Increased response-time intrasubject variability (RT-ISV) has been consistently documented in individuals with ADHD (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005; Halperin, Trampush, Miller, Marks, & Newcorn, 2008; Hervey et al., 2006; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Kuntsi, Oosterlaan, & Stevenson, 2000). Such increased variability could represent greater randomness, that is, noise. Instead, most investigators have observed that increased RT-ISV is characterized by periodic bursts of particularly long response times (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Hervey et al., 2006; Leth-Steensen, Elbaz, & Douglas, 2000). Such increased variability could represent greater randomness, that is, noise. Instead, most investigators have observed that increased RT-ISV is characterized by periodic bursts of particularly long response times (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Hervey et al., 2006; Leth-Steensen, Elbaz, & Douglas, 2000). Such ADHD-related increases of RT-ISV, indexed as RT standard deviation or its coefficient of variation, are robust across different tasks and analytical approaches (Klein et al., 2006; Rubia et al., 2001).

Beyond such standard time-domain analyses, RT time series data are also amenable to frequency-domain analyses. In children with ADHD, frequency analyses have generally found increased rates of extremely long RTs in frequency ranges typically below 0.2 Hz (>5 s/cycle; Castellanos et al., 2005; Di Martino et al., 2008; Johnson, Kelly, et al., 2007; Vaurio, Simmonds, & Mostofsky, 2009). These observations are consistent with the hypothesis that fluctuations in RT reflect intrinsic brain activity fluctuations occurring in similar frequency ranges (Castellanos et al., 2005; Fox, Snyder, Vincent, & Raichle, 2007; Johnson, Kelly, et al., 2007; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Sonuga-Barke & Castellanos, 2007; Zuo et al., 2010). If so, RT fluctuations would be expected to generalize across tasks and laboratories. Yet, to date, this has not been directly explored, as initial studies of the frequency structure of RT in ADHD have used different task paradigms and analytical techniques.

Specifically, in individuals with ADHD, increased RT fluctuations in frequency ranges below 0.07 Hz (period ≥ 14 s)

**Abstract**

**Objective:** Increased response-time (RT) fluctuations below 0.2 Hz have been reported as characteristic of ADHD in some but not all studies, possibly due to methodological differences. Accordingly, we contrasted two tasks and two analytical approaches in the same sample of children with ADHD. **Method:** Fifty-two children with ADHD and 49 typically developing children completed an Eriksen Flanker Task and a fixed-sequence version of the sustained attention to response task. RT fluctuations with two different frequency analyses were examined. **Results:** Robust ADHD-related increases of slow RT fluctuations within all frequencies were found in both tasks. Tasks were significantly correlated in both groups for frequencies above 0.07 Hz. RT fluctuations across all frequencies were greatest in children with ADHD with abnormally elevated omissions. **Conclusion:** We observed significantly increased fluctuations of RT in children with ADHD across two different tasks and methods supporting the hypothesis that slow frequency RT fluctuations reflect neurophysiological processes underlying ADHD. (J. of Att. Dis. 2014; 18(5) 434-446)

**Keywords**

ADHD, childhood psychiatric symptoms, cognitive control, neurobiology

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**Increased Response-Time Variability Across Different Cognitive Tasks in Children With ADHD**

Nicoletta Adamo, Adriana Di Martino, Lidia Esu, Eva Petkova, Katherine Johnson, Simon Kelly, Francisco Xavier Castellanos, and Alessandro Zuddas

**Article**
were found in some studies (Di Martino et al., 2008; Johnson, Kelly, et al., 2007; Vaurio et al., 2009) but not in others (Geurts et al., 2008; Johnson, Barry, et al., 2008). ADHD-related increases in RT-ISV in faster frequencies (e.g., >0.07 Hz; period <14 s) have also been reported when the task design allowed sampling a wider frequency range (Helps, Broyd, Bitsakou, & Sonuga-Barke, 2011; Johnson, Barry, et al., 2008; Johnson, Kelly, et al., 2007; Johnson, Kelly, et al., 2008). Furthermore, the frequency bands distinguishing children with ADHD from typically developing children (TDC) were found to depend on task cognitive load (Vaurio et al., 2009). Differences in results may stem from differences in subject pool variation across studies but could also be explained by task designs and their imposition of task-inherent frequency structure onto RT time series. To better understand the role of task-related factors in the expression of heightened RT-ISV characteristic of ADHD, it is critical to perform within-subject task manipulations.

Different approaches examining RT-ISV fluctuations have not been tested previously in the same individuals. Here, in the same sample of children with ADHD and TDC, we administered two tasks on which RT-ISV differences had been separately established. We used an arrow version of the Eriksen Flanker Task (EFT; Castellanos et al., 2005; Di Martino et al., 2008) and the fixed order version of the sustained attention to response task (SART; Johnson, Kelly, et al., 2007). We aimed to study whether different tasks and analytical approaches would reveal the same pattern of RT fluctuations in our sample. We measured the amplitude of fluctuations in three frequency bands selected a priori (Penttonen & Buzsaki, 2003) through continuous Morlet wavelet transform (CWT). In a parallel analysis, we used the fast Fourier transform (FFT) to examine two frequency bands demarcated by the SART-generated frequency peak about 0.07 Hz (Johnson, Kelly, et al., 2007). We expected that, relative to the TDC, the ADHD group would show an elevated RT power spectrum across all examined frequencies in both tasks and analytical approaches. In addition, beyond group differences in the broad spectrum, we systematically examined correlations between the tasks for each frequency band. Finally, we tested whether combining measures of RT spectral amplitude obtained with both tasks could more strongly discriminate groups than each alone.

**Method**

**Participants**

We enrolled 53 TDC and 70 children with ADHD between 6.8 and 13.6 years of age. Children with ADHD were recruited through the outpatient Clinic of Child and Adolescent Psychiatry of the University of Cagliari, Italy. Signed informed consent and written child assent were obtained from parents and children, respectively, as approved by the University of Cagliari Ethics Committee. Families did not receive any reimbursement for participation.

Inclusion as ADHD required a *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) diagnosis of ADHD, based on the Parent Interview for Children Symptoms (PICS-IV; Ickowicz et al., 2006; Schachar, Icowicz, & Tannock, 1996; Zuddas et al., 2006), child behavioral observation by child psychiatry residents, and a T-score >60 for at least one of the ADHD-related indices of the Conners’ Parent Rating Scale–Revised: Long Version (CPRS-R:L; Conners, 1997; Nobile, Alberti, & Zuddas, 2007). Sixty-eight (97%) of the children with ADHD met criteria for combined type ADHD, the remaining 2 for predominately inattentive type ADHD.

As shown in Table 1, 43 children with ADHD had comorbid diagnoses. The presence of known neurological conditions, major depression, posttraumatic stress disorders, as well as psychosis was exclusionary. Global functioning was quantified with the Children’s Global Assessment Scale (CGAS; Shaffer et al., 1983). Treatment with any psychotropic medications except for stimulants was exclusionary. Among the ADHD group, 45 children (64%) were medication-naïve, and 4 (6%) had discontinued medication treatment for at least 4 months. The remaining 21 (30%) were tested during scheduled medication holidays after discontinuation for at least 7 days (e.g., summer and other school breaks).

Children recruited from the local community through word of mouth and pediatric referrals were included as TDC if all summary indices of the CPRS-R:L were <60. We included only children with full IQ >80 based on a Wechsler Intelligence Scale for Children–Third Edition (Wechsler, 1991) in 67 children with ADHD and all TDC, and the Leiter International Performance Scale–Revised (Roid & Miller, 1997) in 3 children with ADHD. To further characterize the sample, the Italian version of the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001; Frigerio et al., 2004) was collected for all participants. Given reports of increased autistic traits in groups of children with ADHD and autism spectrum disorders (ASD; Geurts et al., 2008). We also obtained parent ratings of the Italian version of the Social Responsiveness Scale (SRS; Constantino et al., 2003; Constantino & Gruber, 2005; Zuddas, Di Martino, Delitala, Anchisi, & Melis, 2010) for all participants but one TDC. Handedness was reported by parents and observed during testing. Siblings were excluded to assure independence of observations. All participants were Caucasian, representing the predominant ethnic group receiving clinical services at the University of Cagliari.

The sample size for the study was selected to allow 80% power of a two-sided test to detect group differences of large magnitude (Cohen’s $d$.8; similarly to previous reports, as Di
Martino et al., 2008, and Johnson, Kelly, et al., 2007), while adequately accounting for multiple testing ($\alpha = .0045$). This required a sample of at least 45 participants per diagnostic group. At the recruitment stage of this study, we oversampled to account for possible data loss related to excessive omission.

**Materials and Procedure**

**Computerized Tasks.** The EFT and the SART were administered to all participants in a single session with task order counterbalanced (see Table 1).

**Table 1. Clinical Characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>ADHD ($n = 70$)</th>
<th>TDC ($n = 53$)</th>
<th>Group comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>$%$</td>
<td>$n$</td>
</tr>
<tr>
<td>Boys</td>
<td>62</td>
<td>89</td>
<td>47</td>
</tr>
<tr>
<td>Right-handed</td>
<td>62</td>
<td>89</td>
<td>49</td>
</tr>
<tr>
<td>Sequence EFT—SART</td>
<td>27</td>
<td>39</td>
<td>26</td>
</tr>
</tbody>
</table>

**ANOVA**

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<th></th>
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<th>SD</th>
<th>M</th>
<th>SD</th>
<th>$F(1, 97)$</th>
<th>$p$</th>
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<td>2</td>
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<td>Full-Scale IQ</td>
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<td>12</td>
<td>108</td>
<td>11</td>
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<tr>
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<td>12</td>
<td>106</td>
<td>10</td>
<td>17.7</td>
<td>&lt;.001</td>
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<tr>
<td>Performance IQ</td>
<td>99</td>
<td>14</td>
<td>108</td>
<td>13</td>
<td>11.9</td>
<td>.001</td>
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<tr>
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<td></td>
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<tr>
<td>ADHD Index</td>
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<td>43</td>
<td>5</td>
<td>370.0</td>
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<tr>
<td>DSM-IV Inattention</td>
<td>76</td>
<td>13</td>
<td>44</td>
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<tr>
<td>DSM-IV Hyper/Impuls</td>
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<td>14</td>
<td>42</td>
<td>5</td>
<td>270.4</td>
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<tr>
<td>DSM-IV Total</td>
<td>78</td>
<td>13</td>
<td>42</td>
<td>5</td>
<td>372.1</td>
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</table>

**CBCL-Syndrome Scale parent**

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<th>M</th>
<th>SD</th>
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<tbody>
<tr>
<td>CBCL Total</td>
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<td>CBCL Internalizing</td>
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<td>9</td>
<td>50</td>
<td>9</td>
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<tr>
<td>CBCL Externalizing</td>
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<td>9</td>
<td>46</td>
<td>8</td>
<td>164.7</td>
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**SRS parent T-scores**

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<th>M</th>
<th>SD</th>
<th>$F(1, 97)$</th>
<th>$p$</th>
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<td>SRS total</td>
<td>69</td>
<td>27</td>
<td>24</td>
<td>15</td>
<td>121.5</td>
<td>&lt;.001</td>
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**Comorbidity**

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<tr>
<td>ADHD + ODD</td>
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<td>30</td>
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<td>ADHD + ODD + LD</td>
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<td>ADHD + ODD + 1 or more Disorder</td>
<td>5</td>
<td>7</td>
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<tr>
<td>ADHD + LD</td>
<td>4</td>
<td>6</td>
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<td>ADHD + GAD</td>
<td>2</td>
<td>3</td>
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<td>ADHD + Expressive language Disorder</td>
<td>1</td>
<td>1</td>
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<tr>
<td>ADHD + Enuresis</td>
<td>1</td>
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<tr>
<td>ADHD + AD</td>
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Note: TDC = typically developing children; EFT = Eriksen Flanker Task; SART = sustained attention to response task; CPRS-R-L = Conners’ Parent Rating Scale–Revised: Long Version; DSM-IV Hyper/Impuls = DSM-IV Hyperactivity/Impulsivity index; CBCL = Child Behavior Checklist; SRS = Social Responsiveness Scale; ODD = Oppositional Defiant Disorder; LD = Learning Disorder (reading disorder, writing disorder, dyscalculia); GAD = Generalized Anxiety Disorder.

*Verbal IQ and Performance IQ were available for 53 TDC and 66 ADHD.

**SRS Ratings** were available for 52 TDC and all children with ADHD.

EFT. We administered the same 6.5-min arrow version of the EFT previously detailed (Castellanos et al., 2005; Di Martino et al., 2008; Scheres, Oosterlaan, & Sergeant, 2001) where three trial types (neutral, congruent, and incongruent) were presented in pseudorandom order with equal probability. Children were instructed to respond to the target stimuli by pressing the right or left keys on a keyboard according to the direction of the target. We administered the same pseudorandomized sequence of trials to all participants. Trials were presented continuously with a 3.0 s interstimulus interval (ISI). The first 30 s were discarded to account for adjustment effects, leaving 120 trials for analyses. This test was preceded by one or two practice
sessions (90 s each) depending on participants’ ability to attain 80% accuracy in the first practice. More children with ADHD completed two practice sessions compared with TDC: 39 versus 16; \( \chi^2(1) = 7.9; p < .01 \).

**SART.** We administered the same fixed sequence version of the SART as previously published (Johnson, Barry, et al., 2008; Johnson, Kelly, et al., 2007, 2008; Johnson, Robertson, et al., 2007). In this Go/No Go task, the digits “1” to “9” are repeatedly presented in ascending order, with a 1.5 s ISI. Participants were instructed to press the left mouse button in response to the target stimulus that followed any digit (Go trial) except “3” (No-Go trial). A total of 225 trials were presented over approximately 5.5 min. As in prior studies, all 225 trials were analyzed (Johnson, Barry, et al., 2008; Johnson, Kelly, et al., 2007, 2008; Johnson, Robertson, et al., 2007).

**Time- and Frequency-Domain Analyses.** We analyzed RT data from children with fewer than 15% missing responses to any given trial type for both tasks. This led to the exclusion of data from 18 children with ADHD versus 4 TDC; \( \chi^2(1) = 6.8; p < .01 \). Of them, 10 children with ADHD and 2 TDC were excluded from both tasks, while data from 8 children with ADHD and 2 TDC were excluded from one task or the other. Children with excluded data were significantly younger. Otherwise, they did not differ significantly on any measures of ADHD severity nor in sex distribution.

**Time domain.** For each task, we analyzed RT data with more than 10% missing responses to any given trial type for both tasks. This led to the exclusion of data from 18 children with ADHD versus 4 TDC; \( \chi^2(1) = 6.8; p < .01 \). Of them, 10 children with ADHD and 2 TDC were excluded from both tasks, while data from 8 children with ADHD and 2 TDC were excluded from one task or the other. Children with excluded data were significantly younger. Otherwise, they did not differ significantly on any measures of ADHD severity nor in sex distribution.

**Frequency domain.** We analyzed data in accordance with previously published approaches applied to each task (Di Martino et al., 2008; Johnson, Kelly, et al., 2007). In one approach (Di Martino et al., 2008), we first interpolated missing and anticipatory responses (RT \( \leq 100 \) ms) with the average RT of the immediate neighbors in both tasks. Given the pseudorandomized sequence of trials used for the EFT, we controlled for potential effects of trial type on RT-ISV applying a linear regression that yielded residual time series. It was not necessary to regress out trial type for the SART as its fixed sequence guarantees containment of trial type effects in the spectral peak at 0.077 Hz, which we subsequently excluded from frequency analyses. We then conducted frequency analyses using CWT with Morlet wavelets (for both tasks: 400 scales, half-length 20) implemented in the Matlab Time-Frequency Toolbox (The MathWorks, Natick, Massachusetts; http://tfdb.nongnu.org). We examined the frequency ranges from 0.0055 Hz to 0.167 Hz, and from 0.006 Hz to 0.34 Hz, for the EFT and the SART, respectively. We determined the upper bound of these ranges based on the ISI for each task (1/2\( \Delta t \), where \( \Delta t \) is the ISI) consistent with the Nyquist theorem. The lower bound of each range was determined by the task duration (1/[n\( \Delta t \)/2]). For each child and for each task, the resulting time-frequency amplitude maps (called scalograms) were averaged across time. We then divided the time-averaged spectra into bands a priori identified based on the model of Penttonen and Buzsáki (2003). Specifically, we computed amplitudes for Slow-5 (0.010-0.027 Hz), Slow-4 (0.027-0.073 Hz), and Slow-3 (0.073-0.2 Hz) for both tasks. The EFT sampling periodicity of 3 s, the upper bound of Slow-3 extended only to 0.167 Hz. Follow-up analyses examining SART Slow-3 with the EFT limits (0.073-0.167 Hz) did not substantially change results. Higher frequencies captured only by the SART were referred to as Slow-2 (0.2-0.34 Hz).

In the alternative spectral analysis approach (Johnson, Kelly, et al., 2007), we implemented the FFT. As above, we used time series of residuals for the EFT and the interpolated RT time series for the SART. For each task, we divided the full-time series in partially overlapping segments, obtaining seven segments of 75 data points (with an overlap of 50) and six segments of 45 data points (with overlap of 30) for the SART and the EFT, respectively. The FFT was applied with Hamming windows to each segment, and the resulting frequency power (amplitude squared) was averaged across segments to obtain the power spectrum for each participant. FFT analyses quantified the power of frequencies in the intervals from 0 to 0.167 Hz and from 0 to 0.34 Hz for the EFT and the SART, respectively. These frequency intervals were divided into two frequency bands, the slow- and fast-frequency area under the spectrum (SFAUS: 0.010-0.071 Hz, for both tasks, and FFAUS: 0.083-0.34 Hz [SART] and 0.083-0.167 Hz [EFT]). These bands were defined as being below or above the spectral peak produced by the fixed SART sequence at 0.077 Hz; we excluded five frequency bins above and below the peak (Johnson, Kelly, et al., 2007).

**Statistical Analyses**

To assess group differences with respect to both time and frequency domain for each task, we conducted analyses of covariance adjusting for age and sex. These analyses did not adjust for IQ, despite group differences, because there were no significant relationships between RT-SD and IQ within either group for either task. Measures of effect sizes were reported as Cohen’s \( d \) (converted from partial \( \eta^2 \)). Statistical significance was conservatively set at \( \alpha = .0045 \) to correct for all 12 comparisons in time and frequency domains.

To measure consistency across tasks in detecting patterns of increased RT-ISV, we computed Pearson’s correlations for each of the frequency bands measured with the same approach between the two tasks in the 44 children with ADHD and 47 TDC who completed both tasks. To test whether these correlations differ significantly between
diagnostic groups, we conducted a regression analysis modeling the frequency measure of one of the tasks (e.g., Slow-3 in EFT) as a function of the same frequency measure from the other task (e.g., Slow-3 in SART), diagnostic group, and their interaction. Then, we tested for significance of the interaction term.

Finally, to assess the effect of combining RT-ISV measures from two tasks in differentiating groups, we first computed z scores of the ISV indices (Slow-3, Slow-4, Slow-5, SFAUS, and FFAUS) for each task (using the mean and SD of the whole sample). Then, we calculated a combined z scores of each ISV index by averaging the two tasks’ z scores for each child. Analyses of covariance adjusting for age and sex were used to assess group differences of combined z scores. Correlation analyses between RT-ISV domain indices and scores of ADHD-related symptoms and autistic traits (CBCL attention problems and SRS total T-score, respectively) were conducted within each groups using a significance threshold corrected for multiple comparisons, of \( \alpha = 0.025 \).

**Results**

**Demographics**

The ADHD and the TDC groups were group-matched on age and sex, and did not differ significantly in handedness (see Table 1). Children with ADHD had significantly lower IQ scores and significantly higher T-scores on all the clinical indices than TDC.

**Time Domain**

As expected, relative to TDC, children with ADHD showed increased RT-ISV indexed by RT-SD for both tasks with large effect sizes (see Table 2). Differences in mean RT on the EFT did not reach statistical significance, and no group differences were detected in SART mean response speed. In both tasks, children with ADHD made a significantly higher number of omissions and errors with medium to large effect sizes relative to TDC.

**Frequency Domain**

Consistent with the increases in RT-SD, both approaches showed greater amplitude of fluctuations across the whole targeted spectra in children with ADHD relative to TDC for both tasks. Specifically, increases in CWT-measured Slow-3 and Slow-4 amplitudes characterized the children with ADHD relative to TDC on both tasks. Slow-5 CWT amplitudes were significantly greater for the ADHD group for the EFT; whereas for the SART, greater Slow-5 amplitude in ADHD did not meet our significance threshold. The SFAUS and the FFAUS measured with the FFT in both tasks were significantly increased in children with ADHD relative to TDC (Figure 1, Table 3). Overall, effect sizes were large for all EFT frequency bands measured with either approach and medium to large for all SART frequency bands, except for Slow-5.

**Consistency Between Tasks**

Figure 2 shows correlations across the tasks for all frequency bands and both groups. At the higher frequencies (Slow-3 and FFAUS), we found significant correlations across tasks within both TDC and children with ADHD. For Slow-4, the correlation across the two tasks was only significant for TDC. Slow-5 did not correlate significantly between tasks for either group. SFAUS amplitude was significantly correlated across tasks only in TDC.

### Table 2. Group Comparisons on Time-Domain Measures for the Eriksen Flanker Task and the Sustained Attention Response Task.

<table>
<thead>
<tr>
<th></th>
<th>TDC (n = 49)</th>
<th>ADHD (n = 52)</th>
<th>Group comparisons</th>
</tr>
</thead>
<tbody>
<tr>
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<td>M SD M SD</td>
<td>M SD M SD</td>
<td>ANCOVA age and sex</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>43 (88)</td>
<td>46 (88)</td>
<td></td>
</tr>
<tr>
<td>Mean RT</td>
<td>600 68 615 58</td>
<td>5.01 .028 0.5</td>
<td></td>
</tr>
<tr>
<td>RT-SD</td>
<td>106 24 126 25</td>
<td>33.59 &lt;.001 1.2</td>
<td></td>
</tr>
<tr>
<td>Omission errors</td>
<td>3.7 4.0 6.9 5.3</td>
<td>21.37 &lt;.001 0.9</td>
<td></td>
</tr>
<tr>
<td>Directional errors</td>
<td>4.0 5.1 6.5 6.7</td>
<td>10.09 .002 0.6</td>
<td></td>
</tr>
<tr>
<td>Commission errors</td>
<td>— — — — — —</td>
<td>3.8 2.4 6.9 3.8</td>
<td>27.33 &lt;.001 1.1</td>
</tr>
</tbody>
</table>

Note: EFT = Eriksen Flanker Task; SART = sustained attention to response task; TDC = typically developing children; RT = response-time; RT-SD = standard deviation of response time; Directional errors (EFT) = failure to detect the direction of the target; Commission errors (SART) = failure to inhibit responses to non-target, namely No-Go Trial Responses.
Figure 1. Average amplitude of each frequency for the EFT and the SART, measured with the CWT and the FFT (top and bottom row, respectively) for children with ADHD (red) and TDC (blue).

Note: EFT = Eriksen Flanker Task; SART = sustained attention to response task; CWT = continuous wavelet transform; FFT = fast Fourier transform; S-5 = Slow-5; S-4 = Slow-4; S-3 = Slow-3; S-2 = Slow-2; TDC = typically developing children; SF = slow-frequency area under the spectrum; FF = fast-frequency area under the spectrum. Frequency bands are represented on the x axis; amplitudes (for CWT) and power (FFT) averaged over time across all subjects per group are displayed on the y axis.

Combined Measures Across Tasks

Significant ADHD-related increases were confirmed across all the RT-ISV indices using combined z scores, with large effect sizes. Of note, where the group comparisons yielded moderate effect sizes using one task alone (e.g., Slow-5 for the SART), combining the indices of the two tasks resulted in large effect sizes (for RT-SD, \( d = 1.3 \); for Slow-3, Slow-4, and Slow-5, \( d = 1.2, 1, \) and \( 0.8, \) respectively; for SFAUS and FFAUS, \( d = 1 \) and \( 1.1, \) respectively).

Correlations With Symptoms

RT-ISV time- and frequency-domain measures did not correlate significantly with parent ratings on the CBCL or the SRS.

Secondary Analyses: ADHD Impaired

Following the approach of a previous study (Johnson, Kelly, et al., 2007), we divided children with ADHD into...
Table 3. Group Comparisons on RT-ISV Measures in the Frequency Domain for the Eriksen Flanker Task and the Sustained Attention Response Task.

<table>
<thead>
<tr>
<th></th>
<th>EFT</th>
<th>SART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDC (n = 49)</td>
<td>ADHD (n = 52)</td>
</tr>
<tr>
<td></td>
<td>Group comparisons</td>
<td>ANCOVA age and sex</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>CWT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow-2 (0.2-0.34 Hz)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Slow-3 (0.073-0.2 Hz)</td>
<td>11,626</td>
<td>5,520</td>
</tr>
<tr>
<td>Slow-4 (0.023-0.073 Hz)</td>
<td>14,384</td>
<td>8,420</td>
</tr>
<tr>
<td>Slow-5 (0.010-0.027 Hz)</td>
<td>15,776</td>
<td>10,021</td>
</tr>
<tr>
<td>Slow whole</td>
<td>14,206</td>
<td>7,585</td>
</tr>
<tr>
<td>FFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFAUS</td>
<td>423</td>
<td>247</td>
</tr>
<tr>
<td>FFAUS</td>
<td>304</td>
<td>149</td>
</tr>
</tbody>
</table>

Note: RT-ISV = response-time intrasubject variability; EFT = Eriksen Flanker Task; SART = sustained attention to response task; TDC = typically developing children; CWT = continuous wavelet transform; FFT = fast Fourier transform; SFAUS = slow-frequency area under the spectrum; FFAUS = fast-frequency area under the spectrum. Amplitudes of each frequency band as measured with the CWT and the FFT for the EFT and the FFT and the SART. For the CWT each band's amplitude is measured in ms/Hz². For the FFT the power of each band is measured in ms².

*aNote that for the EFT, the Slow-3 frequency band is delimited by the upper frequency captured by the tasks (0.17 Hz).

Discussion

Using two different tasks, we examined ADHD-related differences in RT-ISV in time and frequency domains in the same sample of children with and without ADHD. Independently of the task and the frequency-analyses used, we confirmed increased RT-ISV in the time domain (increased RT-SD) as well as in slow (<0.07 Hz) and fast (>0.07 Hz) frequency ranges differentiating children with ADHD from TDC.

Our results are consistent with a growing literature examining RT-ISV in both time (Hervey et al., 2006; Klein et al., 2006; Leth-Steensen et al., 2000; Rubia et al., 2001) and frequency domains (Castellanos et al., 2005; Di Martino et al., 2008; Helps et al., 2011; Johnson, Kelly, et al., 2007, 2008; Vaurio et al., 2009), but they contradict a report that failed to find either time- or frequency-domain differences in RT-ISV between children with ADHD and TDC (Geurts et al., 2008). Instead, Geurts et al. (2008) found that, on a brief simple choice response task, only those children with ASD and comorbid ADHD exhibited significantly elevated RT-ISV. In our sample, the presence of autistic traits, as indexed by the SRS, did not relate to RT-ISV measures. This is consistent with Johnson, Robertson, et al. (2007), who found that children with ADHD showed significantly increased RT-ISV relative to children with ASD and TDC on a 5.5-min-long SART. Future studies with large samples including both children with ADHD and with ASD with and without overlap will clarify the role of autistic traits in RT-ISV.
Our interest in frequency-domain analyses of behavioral measures is based on their hypothesized relationship to the low-frequency intrinsic fluctuations of large-scale brain networks (Sonuga-Barke & Castellanos, 2007). The most studied intrinsic connectivity network, the default network, is largely composed of midline prefrontal and posterior parietal regions that underlie internally oriented and task-unrelated mentation (Buckner, Andrews-Hanna, & Schacter, 2008). Aberrant modulation of the default network has been associated with lapses of externally oriented attention in controls (Prado, Carp, & Weissman, 2011; Weissman, Roberts, Visscher, & Woldorff, 2006) and has been demonstrated in individuals with ADHD (Castellanos et al., 2008). Thus, obtaining objective measures of RT fluctuations that can generalize across tasks and laboratories can advance the search for pathophysiological markers of ADHD.

Task complexity was recently reported to affect the direction and type of ADHD-related differences in ISV (Vaurio et al., 2009). Here, rather than manipulating workload, we used two brief tasks that probe similar processes but differ in capturing specific frequency aspects of RT-ISV. Despite differences in task design and data analyses, we found that both tasks yielded medium to large effect sizes in differentiating children with ADHD from TDC independent of analytical approach. In addition, RT-ISV measures correlated significantly across tasks. Correlation magnitudes were greatest for the faster frequency bands (>0.07 Hz) for both diagnostic groups and were completely absent at the slowest range (Slow-5), whereas at Slow-4, correlations across tasks did not reach significance for children with ADHD.

In prior work, Di Martino et al. (2008) found that fluctuations in the Slow-4 band had the greatest ability to differentiate children with ADHD from controls, even after controlling for the effects of RT-SD. Basal ganglia neurons fire spontaneously at frequencies mostly within Slow-4 (Ruskin et al., 2001; Walters, Ruskin, Baek, Allers, &...
Bergstrom, 2001), and Slow-4 fluctuations in blood oxygen level–dependent signal during magnetic resonance imaging distinguish the basal ganglia in humans (Zuo et al., 2010). In an analysis of error time series, Slow-4 fluctuations were significantly increased in children with ADHD (Yordanova et al., 2011). We speculate that variability at faster frequencies is more likely to correlate significantly across tasks because faster frequencies are estimated with greater precision (Fornito et al., 2011), even if Slow-4 and similarly slow frequencies may be physiologically relevant.

In this vein, fluctuations in the Slow-2 range were reported to be most distinct from underlying 1/f noise, to best differentiate children with ADHD and to show the greatest evidence of familiality (Helps et al., 2011). Although we could only measure Slow-2 with the SART (given its faster ISI), both tasks captured the ADHD-related increases in frequencies >0.07 Hz despite differences in task design. Future work will need to examine directly which frequencies in behavioral fluctuations in RT are most related to which intrinsic fluctuations in brain.

When we subdivided the ADHD group into ADHD-impaired and ADHD-unimpaired subgroups, we found that our group differences in RT fluctuations were specifically driven by the ADHD-impaired subset. This is in line with
the repeated observation that only a portion of participants with ADHD exhibit abnormal performance in specific neuropsychological tests (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002; Nigg, Blaskey, Stawicki, & Sachek, 2004; Nigg, Willcut, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke & Castellanos, 2007). However, we did not observe significant differences in clinical indices between the ADHD-impaired and the ADHD-unimpaired groups, perhaps because the subgroup sample sizes were moderate. Although we did not find a direct relationship between RT-ISV measures and clinical ratings, we hypothesize that children who are particularly characterized by increased slow RT fluctuations will be most likely to exhibit hypothesized differences in neuronal circuitry that have been reported to mediate prolonged RTs that are interpreted as lapses of attention (Weissman et al., 2006). Ongoing work aims to investigate this pathophysiological mechanism in children with ADHD and TDC.

Our results should be considered in light of several limitations. Children with ADHD in our study exhibited substantial comorbidity, including oppositional defiant disorder and learning disorders. However, we did not detect significant between-group differences in any RT-ISV indices when we compared children with and without comorbidity (data not shown). Future studies designed with homogeneous comorbid groups are warranted to explore the effect of specific disorders often comorbid with ADHD on RT-ISV. Although we characterized children included as TDC with three parent rating scales that are widely used in clinical settings, we did not complete a full clinical assessment to definitively exclude psychiatric diagnoses. Thus, we cannot exclude the possibility that undetected psychiatric conditions may have diminished group differences. Due to the limited size of the subsamples, we could not evaluate consistency across tasks for the ADHD-impaired and ADHD-unimpaired groups. Finally, the groups differed in IQ, as is common for studies of ADHD. However, we did not find significant correlations between IQ scores and any of our measures of RT-ISV.

In conclusion, children with ADHD presented with increased RT-ISV indexed as fluctuations within frequency ranges both below and above 0.07 Hz on two distinct cognitive tasks, with medium to large effect sizes. The two tasks converged on identifying the same children with ADHD and the same TDC with elevated RT fluctuations at frequencies faster than 0.07 Hz, but not at frequencies below this cutoff. In addition, a subset of ADHD-impaired children showed the most elevated RT fluctuations, contributing to the observed differences between children with ADHD and TDC. These results confirm that RT-ISV is characteristic of many individuals with ADHD and support the validity of investigating RT fluctuations in the search for neurophysiological mechanisms underlying the disorder.

Declaration of Conflicting Interests

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