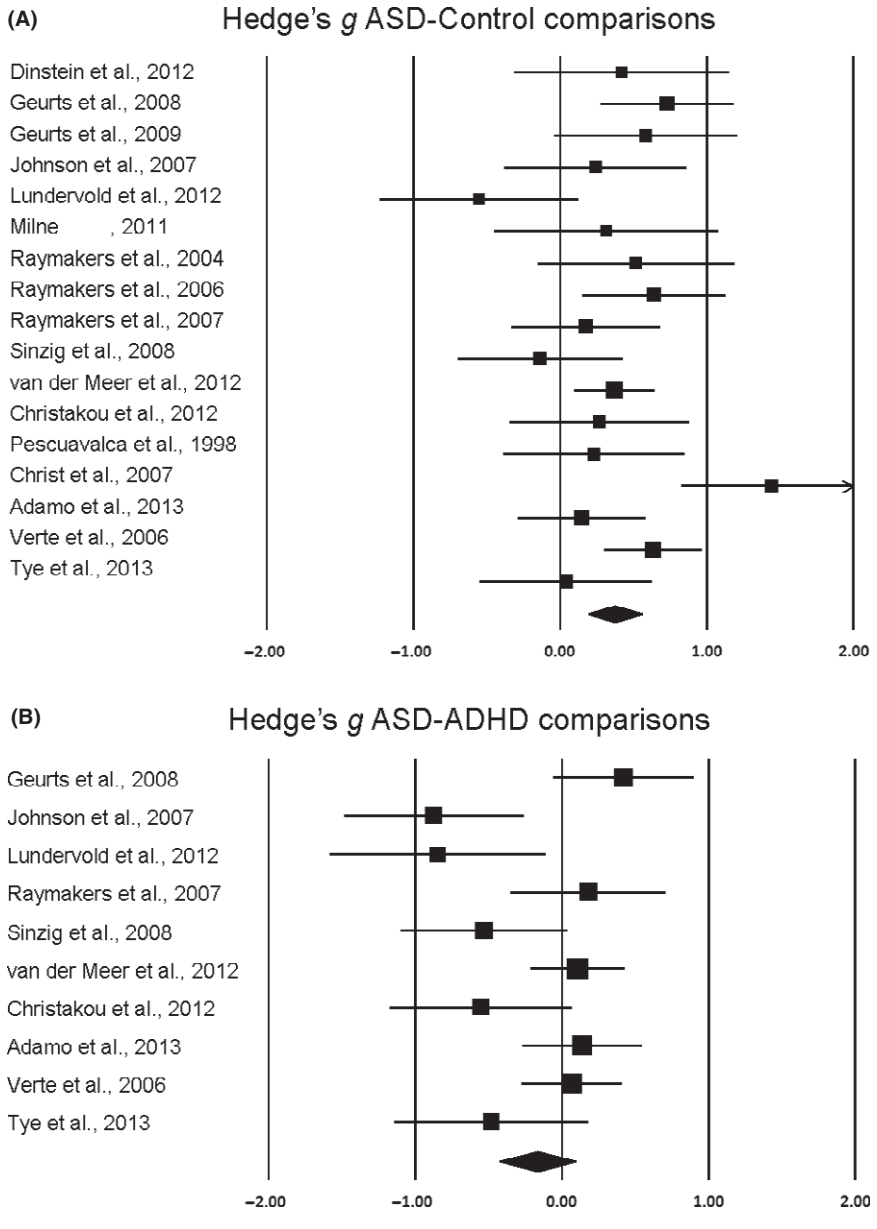

Figure 2 Forest plot of Hedge's *g* and 95% CI for studies reporting (A) ASD-Control comparisons and (B) ASD-ADHD comparisons of SDRT in the meta-analysis

selection bias that would confound comparison of this finding to the larger analysis by Kofler et al. (2013), which included ADHD studies without an ASD comparison group. The ADHD-Control pooled ES (total $N_{ADHD} = 426$, $N_{control} = 1{,}065$) was $g = 0.37$ (*SE* = 0.15; 95% *CI*: 0.17–0.66; $p = .015$), indicating small to moderate increases in RT variability in the ADHD samples as compared to non-ADHD controls in studies that also included an ASD group. Thus, for this group of studies, ES was similar for ADHD and ASD and obviously somewhat smaller than that seen in the larger population of studies in meta-analyses that could ignore ASD. There was significant between-study heterogeneity in the size of the ADHD-Control ES ($Q = 44.9$, $p < .001$, $I^2 = 79.9$); however, this was not pursued further as it is handled with more power in the meta-analyses cited earlier (Kofler et al., 2013).

The pooled ES for the 10 studies reporting direct comparisons of ASD ($N = 455$) versus ADHD ($N = 426$) groups was $g = -0.17$ (*SE* = 0.13; 95% *CI*: −0.43 to 0.09; $p = .207$), indicating that children with ADHD were nonsignificantly more variable than children with ASD. Funnel plots showed no evidence of publication bias. The *Q* statistic indicated significant between-study heterogeneity ($Q = 21.78$, $p = .003$, $I^2 = 67.9$). Leave-one-out sensitivity analyses indicated the effect was not driven by any single outlier study (with each study in turn removed, *g* ranged from −0.23 to −0.09, all $p > .05$); however, given the small number of studies reporting this comparison, between-study heterogeneity was not pursued further for the current review.

Moderators of between-study heterogeneity for ASD-control group comparisons

Meta-regression analyses indicated that age, sample gender composition (% male), and IQ were not

related to the observed ESs for the ASD-Control group comparisons (all $p > .302$).

Quality of the ASD diagnosis (coded as either "High Quality," including observational schedules and clinical interviews given individually or in combination, and "Low Quality," including prior clinical diagnosis and diagnosis based on rating scales only) significantly moderated the size of effect observed ($p = .048$). Studies relying on Low Quality diagnostic procedures had larger ESs ($g = 0.63$, $SE = 0.16$) than those relying on High Quality diagnostic procedures ($g = 0.24$, $SE = 0.11$).

We next compared studies that excluded children with comorbid ADHD from their ASD sample, versus those that did not. (In cases where no information was reported to determine this, studies were assumed *not* to have excluded ADHD as this would be an important exclusionary criterion likely to have been highlighted in the methods.) Exclusion of ADHD significantly moderated the ES ($p = .043$) with a smaller ES for studies that excluded ADHD ($g = 0.15$, $SE = 0.15$, $p = .341$) than for those that did not ($g = 0.52$, $SE = 0.10$, $p < .001$). All studies excluding ADHD from the ASD sample also used "High Quality" diagnostic procedures for diagnosing ASD, so the effects of diagnostic quality and ADHD exclusion cannot be separated. These results suggest, however, that the small to moderate increase in RT variability in ASD versus typically developing controls reported above is explained by the subgroup of children with comorbid ADHD.

Summary. Increased RT variability was observed in ASD only when children with comorbid ADHD were included. The aggregate data suggest that there is a more reliable RT variability deficit in ADHD than in pure ASD. Most studies relied on comparison of categorical diagnostic groupings and thus do not account for subthreshold symptoms. It may be informative to see dimensional studies that examine relationships between level of inattention and/or hyperactivity-impulsivity symptoms and level of RT variability in both disorders, to further inform whether RT variability is specific to the ASD group meeting full ADHD diagnostic group, or is related to level of ADHD symptoms along a continuum regardless of diagnostic assignation. Of note, the pooled ES for the ASD-control group comparison ($g = 0.37$, and $g = 0.15$ if samples with comorbid ADHD are excluded) is smaller than has previously been found in ADHD using a larger sample of studies (0.72–0.85, Klein et al., 2006; Kofler et al., 2013; Lijffijt et al., 2005; Metin et al., 2012); however, the ADHD-Control ES in the set of studies looked at here ($g = 0.37$) was also smaller than in prior larger meta-analyses, so our ASD effect should not be directly compared to the larger number of studies of ADHD.

Cognitive and neural mechanisms of RT variability

The review to this point suggests that there may be partial specificity of RT variability effects to ADHD (vs. ASD), and that effects seen in ASD may be restricted to the group with comorbid ASD+ADHD. However, this does not tell us *why* either group is more variable. RT variability may be determined by multiple processes, such as stimulus encoding, speed of information processing (itself varying with arousal, effort, motivation, and other state factors), speed-accuracy trade-offs (also varying with incentives and instructions), post-error slowing, motor preparation, and response execution. As a result, multiple neural and physiological processes are also involved.

Isolating these components has been addressed, in part, by applying statistical models to decompose RT variability. If the study of RT variability is to progress, characterizing the specific nature of RT variability in different clinical groups and the most sensitive and specific ways to measure this variability will be crucial. In the following section we discuss these alternative measurement approaches in detail, and then turn to how results may be interpreted. To-date, these alternative analysis approaches have been applied primarily in ADHD, so we focus on it here. However, if comorbid ADHD accounts for increased RT variability in ASD, we would expect the cognitive and neural mechanisms to be similar in both populations (ADHD, and ASD+ADHD). Empirically evaluating this claim using some of the approaches described below will be of interest.

Methodological concerns and alternative analytical approaches to RT variability

The majority of studies of RT variability in both ADHD and ASD, as well as in other conditions, have used standard deviation (SDRT) to quantify RT variability. However, in addition to being multidetermined, SDRT has two other major limitations. First, although mean RT and RT variability are often assumed to represent different cognitive mechanisms (e.g. speed and attention lapses, Hervey et al., 2006; Leth-Steensen, Elbaz, & Douglas, 2000; Wagenmakers, Grasman, & Molenaar, 2005), SDRT is typically highly correlated with mean RT (r between 0.7 and 0.9 in many studies). To try to address this, some studies calculate the coefficient of variation: SDRT/mean RT. However, if the RT variance and mean are driven by the same mechanism, then the coefficient of variation would not clarify matters (Karalunas & Huang-Pollock, 2013; Karalunas, Huang-Pollock, & Nigg, 2012a; Klein et al., 2006; Wagenmakers et al., 2005; Wood et al., 2010).

Second, standard statistics using SDRT assume that RTs fit a Gaussian (normal) distribution, but in fact RT distributions are nearly always positively

skewed to some extent (see Figure 3 for example). Because Gaussian measures do not accurately reflect the shape of RT distributions, they are underpowered to detect group differences (Ratcliff, 1993). Alternatives include ex-Gaussian, time series, and diffusion models to decompose the RT signal. We briefly describe each analysis approach.

Ex-Gaussian decomposition. Ex-Gaussian decomposition can handle skewed RT distributions and model them more accurately than a regular Gaussian RT variability analysis. It provides estimates of the mean (μ) and standard deviation (σ) of the normal (Gaussian) portion of the distribution and the mean and standard deviation of the exponential tail of the distribution (τ). Figure 3 depicts the approach. Ex-Gaussian analyses help clarify which portions of the RT distribution differ between groups. However, cognitive interpretations of these parameters are not agreed upon, a point to which we return below.

Frequency decomposition. Traditional RT analyses also discard potentially relevant information about the temporal ordering of RTs (i.e. whether very fast or slow RTs occur at predictable times throughout a task). Time series approaches to analyzing RTs preserve this information. Frequency-domain analyses, such as fast-Fourier transform (e.g. Geurts et al., 2008; Karalunas et al., 2012b) or wavelet analyses (e.g. Di Martino et al., 2008) make use of the full series of RTs to look for patterns in regard to when long RTs occur. Figure 4 depicts this approach. Frequency-domain approaches, in the case of ADHD, grew out of interest in putative oscillatory abnormalities in specific brain networks that might cause long RTs to occur in a specific low-frequency time course of ~0.10 Hz (Castellanos et al., 2009).

Diffusion model decomposition. One limitation of both the ex-Gaussian and time series approaches is that they do not take into account response accuracy. When more than one response is possible or accuracy is not extremely high, then speed-accuracy trade-offs can confound the interpretation of RT data (Matzke & Wagenmakers, 2009). This has been long recognized (van der Meere & Sergeant, 1988; Sergeant & Van der Meere, 1988) but not regularly taken into account in the clinical literature. A drift diffusion model of RTs (Ratcliff & Rouder, 1998) provides an approach that addresses this concern. Widely used in the cognitive psychology literature to study normative adult cognition (Balota & Yap, 2011; Kühn et al., 2011; Ratcliff, Thapar, Gomez, & McKoon, 2004; Schmiedek, Lövdén, & Lindenberger, 2009; Spaniol & Bayen, 2005; Thapar, Ratcliff,

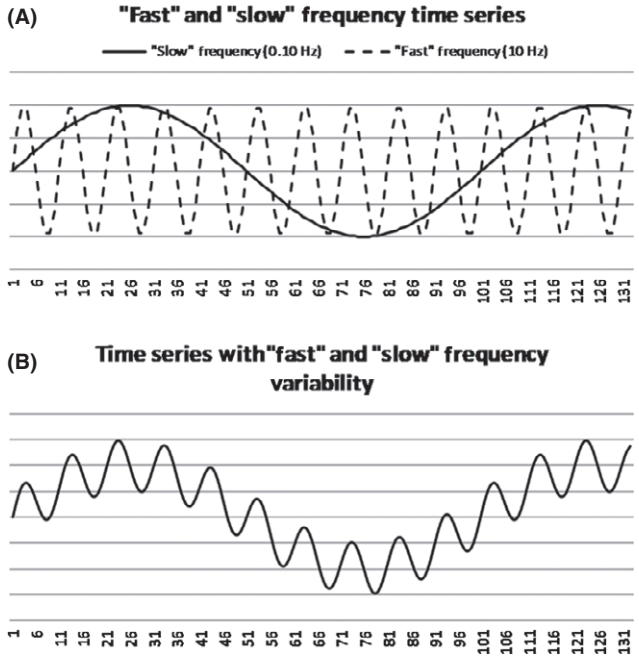

Figure 4 Frequency-domain apprach to reaction time series. (a) shows two different frequency time series; (b) depicts the time series created by combining the fast and slow frequency variability into a single time series. Frequency-domain analyses are used to quantify the contribution of different frequency patterns to the final time series. In this case, the slow frequency contributes twice as much as the fast frequency, and so frequency-domain analyses would indicate twice as much "power" in the low as the high frequency

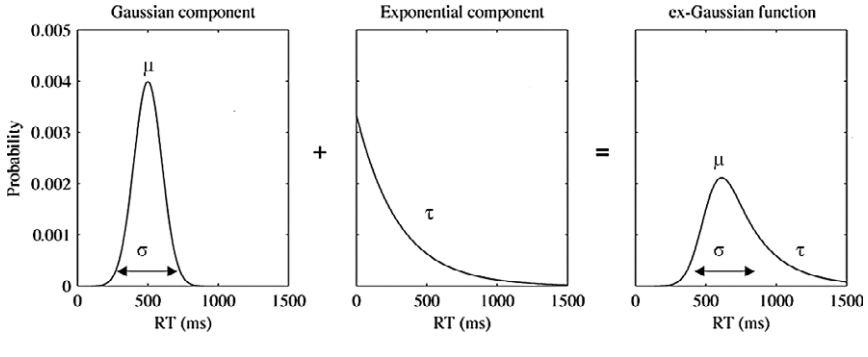

Figure 3 Ex-Gaussian approach to reaction time data. Adapted from Lacouture & Cousineau (2008). In ex-Gaussian analyses, μ reflects the mean of the normal (Gaussian) portion of the distribution, σ captures the standard deviation of the normal portion of the distribution, and τ reflects both the mean and standard deviation of the exponential portion of the distribution

& McKoon, 2003), these models were developed to explain decision-making in forced-choice paradigms for which relatively rapid (~1 s) response decisions are required. Initially developed for two-choice paradigms, diffusion models have been extended to apply to one- and multiple-choice paradigms as well (Leite & Ratcliff, 2010; Ratcliff & Van Dongen, 2011). However, they have only to a limited extent been employed to understand abnormal cognition or development (White, Ratcliff, Vasey, & McKoon, 2010).

In brief, drift-diffusion models assume that information about a stimulus is accumulated via a noisy information accumulation process until a decision criterion is met, at which point a response is initiated. Thus, how quickly a person responds is related both to the conservativeness of the criteria they have set for responding (called boundary separation), and to the rate at which information is accumulated in favor of one of the response criterion (called drift rate). Processes that are not directly related to the response decision, such as stimulus encoding and motor preparation and execution, also influence the final RT and are modeled in a "non-decision time" parameter (Ratcliff, 2006). Figure 5 depicts this approach (Ratcliff & Rouder, 1998).

What do alternative analyses reveal about the nature of RT variability? Summary and new meta-analysis. Do these alternative analysis approaches clarify anything about the specific changes in portions of the RT distribution that drive RT variability? The answer here depends on approach.

Using the ex-Gaussian approach, the most consistent group differences in ADHD are in the τ parameter (e.g. Epstein et al., 2011; Karalunas & Huang-Pollock, 2013). As a part of the recent meta-analysis of RT variability in ADHD described earlier (Kofler et al., 2013), the size of effects for traditional (SDRT) and ex-Gaussian parameters were compared directly. The pooled ES for τ (g = 0.99, 95% *CI* = 0.64–1.34) was not significantly larger than the estimate for SDRT (g = 0.70, 95% *CI* = 0.62–0.77). The τ ES was, however, significantly larger than that for σ (g = 0.39, 95% *CI* = 0.15–0.63). This suggests that that increased SDRT in ADHD is driven by RTs in the exponential tail of the distribution, confirming at the level of pooled effects something that has been identified in many individual studies (e.g. Hervey et al., 2006; Leth-Steensen et al., 2000). However, the pooled ES for τ is based on a small number of available studies and there is a wide *CI* around the effect. So, these conclusions could be overturned with additional study, or, more notably, it may emerge that τ is reliably more sensitive than SDRT when more studies are available to pool.

Frequency-domain approaches have, in aggregate, failed to find effects confined to specific frequency ranges (for review see Karalunas et al., 2012b), suggesting that no specific frequency band drives RT variability in ADHD and that no consistent, predictable time course of long RTs can be identified within the RT bands studied. Furthermore, meta-analysis again suggests a similar ES for frequency measures (g = 0.63, 95% *CI* = 0.35–0.90) and SD (g = 0.70, 95% *CI* = 0.62–0.77; Kofler et al., 2013). Again, the relatively small number of studies and wide *CI* around the frequency effect suggest that additional comparison using frequency approaches may be warranted. However, given that group differences do not appear limited to a specific frequency range, studies will need to carefully explore a range of frequencies rather than comparing groups only in a single band.

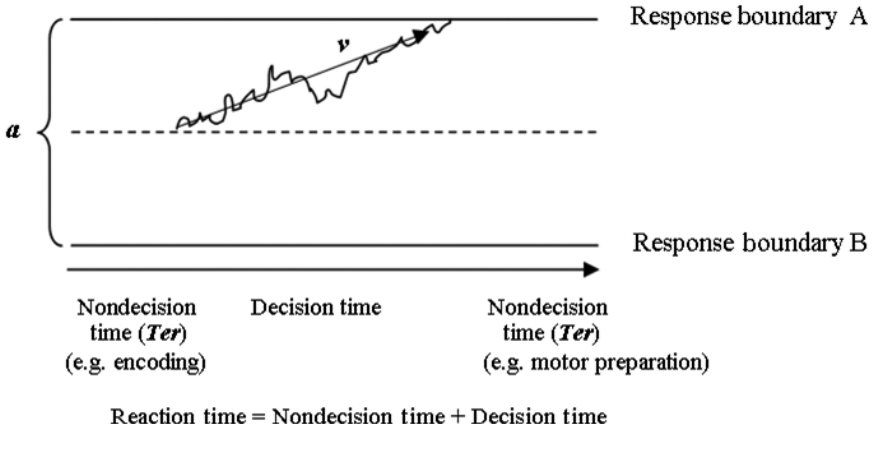

Figure 5 Adapted from Ratcliff and Rouder (1998). Diffusion model approach to characterizing reaction time data. Diffusion model parameters are depicted for a hypothetical single trial. Drift rate (*v*) is the rate at which information accumulates toward a decision boundary, as reflected by the average slope of the line. It is determined by speed of information processing and "noise" unrelated to the decision processes (which is represented by the hypothetical jagged deviations from the average slope shown in the Figure). Larger values of *v* indicate faster processing. Boundary separation (*a*) indicates the conservativeness of the response criterion with wider separations indicating more conservative responding. Finally, nondecision time (*Ter*) includes all nondecision processes, such as stimulus encoding and motor preparation. Larger values of *Ter* indicate longer nondecisional processing times

ES estimates for diffusion models, because of their relatively recent introduction into the clinical literature (White et al., 2010), have not yet been pooled, and so we undertook that effort here.

Methods. Focusing on our populations of interest, we searched PubMed and PsychInfo databases in August 2013 for combinations of the terms, ADHD, attention deficit disorder, and ADD with diffusion model, drift rate, boundary separation, and nondecision time to identify articles reporting ADHD-Control group comparisons on any of the diffusion model parameters. Similar literature search was conducted using variations of the ASD diagnostic label; however, no studies reported diffusion model analysis in ASD. Given Kofler et al.'s (2013) finding that SDRT was more sensitive to ADHD in children than in adults, and that only one study of adults with ADHD was available (Merkt et al., 2013), we limited our meta-analysis to children and adolescents. Five studies including six independent samples (Karalunas & Huang-Pollock, 2013; Karalunas et al., 2012a; Metin et al., 2013; Mulder et al., 2010; Salum et al., 2013) reported ADHD-Control group comparisons on at least one diffusion model parameter in child/adolescent samples. See Table 2 for a list of studies and the number of participants included in analysis for each parameter. The analytic approach was the same as in our meta-analysis of ASD above. Due to the small number of studies, moderator analyses were not performed.

Results. Children with ADHD had significantly slower drift rates than non-ADHD controls (g = 0.63, 95% *CI*: 0.42–0.83, $p < .001$) with a moderate to large ES, as well as significantly faster nondecision times (g = −0.32; 95% *CI*: −0.49 to −0.15, $p < .001$) with a small ES. Groups did not differ in their boundary separations (g = 0.01; 95% *CI*: −0.19 to 0.16, p = .90) with the effect close to 0 (see Figure 6 for plot of ESs for each study). Funnel plots showed no evidence of publication bias for any of the measures. No significant between-study heterogeneity was present for drift rate (Q = 8.9, $p > .05$; I^2 = 55.3), boundary separation (Q = 8.7, $p > .05$; I^2 = 42.3), or nondecision time (Q = 7.9, $p > .05$; I^2 = 37.1). Leave-one-out sensitivity analyses indicated that none of the effects were driven by any single outlier study (with each study in turn removed, g ranged from 0.56 to 0.70 for drift rate, −0.06 to 0.06 for boundary separation, and −0.26 to −0.35 for nondecision time, with no change in significance).

The pooled ES for drift rate was significantly larger than ESs for boundary separation and marginally larger than for nondecision time. The ES for drift rate, the most sensitive measures using this decomposition approach, did not differ from the ES for SDRT in the subset of these studies that reported it (g = 0.65, 95% *CI*: 0.46–0.83, $p < .001$).

Summary: Two conclusions, while tentative based on the relatively small number of studies available, emerge from this section to guide future work. First, decomposition approaches do not increase measurement sensitivity to ADHD deficit versus simply using SDRT. Second, however, increased SDRT in children with ADHD is not attributable to specific

Table 2 Summary of studies included in the meta-analysis of diffusion model parameters in ADHD

Parameter	Study	N Control	N ADHD	ES (g)	95% *CI*	Q	I^2
Drift rate	Karalunas and Huang-Pollock (2013)	62	91	0.81	0.48–1.15		
	Karalunas et al. (2012a, Cohort #1)	50	164	0.40	0.08–0.72		
	Karalunas et al. (2012a, Cohort #2)	91	81	0.68	0.37–0.98		
	Metin et al. (2013)	48	65	0.96	0.57–1.35		
	Salum et al. (2013)	378	100	0.42	0.20–0.65		
	Overall effect	629	501	0.63	0.42–0.83	8.9	55.3
Boundary separation	Karalunas and Huang-Pollock (2013)	62	91	0.21	−0.11 to 0.53		
	Karalunas et al. (2012a, Cohort #1)	50	164	0.21	−0.11 to 0.52		
	Karalunas et al. (2012a, Cohort #2)	91	81	−0.11	−0.41 to 0.19		
	Metin et al. (2013)	48	65	−0.09	−0.46 to 0.28		
	Mulder et al. (2010)	30	25	0.13	−0.40 to 0.66		
	Salum et al. (2013)	378	100	−0.25	−0.47 to −0.03		
	Overall effect	629	501	0.01	−0.19 to 0.16	8.7	42.3
Nondecision time	Karalunas and Huang-Pollock (2013)	62	91	−0.37	−0.04 to −0.69		
	Karalunas et al. (2012a, Cohort #1)	50	164	−0.22	−0.54 to 0.09		
	Karalunas et al. (2012a, Cohort #2)	91	81	−0.19	−0.49 to 0.11		
	Metin et al. (2013)	48	65	−0.77	−1.55 to −0.39		
	Mulder et al. (2010)	30	25	0.01	−0.52 to 0.53		
	Salum et al. (2013)	378	100	−0.32	−0.54 to −0.10		
	Overall effect	629	501	−0.32	−0.48 to −0.15	7.9	37.1
SDRT	Karalunas and Huang-Pollock (2013)	62	91	0.62	0.30 to 0.95		
	Karalunas et al. (2012a, Cohort #1)	50	164	0.53	0.21–0.85		
	Karalunas et al. (2012a, Cohort #2)	91	81	0.78	0.47–1.09		
	Overall effect	203	336	0.65	0.46–0.83	1.3	0

SDRT, standard deviation of reaction time; CI, confidence interval.

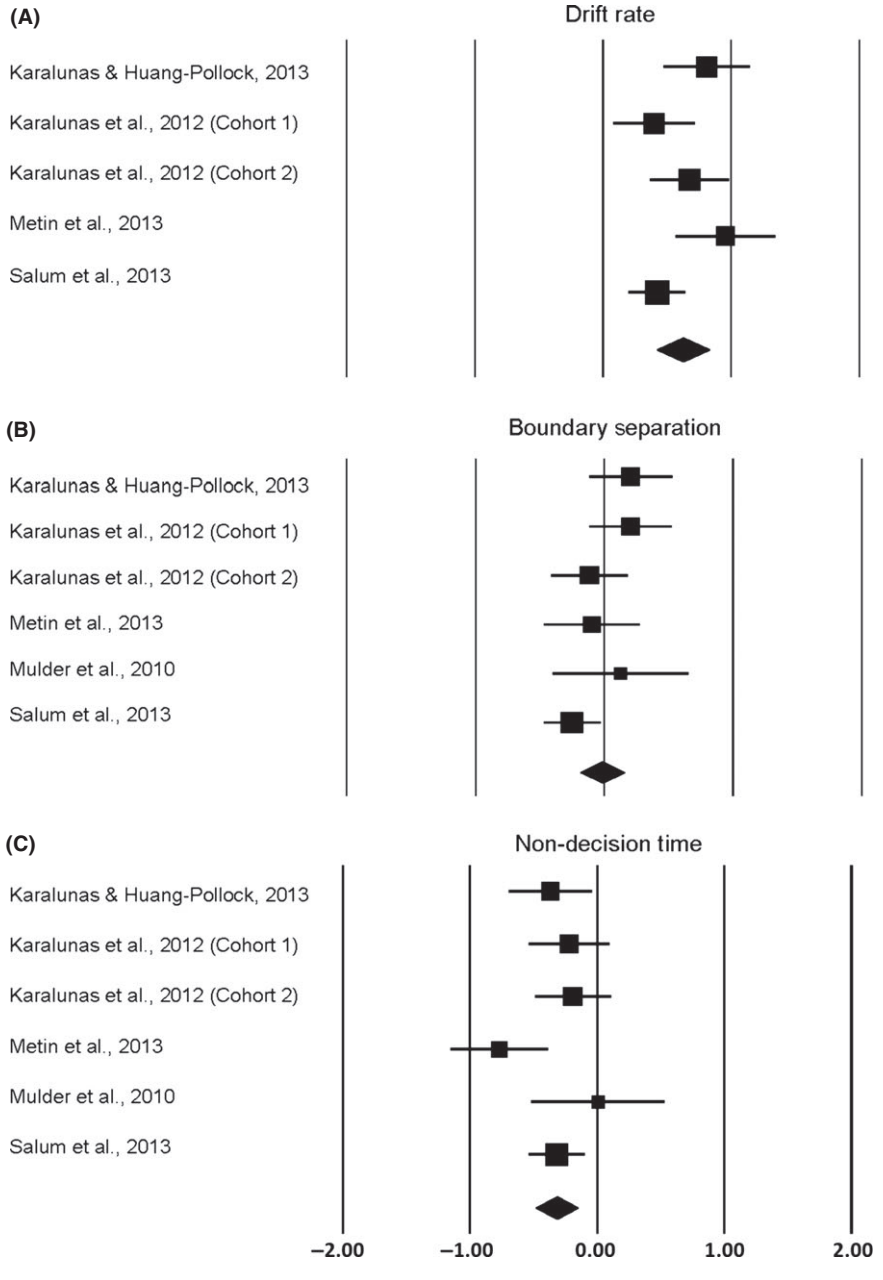

Figure 6 Forest plot of Hedge's *g* and 95% CI for studies reporting ADHD-Control comparisons on diffusion model parameters. (A) Drift Rate (positive ESs indicate slower drift rates for the ADHD group), (B) Boundary Separation (positive ESs indicate narrower boundary separations for the ADHD group), (C) Nondecision Time (negative ESs indicate faster nondecision times for the ADHD group)

low-frequency patterns of variability, group differences in μ, or group differences in boundary separation (speed-accuracy trade-off strategy). Instead it is largely explained by increased τ and slow drift rate. Although a perfect isomorphism between diffusion model and ex-Gaussian parameters does not exist, slow drift rate exerts the largest effects on the upper tail of the RT distribution, so the findings of slow drift rate and large τ values are fully consistent with each other. Thus, we suggest that a single mechanism likely unifies these findings, which we discuss next. Finally, group differences in nondecision time may reflect a distinct influence that also contributes to RT variability but to a smaller extent. What these mechanisms might be is discussed subsequently.

Although we reported that RT deficits in ASD apart from ADHD are doubtful, it is still interesting to consider whether any effect that is present in ASD may be also characterized by similar patterns of increased τ and drift rates. Few data are available to address this. Only one study has reported comparison on ex-Gaussian measures (Geurts et al., 2008); they did find increased τ in children with ASD-only and with ASD+ADHD. However, RT variability in the latter group was also characterized by increase σ with a similar size of effect. This may suggest a combination of shared and unique mechanisms of RT variability in comorbid ASD+ADHD groups, but clearly additional study is required.

Mechanistic interpretation of RT variability. If slow drift rate, effects on τ, and/or differences in nondecision times account for RT variability in ADHD (or in comorbid ASD+ADHD), what mechanisms might this implicate either cognitively or neurobiologically? Numerous cognitive and neural hypotheses have been suggested to account for RT variability, including attention lapses (e.g. Leth-Steensen et al., 2000), poor behavioral inhibition (e.g. Barkley, 1997), deficient neuroenergetic supply (Killeen, Russell, & Sergeant, 2013), temporal information processing deficits (e.g. Sonuga-Barke, Bitsakou, & Thompson, 2010), deficits in motor preparatory and output processes (e.g. Suskauer et al., 2008), abnormalities in default-mode network functioning (e.g. Castellanos et al., 2005), and working memory deficits (e.g. Rapport et al., 2008), to name but some of the many proposed (see Kofler et al., 2013; Table 1 for a complete list of these with additional explanation.) Here, we focus on cognitive interpretations that are consistent with the results of the alternative analysis approaches we have described, as well as how these may inform the search for neural correlates of RT variability in ADHD or ASD.

Interpretation of the nondecision time parameter is not reducible to a single function because it encompasses multiple components, including both predecision processes, such as encoding, and post-decision processes, such as motor organization and output. However, given a long standing and relatively more robust literature implicating motor preparation and output as compared to encoding problems in ADHD (e.g. Carte, Nigg, & Hinshaw, 1996; Sergeant & Scholten, 1985), our hypothesis would be that faster nondecision times indicate differences in motor processing in this population. If this is the case, faster nondecision times may be related to less efficient motor preparation (Metin et al., 2013), or to motor impulsivity, although it is important to note that not all differences between ADHD and typically developing children need to be interpreted as deficits.

One important caveat for future studies will be to determine the relationship of nondecision times to mean RT versus RT variability. While slow drift rates are directly related to distributional skew, and thus variability, faster nondecision times may have a more uniform effect across the RT distribution. Alternatively, inconsistency in the nondecisional processes (e.g. particularly fast nondecision times on some trials) could lead to increased RT variability and differences in the mean nondecision parameter estimate. The trial-to-trial variability of diffusion model parameters can be directly modeled to address this question.

What mechanisms account for slow drift rates and larger τ? Although these two metrics may be related, they are usually interpreted differently in terms of their cognitive mechanisms. The ex-Gaussian parameter τ is commonly interpreted as reflecting "attention lapses" (de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012; Sonuga-Barke & Castellanos, 2007; Unsworth, Redick, Lakey, & Young, 2009; Weissman, Roberts, Visscher, & Woldorff, 2006). This interpretation is interesting, yet for several reasons it is problematic. First, although an attention lapse interpretation may be consistent with older work suggesting that τ reflects higher-order decision processing while μ and σ index motor response (Hohle, 1965), precisely the opposite interpretation of τ, that it primarily reflects motor processes, has also been made (see Matzke & Wagenmakers, 2009). Second, empirical and simulation studies suggest that τ may reflect the influence of multiple processes (Heathcote, Popiel, & Mewhort, 1991; Matzke & Wagenmakers, 2009).

The interpretation of "attention lapses" is also complicated by the multicomponent nature of attention itself (Huang-Pollock & Nigg, 2003; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991; Mirsky, Pascualvaca, Duncan, & French, 1999; Petersen & Posner, 2012; Posner & Petersen, 1990), which includes components like filtering, alerting/arousal, orienting, and executive control (Deutsch & Deutsch, 1963; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Treisman, 1964). Which component is involved in the lapse? In other words, a lapse is an event, but not a component mechanism, so it leaves us with our fundamental interpretive problem.

Which component of attention might explain RT variability in ADHD? Some task comparisons within ADHD samples initially suggested that RT variability may be higher on tasks with higher executive demands (Klein et al., 2006); however, as noted, a recent meta-analysis suggests that task demands do not moderate the RT variability ES in this population (Kofler et al., 2013). As noted in our own meta-analysis, the small number of studies and wide variety of tasks used precludes drawing conclusions about task effects in ASD.

Slow drift rate, although expected to lead to larger τ values, has not typically been interpreted in terms of attention lapses. Instead, the diffusion model conceptualizes drift rate as an RT counterpart to a signal detection model of accuracy. From this perspective, the drift rate parameter is conceptually and mathematically similar to discriminability (d') in traditional signal detection theory (Ratcliff & McKoon, 2008; Ratcliff & Rouder, 1998).[1] Within a signal detection framework, *d'* is often interpreted as an index of arousal (van der Meere & Sergeant, 1988; Sergeant, Oosterlaan, & van der Meere, 1999). Optimal arousal (neither too high nor too low) maximizes the individual's ability to detect signal from noise. Analogously, the drift rate parameter in the diffusion model is linked conceptually to neural noise, with slower drift rate (i.e. slower, less efficient information processing) indicative of a low signal-to-noise ratio in neural circuits underlying

decision-making (Ratcliff, Cherian, & Segraves, 2003; Ratcliff, Philiastides, & Sajda, 2009; Ratcliff & Rouder, 1998). In this sense, rather than implicating a new mechanism as explaining RT variability, slow drift rate may be consistent with classic theories of ADHD emphasizing a deficit in cortical "arousal" (Satterfield, Cantwell, & Satterfield, 1974; Zentall & Zentall, 1983) or, concomitantly, disruption in ascending noradrenergic neural systems that facilitate signal detection (McCracken, 1991). We address definitions, complexity in this conclusion, and alternative possibilities below.

Arousal has also been implicated in ASD, although unlike in ADHD, where *d'* tends to show under-arousal in ADHD (Huang-Pollock et al., 2012; Losier, McGrath, & Klein, 1996), in ASD both under- and over-arousal are reported, leaving the main trend unclear (Geurts et al., 2009; Raymaekers, van der Meere, & Roeyers, 2004; Raymaekers et al., 2006, 2007; Rogers & Ozonoff, 2005). Given the results of the present ASD meta-analysis, accounting for sample differences in ADHD symptoms may help clarify ASD results, but more work is needed in both populations to relate abnormal arousal levels to RT variability.

Neural Mechanisms of RT variability: Conceptual considerations. What neural processes are related to increased RT variability? Neural correlates of RT variability have been extensively studied in animals, including primates, using single, and multiunit recordings. In humans, noninvasive approaches, such as such as functional magnetic resonance imaging (fMRI) and electroencephalograph (EEG) recordings have been used to study cortical activity and its relationship to RT variability (Toga & Mazziotta, 2002). RT variability has been discussed as a general indicator of the integrity of brain networks (MacDonald, Li, & Bäckman, 2009), and has been variously empirically linked to amount of myelination (Tamnes, Fjell, Westlye, Østby, & Walhovd, 2012), latency jitter in evoked electrocortical response potentials (ERPs, Saville et al., 2011), localized group differences in activation in brain regions underlying executive control and decision-making (Philiastides, Auksztulewicz, Heekeren, & Blankenburg, 2011; Philiastides & Sajda, 2006), and group differences in activation in large-scale brain networks, particularly those associated with rest (Weissman et al., 2006). Thus, a wide range of correlated brain patterns have been associated with RT variability in normal adult populations, and it is difficult to use that literature to identify a single brain mechanism being implicated in RT variability in ADHD, specifically.

Of particular concern is that the basis of RT variability may vary in different populations, and so population-specific studies may be of most help in understanding RT variability mechanisms in developmental psychopathology. However, despite the resurgence of interest in RT variability and its neural underpinnings in neurodevelopmental disorders such as ADHD and ASD, there is still a relatively small literature that directly links RT variability to measures of brain function in these populations. As one illustration, over 1,900 articles are found when "ADHD," "reaction time," and "brain," "neural," or "imaging" are used as search terms in PubMed, while only 19 publications are found if these terms are required to be in the abstract, and few of these actually address the correlation of RT variability to brain metrics as we describe below. A similar picture exists for ASD with 204 versus only 10 studies in the general and more restrictive searches respectively.

Given the vastness of the relevant literature that could be used to make circumstantial arguments related to brain mechanisms of RT variability, the wealth of existing reviews on ADHD and brain imaging generally, and the dearth of literature directly examining ADHD (or ASD), the brain, and RT variability at the same time, we do not attempt comprehensive review of all brain findings related to RT variability. Rather, we focus only on the final, small set of directly relevant data, bringing in other studies selectively to amplify key questions.

Bounding the literature, even when restricting it to ADHD (or ASD), is debatable. For example, virtually all brain imaging studies of ADHD also report on some behavioral measures, including RT variability, that one might use to bolster a circumstantial argument of one form or another. Nevertheless, unless these were directly analysed in relation to brain imaging data (either MRI or EEG/ERP), we did not review those studies. With these foci in mind, we identified a handful of studies directly relevant to the question of neural correlates of RT variability in ADHD or ASD that we discuss below. We discuss these findings in relation to attention functions, including both alerting/arousal and executive control of attention; motor response and preparation; and "neural noise," as these have been some of the most prominent theories in the literature to-date and are consistent with the decomposition analyses presented earlier.

Our use of terminology is guided by Posner and Petersen (1990); Petersen and Posner's (2012) influential attention model because they propose specific neural systems related to attention components. We then discuss in detail at the end of the section how these may map onto another very influential model in the ADHD and ASD fields: the cognitive-energetic model. The primary goal here is to highlight the potential for cross-disciplinary studies of RT variability that bridge cognitive, neural, and psychopathology theories.

RT variability and attention functions. In the Petersen–Posner perspective (Petersen & Posner, 2012; Posner & Petersen, 1990), the brain is organized by modular interconnected networks

responsible for distinct attentional functions including orienting, altering (arousal), and executive control. Both the alerting/arousal and executive control functions of attention have been suggested as putative contributors to RT variability so we pause to describe those networks here.

The alerting network is responsible for establishing and maintaining an alert state suitable to task demands, as well as enhancing the signal:noise ratio for novelty detection. It is quite isomorphic with what has also been referred to in the earlier ADHD literature as arousal. Arousal and alerting have historically been associated with a right-hemisphere fronto-parietal-thalamic-brainstem network modulated by the norepinephrine (NE) system (Pardo, Fox, & Raichle, 1991; Posner & Petersen, 1990; Sturm et al., 2004), with the anterior cingulate cortex (ACC) and the right dorsolateral prefrontal cortex exerting top-down control during alertness, in order to regulate noradrenergic activation originating from the brainstem (Mottaghy et al., 2006).

Consistent with that literature, Posner and Petersen (1990) noted two distinct functions: phasic alerting to a stimulus and tonic sustaining of attention to the stimulus, which they called vigilance. A recent revision of this historical model (Aston-Jones & Cohen, 2005; Petersen & Posner, 2012 the latter referring again to "alerting"), emphasizes ascending norepinephrine systems that project to frontal and parietal cortices and are involved in bottom-up optimization of behavioral performance by influencing responsivity (i.e. a gain parameter) in those cortical systems. In addition, projections from the anterior cingulate cortex and prefrontal cortex can regulate the NE system in response to the perceived utility of the task to the individual, helping to explain how top-down cognitive control can be involved in deliberate regulation of arousal and task efficiency. Within this framework, phasic release of NE (via the locus coeruleus [LC]) is associated with optimal decision-making and task performance, whereas less phasic and greater tonic LC activation produces a less optimized and more distractible behavioral pattern. Elevated tonic LC activity is associated with both lower *d'* (signal detection in an accuracy task, such as the continuous performance task) and lowered response thresholds (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994) and thus, we would hypothesize, is also associated with slower drift rate (signal detection in a reaction time framework).

Executive control of attention is required for suppressing interference, handling response conflict, complex working memory, and top-down regulation of arousal and motivation. As pointed out by Petersen and Posner (2012), cognitive neuroscientists disagree as to whether executive control is handled by one or two neural networks (Carter & Krug, 2012; Petersen & Posner, 2012). The perspective that argues for two such networks (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Petersen & Posner, 2012) proposes that a fronto-parietal task network includes lateral frontal and parietal nodes, and is involved in the initial onset of task control. Maintaining task set over time is handled by a second network, termed the cingulo-opercular network, which includes medial PFC, dorsal anterior cingulate, dorsal anterior prefrontal cortex, lateral frontal pole, and anterior insula. The cingulo-opercular network is likely involved in many other functions (such as task switching), but here we highlight its putative role in maintaining task set—a function that would seem relevant to RT variability.

Very few studies have directly examined functional brain activation in relation to RT variability in children with ADHD or ASD specifically. Two fMRI studies in ADHD demonstrated that children with ADHD showed greater RT variability and reduced brain activity in the right-sided anterior cingulate gyrus (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006) and in fronto-parietal brain regions (Cao et al., 2008). A third study also found a negative correlation between RT variability and activation in the anterior cingulate in ADHD subjects (Rubia, Smith, Brammer, & Taylor, 2007), although here the measure of brain activation reflected the difference in activity on standard versus oddball trials of a go/no-go type task, making it difficult to interpret in the current framework. The authors suggest that in this case the pattern of activation may implicate motor output functions, relevant to our findings on the diffusion model earlier. This study also found a different pattern of correlations between typically developing and ADHD children, highlighting the importance of studying typically developing and nontypically developing populations together.

Interestingly, where differences have been found, these abnormalities are primarily located in cortical areas which are proposed to reflect top-down control (rather than bottom-up activation) of arousal/alerting functions. The ADHD findings are consistent with research identifying reduced fronto-parietal activation during cognitive tasks in ASD as well (Solomon et al., 2009), although RT variability was not directly assessed. Most interesting for the ASD study is that the reduced fronto-parietal activation was related to symptoms of ADHD in the ASD groups, making it a promising target for study of neural correlates of RT variability in both groups.

RT variability and the default network. Another neural network that has taken a primary role in discussion of RT variability in relation to "attention" functions is the default-mode network. The default-mode network includes the precuneus/posterior cingulate cortex (PCC), the medial prefrontal cortex and the medial, lateral, and inferior parietal cortex (Laird et al., 2009; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008), and is believed to be characterized by slow neural oscillations at a rate of

less than ~0.10 Hz. Its functions are debated but it activates when task control is relaxed (for example, during stimulus-independent thoughts and mind wandering, Andrews-Hanna, 2012; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Spreng, 2012). Activity in the default-mode network is attenuated, although not extinguished, during the transition from rest-to-task states (Eichele et al., 2008; Greicius, Srivastava, Reiss, & Menon, 2004; Raichle et al., 2001). Stronger deactivation is associated with increased task difficulty (Singh & Fawcett, 2008), thus it is anticorrelated with executive control networks in typically developing individuals. The posterior cingulate cortex, a key hub in the default-mode network, may be involved in regulating consistency of responding (Leech & Sharp, 2013) and so may be particularly relevant to RT variability.

Because ADHD has been correlated with weaker connectivity of the default mode network to the task control networks, an initial hypotheses in the ADHD field was that a failure to sufficiently suppress default-mode network activity would be mirrored by periodic and transitory performance deficits manifested in specific frequency patterns in the RT time series (Castellanos et al., 2009). Frequency-domain analyses of RT data described in the prior section do not support this particular hypothesis. It remains plausible, however, that default-mode network activity could contribute to increased RT variability in some manner not yet detected at the behavioral level due to the many processes that affect the final RT. One study has found that reduced deactivation of the default-mode network is correlated with more variable RTs for children with ADHD (Fassbender et al., 2009). In addition, by using a diffusion tensor imaging approach in a sample of children with ADHD, Lin et al. (2013) found that τ correlated with fractional anisotropy (a putative measure of white matter integrity) in white matter tracts in the midcingulum bundle connecting ACC and PCC, which they suggest is consistent with default network involvement in distributional skewing. However, another study found no significant correlation between RT variability and activation in other regions considered to be part of the default network (medial PFC, precuneus) in either ADHD or ASD (Christakou et al., 2013), although the relationships between RT variability and medial PFC activity was significant for typically developing children. Other studies and pooled data sets that allow more powerful analyses will be helpful to resolve these relationships. In addition, other work in healthy adults now suggests that, rather than absolute activation in any one network, it is balance of activation in the default-mode network and an anti-correlated "task--positive" network that is active during goal-directed, attention-demanding cognition that is important, with greater negative correlation between these networks predicting lower RT variability (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008).

Replication of studies showing correlations between RT variability and activity in the default network would be helpful, particularly in children. In addition, the exact nature of default-mode network abnormalities in both ADHD (Konrad & Eickhoff, 2010) and ASD (Minshew & Keller, 2010), remains unclear with both hyper- and hypo-activation variously found and disagreement about whether differences are present at rest (e.g. Fair et al., 2010) or only during task completion. Thus, the relationship of default-mode network activity and RT variability is an interesting area for further work, but one in which clear conclusions cannot yet be drawn.

EEG and ERP measures of attention functions. Electroencephalograph (or scalp electrical recordings) is another brain measure that can further help to quantify attention processes, as well as their relationship to RT variability. Brain localization with EEG is not as robust as with MRI, but temporal resolution is superior to MRI. Two major approaches have been used: (1) the power spectrum of the EEG signal and (2) examination of specific components of event-related potentials. Both ADHD and ASD have been associated with alterations in the power spectra in EEG signal (Barry, Johnstone, & Clarke, 2003; Broyd, Helps, & Sonuga-Barke, 2011) and with alterations in ERP markers (Johnstone, Barry, & Clarke, 2012). In addition, EEG metrics have been proposed as a potential therapeutic tool to improve arousal and attention via neurofeedback methods (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009), and so understanding their relationships to behavioral measures is particularly relevant for guiding clinical applications.

First, the frequency or power spectrum of the EEG can serve as a central nervous system indicator of arousal in the sense of the Petersen and Posner (2012) alerting network (Minkwitz et al., 2011). The relationship between EEG power spectrum and arousal, however, is a complex one. As a rule of thumb, higher power in fast frequencies (e.g. the beta band) is indicative of high arousal, while higher power in slow frequencies (e.g. theta band) is indicative of low arousal (Arns, Conners, & Kraemer, 2013; Pizzagalli, 2007). The theta/beta ratio, historically interpreted as an index of central arousal, is altered in both ADHD (Arns, Conners, & Kraemer, 2013) and ASD (Kouijzer, de Moor, Gerrits, Congedo, & van Schie, 2009). This effect is not specific to either disorder, although ASD studies have generally not considered comorbid ADHD. Furthermore, the arousal interpretation has been questioned by recent findings that the theta/beta ratio is unrelated to measures of skin conductance, an accepted peripheral nervous system indicator of arousal (Clarke et al., 2013). RT variability studies may wish to examine skin conductance. Alternatively, alpha power, which is related to skin conductance, may be informative to test an arousal hypothesis of RT

variability in ADHD or ASD (Barry, Clarke, Johnstone, & Brown, 2009). It is also possible that cortical and peripheral nervous system arousal are, at least to some extent, dissociable and that measures of both are needed.

Traditionally examined EEG bands (i.e. alpha, theta, beta) may also be modulated by underlying very low frequencies (Buzsaki & Draguhn, 2004; Monto, Palva, Voipio, & Palva, 2008; Novak, Lepicovska, & Dostalek, 1992; Vanhatalo et al., 2004; Voipio, Tallgren, Heinonen, Vanhatalo, & Kaila, 2003), that are the neurophysiological correlates of default-mode network activity (He, Snyder, Zempel, Smyth, & Raichle, 2008). Fluctuations in EEG-indicated arousal states, including both higher frequency indicators and very low frequencies, have been used to predict single trial RTs in adults with and without ADHD (Helps, Broyd, James, Karl, & Sonuga-Barke, 2009; Minkwitz et al., 2011). However, studies were small and thus preliminary. More work is needed to confirm findings, determine whether magnitude of effects are sufficient for further development, and extend findings into child clinical populations.

Event-related (ERP) components of the EEG signal can also be used to understand attention components in relation to RT variability. Such designs measure alterations in the EEG signal at specific millisecond time points preceding or following stimulus presentation. Several attention-dependent ERP components could be related to RT variability. Here, we discuss the positivity at 300 ms (P300) as an example of how ERP components can serve to disentangle RT variability. We later discuss the contingent negative variation (late CNV) as an additional example when considering motor preparatory processes.

The 'P300' is believed to reflect working memory updating and the decision about which is the correct response (Verleger, 1997). Because P300 depends on attention deployment, it is thought to represent the allocation of executive control resources to the task (Polich, 2007). P300 amplitude and latency have been found to be altered in both ADHD (Johnstone et al., 2012) and ASD (Jeste & Nelson, 2009). Furthermore, both amplitude and latency of the single trial P300 have been correlated with RTs on individual trials (van Deursen, Vuurman, Smits, Verhey, & Riedel, 2009; Holm, Ranta-aho, Sallinen, Karjalainen, & Muller, 2006; Jung et al., 2001; Nakata, Sakamoto, & Kakigi, 2012; Saville et al., 2011; Verleger, Paehge, Kolev, Yordanova, & Jaskowski, 2006), suggesting a role for executive control resources in determining RT variability. Taken together, results from EEG and ERP studies are broadly consistent with those using functional MRI approaches, and provide some evidence for both arousal and executive control contributions to RT variability. However, also similar to studies using fMRI approaches, considerably more work is needed to replicate and extend these findings and to understand the interaction of bottom-up arousal and top-down control processes.

General "noise" in neural information processing. Poor signal-to-noise ratio, either via low arousal, inefficient executive control of attention, or for other reasons, is implicated as a mechanism of RT variability in our review of behavioral data earlier. We discuss here several metrics that may be useful in future studies to better understand the role of "noise," or signal variability more generally, in relation to RT variability.

First, the EEG measure of intertrial phase coherence (ITC) is a measure of the degree to which the phase (or timing) of the frequency-domain evoked responses aligns across trials, independently of amplitude (Delorme & Makeig, 2004; Groom et al., 2010; Makeig, Debener, Onton, & Delorme, 2004). ITC is thought to be related to the temporal stability of information processing (i.e. latency variability) in traditional evoked response potentials. ITC can be used to examine the temporal stability of neural transmission in the brain in relation to cortical noise (Koychev, Deakin, Haenschel, & El-Deredy, 2011) and the degree of synchronization between cortical neuronal networks (Shin et al., 2010; Winterer et al., 2000). Using measures of latency variability and ITC, several studies have demonstrated that the cortical responses of individuals with ASD (e.g. Dinstein et al., 2012; Milne, 2011) and ADHD (e.g. Groom et al., 2010; McLoughlin, Palmer, Rijsdijk, & Makeig, 2014) are less consistent when compared to typically developing controls. This is interesting in regard to whether behavioral inconsistency could be related to cortical variability. The aforementioned studies have provided preliminary evidence of a positive relationship between this cortical signal variability and RT variability (Groom et al., 2010; McLoughlin et al., 2014; Milne, 2011). However, at least one study in ASD failed to find increased signal variability to simple sensory stimulation (Coskun et al., 2009), and so again these findings are tentative.

Second, several measure of brain signal complexity on EEG or MRI have also been applied in the study of RT variability, although not yet within the context of ADHD or ASD (Garrett et al., 2013). These include measures such as frequency-domain analyses, multiscale entropy, and principal components analysis applied to either the EEG or BOLD time series. Signal complexity may be related to the concepts of signal variability and neural "noise," although an exact correspondence between the many measures of each of these constructs requires further study. Interestingly, however, greater signal variability and complexity have been *negatively* correlated with RT variability in typically developing child and adult populations (Garrett, Kovacevic, McIntosh, & Grady, 2011; McIntosh, Kovacevic, & Itier, 2008), such that increased complexity in the

neural signal is associated with decreased RT variability.

Overall, these two domains together highlight an important caveat to be considered in future studies of RT variability: that "noise" within neural systems may have functional significance, including allowing these systems to flexibly adapt to changing tasks or demands (see Garrett et al., 2013 for detailed discussion). In other words, within-person brain signal variability may not simply reflect "noise" but may be functional. For example, connectionist and cellular research suggest that networks formed in the presence of greater noise are more robust to disruption, thus enhancing learning and environmental adaptation, and helping to maintain optimal performance (Basalyga & Salinas, 2006; Faisal, Selen, & Wolpert, 2008). In this sense, either too much or too little "noise" may impair performance. Signal complexity measures have also been studies as putative biomarkers of neurodevelopmental disorders (Bosl, Tierney, Tager-Flusberg, & Nelson, 2011) with some success and so understanding their relationships to behavioral measures such as RT variability may prove informative.

Motor preparation and response output. A considerable and long standing literature calls into question motor preparation and output processes in ADHD (e.g. Carte et al., 1996; Sergeant & Scholten, 1985). Thus, group differences in nondecision times, despite the complications in interpretation noted earlier, may add to this literature. Both EEG and task-based fMRI provide some support for a contribution of motor processes to RT variability. For example, contingent negative variation (CNV), one example of a slow cortical potential, can be an index of cortical activation in terms of either an orienting (initial alerting) reaction (early CNV) or preparation of a rapid execution of the motor response (late CNV). Late CNV has been found to be reduced in ADHD (e.g. Albrecht et al., 2012; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2012). Furthermore, in typically developing child populations, slow cortical potentials associated with response preparation and output have been correlated with RTs (Bender et al., 2012; Kok, 1988; Wascher, Verleger, Jaskowski, & Wauschkuhn, 1996), suggesting a role for motor preparation in determining RT variability.

Using fMRI in typically developing children, less RT variability on a go/no-go task was associated with activation in premotor circuits, and more RT variability was associated with activation in prefrontal circuits (Simmonds et al., 2007). Together, results suggests that the use of premotor circuits might be "more efficient" as compared to the use of prefrontal circuits associated with top-down cognitive control (Simmonds et al., 2007).

These findings are particularly relevant to children with ADHD, since previous studies provided evidence for structural and functional abnormalities of the pre-SMA in subjects with ADHD (Shaw et al., 2006; Tamm, Menon, Ringel, & Reiss, 2004) leading to the hypothesis that children with ADHD may recruit prefrontal regions to compensate for less efficient use of premotor systems. Indeed, a reverse brain activation pattern was observed in children with ADHD during the identical task with increased pre-SMA activation associated with more RT variability and greater prefrontal activation associated with less RT variability in the patients' group (Suskauer et al., 2008). It may be that recruitment of prefrontal resources as a compensatory mechanism for motor task performance precludes the use of those prefrontal resources for higher order executive functions with which children with ADHD often struggle.

Nevertheless, the interpretation is not straightforward. The interplay of PFC and premotor, as well as other circuits, is not necessarily linear but can include compensatory effects. The question of how PFC and motor regions interact is similar to questions raised about the interaction of top-down and bottom-up aspects of arousal networks. Contemporary models, such as dynamic causal modeling (Friston, Harrison, & Penny, 2003; Smith et al., 2011), that may address questions about complex causal network interactions have yet to be applied here although it should be noted that even these advanced models rely on model comparisons to make causal inferences, and so conclusions need to be interpreted carefully.

Summary: The most widely used neuroimaging approaches to this point in child psychopathology, MRI and EEG, provide substantial information to enable the development of behavior-brain linkages related to RT variation in ADHD, ASD, and other disorders. Nevertheless, the imaging literature related to RT variability must be considered to be preliminary because, as noted, there are relatively few studies directly linking RT variability to specific measures of neural functioning in ADHD or ASD. Findings are amenable to competing interpretations, but have some convergence with the cognitive studies summarized. SDRT in ADHD has been correlated with breakdowns in top-down control circuits, with measures of arousal states, and with neural measures of motor preparation (and thus activation, discussed in the next section). The interaction of top-down circuits with arousal or motor response networks in ADHD remains poorly understood. As with the behavioral literature, there is more available neuroimaging literature examining correlates of RT variability in ADHD than in ASD (or ASD+ADHD), and so our discussion of neural networks that may be involved in RT variability necessarily applies to a greater extent to ADHD than to ASD. Nevertheless, if comorbid ADHD accounts for increased RT variability in ADHD, then similar neural correlates

should be identified in the ASD+ADHD populations as well. If similar neural correlates are not identified, this would require re-evaluation of the suggestion that ADHD drives RT variability in ASD samples. Regardless, in both populations, convergence in understanding neural correlates, particularly of components of RT variation like drift rate, τ, or nondecision times appears tractable over time, and should help elucidate mechanisms.

A cognitive-energetics perspective on RT variability

The cognitive-energetic model (CEM) is an influential state-regulation model applied in the ADHD literature (Sergeant, 2000; Sergeant et al., 1999), and, to a lesser extent in the ASD literature. It is derived from a somewhat different intellectual tradition than the Peterson and Posner model which guided our discussion of neuroimaging findings, but also speaks to the coordination of bottom-up and top-down processes required for optimal performance on attention-demanding tasks. Although it is not explicitly a neural model, it has had a greater influence to-date on the ADHD field than other models and is frequently cited in papers attempting to interpret RT variability findings. Therefore, its consideration provides important additional insight for interpreting RT variability.

Briefly, the CEM suggests that task performance is affected by three distinct, hierarchically organized energetic pools: effort, arousal, and activation. Arousal modulates early stages of processing (such as stimulus encoding) and is related to phasic neural activity. Activation influences response preparation and motor output and is hypothesized to be related to tonic neural activation (Sergeant, 2000). The effort pool feeds each of the other energetic pools and drives central decision-making (computational) processes. The effort pool is hypothesized to be further regulated in a top-down manner by an "executive management" system (Sergeant, 2000), which we take to be similar to the top-down executive or cognitive control systems pointed out by Petersen and Posner and many other authors.

Given that all cognitive tasks require optimal management of all three energetic pools for optimal performance, differentiating their effects experimentally requires careful analysis. For example, manipulating event rates on tasks with high motor output demands (e.g. go/no go tasks) is interpreted in terms of activation, whereas increasing event rates on tasks with greater perceptual demands (e.g. continuous performance tests) is interpreted in terms of changes in arousal (Sergeant et al., 1999). In addition, in a cognitive-energetic framework, rewards may increase arousal, but they do so indirectly through the effort pool (in contrast with other models of motivation effects which cite arousal as the mediating function of reward cues; e.g. Gray, 1981).

Although effects on specific energetic pools are difficult to isolate, in general, studies of cognitive deficits in ADHD using a CEM perspective have been interpreted as supporting deficits in activation or effort more consistently than deficits in arousal. In contrast with that suggestion, it is notable that a recent meta-analysis (Metin et al., 2012) found no evidence of event rate effects on SDRT in go/no-go tasks despite finding effects on other performance variables, such as mean RT. How this converges with the small but significant differences reported here in the diffusion model parameter related to motor output (and thus to activation) is unclear; however, findings in both studies may actually be consistent with the suggestion that motor output processes (indicated by event rate measures of activation and nondecision times) are related to mean RT differences in ADHD but less so to RT variability. This hypothesis requires further evaluation in future studies.

Despite our caution that these models are not isomorphic, the CEM does have some parallels to the attention models used to guide our discussion of neural findings. For example, Aston-Jones and Cohen (2005) hypothesize that the balance of tonic and phasic NE release is related to perceived task utility, which may be determined, in part, by reward contingencies as well as by executive (strategic) considerations. This provides an important conceptual link to the CEM, which similarly suggests that cognitive performance is dependent on the state of the individual (i.e. their regulation of state in response to perceived strategic value). Nevertheless, the precise correspondence in the terminologies applied in different models is not entirely clear. For example, the "arousal" energetic pool from a CEM perspective primarily affects stimulus encoding and is related to phasic NE release based on related earlier work by Pribram and McGuinness (1975). In comparison, the phasic NE release that defines part of the "arousal" function as discussed by Aston-Jones and Cohen (2005) is empirically linked to central decision processing, a function that the CEM more closely aligns with "effort." Similarly, evidence that reward incentives may help normalize default network activation in ADHD may suggest that this network corresponds inversely to the effort construct in the CEM framework (Liddle et al., 2011) but such a suggestion must be considered speculative. Integrating the substantial literature of CEM findings in ADHD with more recent neuroscience based models of attention is beyond the scope of the current review but will be in important part of ongoing consolidation of neuroscience models of RT variability and of ADHD and ASD over time.

Future directions and key hypotheses for research

The data so far at hand suggest some specificity of RT variability effects to ADHD and a subgroup of

children with comorbid ASD and ADHD. Effects for ADHD are marginally (but not reliably) larger than for other child disorders as well. Even so, ESs for RT variability for ADHD (with or without ASD) remain moderate, and similar in size to other cognitive measures in these disorders, suggesting that only a subset of children in either population are characterized by increased RT variability or that it is quite distant from pathophysiology. For this reason, sensitivity and specificity will likely remain limited when using a strictly categorical approach to compare diagnostic and comorbid groups.

In part, many experts would propose that this is because the consensus cutoffs used to diagnose individuals with the disorders are partially arbitrary, so that a child with ASD and five symptoms of inattention and five of hyperactivity would not meet criteria for ASD+ADHD, but may be more similar to a child who did meet criteria for both disorders than to a child with ASD and few ADHD symptoms. This concern may be partially resolved by combining dimensional and categorical approaches to flesh out the relationships between ADHD, ASD, and RT variability, for example by covarying ADHD symptoms in the ASD group or by looking dimensionally to see if RT variability is related in the same way to inattention and/or hyperactivity symptoms regardless of diagnostic groupings.

Alternatively, instead of starting with diagnostic categories, it may prove fruitful to identify those children who are characterized by increased RT variability (regardless of the diagnosis) and then determine whether they share other similarities in associated neural, genetic, cognitive, behavioral, or clinical outcomes. Within the ADHD literature, person-centered approaches that can identify subgroups of children who share features are just beginning to be applied to cognitive profiles (e.g. using graph theory community detection approach, Fair, Bathula, Nikolas, & Nigg, 2012), but have not yet been applied with the ASD literature or within samples containing children with a range of diagnostic designations, which will be an important future direction for the field. Which cognitive parameters to include in these types of grouping analyses will also be an important consideration. RT variability's relationship to other measures of cognitive processing, such as working memory, attention, or inhibition remains unclear. It may mediate deficits in these other cognitive domains (Karalunas & Huang-Pollock, 2013) or reflect a distinct cognitive problem, and exploring these relationships will be important for determining which input features are needed to understand heterogeneity based on cognitive function.

In addition to questions about how best to approach diagnostic heterogeneity, the field has also wrestled with the best measurement approach to quantifying RT variability. Alternative analysis approaches have not increased measurement sensitivity (at least in ADHD), but have helped characterize specific ways in which RT distributions differ and narrowed the focus as a target for future neuroimaging work. A key task for the field is to empirically evaluate the association of these conceptually more well-defined parameters with cognitive (e.g. Karalunas & Huang-Pollock, 2013) and neural (e.g. Jackson, Balota, Duchek, & Head, 2012; Lin et al., 2013) correlates in clinical populations, which will not only address questions about mechanisms of RT variability, but also has the potential to aid in linking cheap, reliable behavioral measures with specific neural markers of disease.

Nevertheless, these cognitive models have their own limitations. Ex-Gaussian models can be applied to a wide range of task types, however, they do not take into account response accuracy and the cognitive interpretation of parameters remains unclear. Conversely, diffusion model parameters have somewhat clearer cognitive interpretations, but cannot easily be applied to tasks other than forced two-choice paradigms, which leaves out many tasks commonly used in the clinical literature. In both cases, defining and eliminating outlier data points can be somewhat arbitrary. Thus, additional models are needed, as are studies that examine the relationships between parameters in different models (e.g. Feige et al., 2013), so that those with broader applicability can be more firmly interpreted in terms of mechanisms.

In the future, an emphasis should also be placed on studies that simultaneously test competing hypotheses about possible mechanisms. It seems unlikely that RT variability reflects one unitary cognitive mechanism. Rather, RT variability may reflect different antecedents depending on task, practice (Allaire & Marsiske, 2005), and time scale (Schmiedek et al., 2009). For this reason, it is important to consider the possibiltiy that grouping individuals who share the common feature of RT variability, as suggested above, may not reduce within-group heterogeneity. Combining studies using person-centered approaches with RT decomposition and neuroimaging approaches that can help clarify which mechanisms are at play for different individuals will be important.

In addition, in future studies it will be important to employ methods suitable for quantifying the complex interactions between different brain regions and networks. In functional imaging studies, contemporary models, such as dynamic causal modeling (Friston et al., 2003; Smith et al., 2011), have yet to be applied to the study of RT variability. In addition, neuroimaging methods with high temporal resolutions, such as EEG or MEG, combined with new statistical approaches to characterize RT variability might be particularly suited to clarify the neurobiological basis of trial-to-trial variability. For example, more research is needed on ERP single trial variability focusing on the relative contributions of

latency, amplitude, and topography variability of different ERP components to RT variability.

It may also be particularly useful to apply broader range of measures to look for convergent validity across biological systems. Processes such as arousal can be assessed via peripheral nervous system measures of skin conductance and pre-ejection period (Berntson, Quigley, & Lozano, 2007; Dawson, Schell, & Filion, 2007). Peripheral nervous system measures have only rarely been studied in conjunction with RT variability (but see for example Börger et al., 1999; Sroufe, Sonies, West, & Wright, 1973), but future studies employing these measures may prove informative.

Conclusions

Where does this leave us? While certain of our conclusions are necessarily quite preliminary, the review leads to several specific hypotheses that can be tested and challenged going forward, as well as highlights the need for studies addressing specific questions. First, RT variability shows some specificity to ADHD, including to a subset of children with ASD who share comorbid ADHD diagnosis, but more comparison across clinical populations that considers task decomposition will remain helpful in understanding subgroups. Second, RT variability in ADHD is explained by very slow RTs on some trials (τ parameter) and by slow drift rate, as well as to a lesser extent by faster nondecision times, which may be related to inefficient motor organization. Third, there remains ample need for more studies attempting to distinguish the role of top-down executive control from resource allocation or availability (e.g. effort, activation, or arousal) explanations of RT variability in ADHD or ASD. Nonetheless, at the behavioral level, we can suggest that RT variability is likely a measure of mechanisms already under investigation in ADHD (cognitive control, arousal, motor output problems) rather than a distinct or novel mechanism. The neuroimaging literature converges with this picture and highlights the importance of considering the interaction of top-down control networks with those involved in arousal and motor preparation. A match of cognitive decomposition with imaging methods may help to resolve apparent differences between studies and to better understand individual differences in response style, which are key goals for the next set of studies in the field.

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Key points

- Intraindividual variability in reaction times has received extensive discussion as an indicator of cognitive performance and a putative intermediate phenotype of many clinical disorders, including ADHD and ASD.
- Reaction-time (RT) variability is well-documented in ADHD. Although relatively few studies have examined RT variability in ASD, the current review and meta-analysis suggest that RT variability is present in ASD only when a comorbid ASD+ADHD group is included in analyses.
- RT variability in ADHD is primarily explained by very slow RTs on some trials (τ parameter) and by slow drift rate, which may implicate low alertness/arousal as a mechanism of increased RT variability and difficulty distinguishing signal from noise in speeded decision-making.
- In turn, this could be related in the brain to alterations in ascending norepinephrine systems and/or in top-down circuits that regulate arousal via dampening effects on sub-cortical norepinephrine neurons. That said, the neuroimaging literature also provides some evidence for motor preparation or activation in determining RT variability, which may be consistent with the small but significant effects found for group differences in nondecisional processing in ADHD.
- Future studies employing dimensional and person-centered approaches, testing multiple competing theories within the same samples, and identifying convergent evidence across cognitive, central, and peripheral nervous system measures are needed to better characterize mechanisms contributing to increased RT variability in ADHD or ASD populations.

Note

1. One conceptual difference is that whereas signal detection parameters are based on accuracy data, diffusion model parameters are estimated from RT distributions. This is a potential benefit because signal detection parameter estimates (which rely on accuracy scores) are most reliable when accuracy is around 50%, but many tasks used have higher or lower accuracy rates, making analysis of signal detection measures problematic (Chapman & Chapman, 1973, 1978).

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