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Low frequency oscillations of response time explain parent ratings of inattention and hyperactivity/impulsivity

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Abstract

Greater intra-subject variability (ISV) in response time is a heritable endophenotype of Attention-Deficit/Hyperactivity Disorder (ADHD). Spontaneous low frequency oscillations (LFO; 0.01–0.1 Hz) observed in brain functional magnetic resonance signals might account for such behavioral variability. Recently, we demonstrated that ISV in response time (RT) explained ratings of ADHD symptoms. Building on this finding, here we hypothesized that LFO in RT time-series would explain these ratings, both independently and in addition to RT coefficient of variation (CV). To measure RT-LFO, we applied Morlet wavelet transform to the previously collected RT data. Our community sample consisted of 98 children (including 66 boys, mean age 9.9±1.4 years), who completed four computer Tasks of Executive Control. Conners' Parent Rating Scale ratings were obtained. RT-LFO of three tasks significantly explained ratings of inattention, hyperactivity and three global Conners subscales. Additionally, RT-LFO during two tasks that included an inhibitory component increased the proportions of variance explained in subscales of both inattention and hyperactivity/impulsivity, beyond the effects of RT-CV. Three specific low frequency bands (Slow 5: 0.01-0.027 Hz; Slow 4: 0.027-0.073 Hz; Slow 3: 0.073-0.20 Hz) were

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strongly related to the ADHD scales. We conclude that RT-LFO predict dimensional ratings of ADHD symptoms both independently and in addition to RTCV. Results suggest that frequency analyses are a suitable methodology to link behavioral responses to putative underlying physiological processes.

Keywords

Attention-Deficit/Hyperactivity Disorder; Intra-subject Variability; Frequency Analyses; Rating Scales

INTRODUCTION

Elevated intra-subject variability has been increasingly associated with Attention-Deficit/Hyperactivity Disorder (ADHD) based on clinical and phenomenological observations of 'consistent inconsistency' [5] and corresponding laboratory findings [20]. Increased variability has been found to be one of the most heritable neuropsychological indices [22]. In a recent comparison of speed, variability and timing of motor output in ADHD, variability of motor timing was found to have the most promise as a potential endophenotype [31]. In a similar vein, reaction time (RT) variability was found to be significantly associated with a specific single nucleotide polymorphism in the norepinephrine transporter gene [21].

Recently we demonstrated that RT ISV, measured as the coefficient of variation ($CV = SD/\text{mean RT}$) [20]), explained severity of ADHD symptoms in a clinic-based sample of school-age children [14]. In the present study, we aim to extend our examination of ISV to measures of low frequency oscillations (LFO) in RT to test whether specific RT LFO explain parent ratings of ADHD symptoms independent of and in addition to RT-CV, a global measure of RT variability.

Slow oscillations in RT might be a more suitable index for translational linkage to underlying physiological processes than other indices of RT variability [15,20,23]. This potential link to biological mechanisms lies on the observation of intrinsic LFO with brain functional magnetic resonance imaging (fMRI) [2,10]. These oscillations appear to regulate reciprocal relationships between task positive networks and resting state networks in the brain [9,11,12], such as the default network [7], which has been suggested to underlie attentional lapses in ADHD [19]. These lapses might be related to the failure of transitioning from a resting state to an active mode of processing information. Several studies using fMRI show that LFO are related to behavioral trial-to-trial variability [10,19,33] and LFO in direct current EEG [25]. Monto et al. noted that subjects' ability to detect sensory stimuli was strongly correlated with the phase of LFO, suggesting that attention is also related to these oscillations. Di Martino et al. [8] hypothesized that fluctuations in RT would show an oscillatory pattern in the same low frequency range as intrinsic LFO.

Applying frequency analyses such as fast Fourier transform (FFT) [4,17,18] or Morlet wavelet transform, several investigators (with one exception [13]) have reported increased RT LFO in children with ADHD. These earlier studies [8,13,17] dichotomized samples on the basis of the presence or absence of ADHD. In contrast, we used dimensional parent ratings of ADHD, motivated by the perspective that ADHD can be construed as the extreme of a continuum of functioning rather than a discrete disorder [24]. Therefore, we expected a link between variations in RT and parent ratings of ADHD. Using the same RT data from the clinic-based sample described in our earlier study [14], we hypothesized that 1) RT LFO, ranging from 0.01 to 0.1 Hz [25], would significantly explain parent ratings of symptoms

related to ADHD; and 2) that the power of this LFO spectrum would explain a significant proportion of the variance in ratings beyond that explained by RT-CV. We also explored the relationships between parent ratings of ADHD and the power of three non-overlapping low frequency bands described by Penttonen and Buzsaki [26].

METHOD

Participants and Procedure

This study was approved by the institutional review board of New York University School of Medicine and by the Research Committee of Bellevue Hospital Center. Therefore, the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Subjects were recruited from pediatric clinics at Bellevue Hospital Center and from the Roberto Clemente Family Therapy Center in New York City. A total of 102 children were enrolled. Three children were excluded due to incomplete parent responses to questionnaires and one child was excluded due to parent report of neurological problems. The final sample consisted of 98 children (66 males) between the ages of 8 and 12 years (mean 9.9, SD 1.4 years) from 73 families. The same participants are included in Gómez-Guerrero et al.[14].

During phone screening interviews families were offered a \$25 bookstore certificate per child enrolled in the study. Parents of children who were being treated with psychostimulant drugs (n=11) were asked to withhold the stimulant on the day of testing. A parent provided signed consent, in English or Spanish as preferred, and informed assent was obtained from each child. Enrolment was not based on presence or absence of ADHD diagnosis. As reported by parents, the sample consisted of children representing a spectrum of ADHD symptoms, ranging from none or few to many. Normal cognitive functioning and intelligence sufficient to understand the study tasks, assessed informally, were required for inclusion. Exclusion criteria included parental report or evidence of sensory and motor dysfunction, autism spectrum disorder, psychosis or mental retardation. Included children were invited to complete a battery of cognitive tasks (see below) in a single session, while parents were asked to complete forms and questionnaires available in English or Spanish based on their preference. The ratings for this report were obtained with the *Conners Parent Rating Scale-Revised: Long Version* (CPRS) [6]. Additionally, parents completed questionnaires about demographic, educational and basic clinical history regarding their child, which included information about prior diagnoses. Children were tested in a small, silent room that was located close to the waiting hall.

Cognitive Tasks

Children performed five computer tasks, which included four tasks of the Tasks of Executive Control (TEC) [16]. In the first TEC task (Zero-Back, 0B), a simple choice response task, participants are asked to sort all zebras appearing in the center of the screen into a red box, while non-zebra objects are to be sorted into the blue box. Sorting is done by pressing the relevant shift key, identified with a red or blue dot, with the corresponding right or left hand. The second task (Zero-Back with Inhibition, 0BI) involves an additional inhibitory component, as the participant is requested to not press any key when a target is framed by a square. The third task (One-Back, 1B) is a variation of the 0B task. Participants are asked to place an object in the red box if it appears twice in a row, instead of sorting on the basis of detecting target such as zebras. The fourth task (One-Back task with inhibition, 1BI) added an inhibitory component similar to 0BI. Stimuli are presented for 400 ms. The interstimulus interval (from stimulus onset to onset of the next stimulus) was 2000 ms on average (jittered in 250 ms steps between 1750 and 2250 ms). Participants performed 100

trials per each task. Each task lasted approximately 3 min and 25 s, being followed by a short break (< 1 min).

The TEC tasks were followed by a 3 min version of the Eriksen flanker task which differed in number of trials (60) and intertrial interval (3 s) from the TEC tasks. Because of these incompatibilities with the TEC battery, flanker data were excluded from frequency analyses.

DATA ANALYSES

Time Domain

Tasks with more than 15% omissions were excluded [8]. This occurred in one 0B, two 0BI, two 1B and five 1BI. Responses below 100 ms were considered anticipatory errors and were discarded [8]. CV (SD/mean RT) of the remaining RT were computed for each participant. For the tasks involving inhibitory trials (0BI and 1BI), these measures were computed on only the go-trials, except for commission errors [17].

To maintain a continuous series of response times, omissions, impossible responses below 100 ms, and no-go trials were interpolated by averaging the preceding and following available RT. The two first trials of each task were excluded to minimize transition effects [8]. To control for the effects of trial types within each task, for each subject mean RTs of trial types were regressed out from the individual RT data. For the 0B and 1B tasks, two trial types were considered (blue or red button). For the tasks with no-go trials (0BI and 1BI), an additional trial type (no-go trial) was considered. Displaced logarithmic transformation (i.e., $f[x] = \ln [x-a]$ with displacement parameter $a=100$) was used to normalize the skewed RT distributions [8]. The time series on which spectral analysis were performed were the residuals from the log-transformed RTs.

Frequency Domain Analyses

Frequency domain analyses measure the degree to which time series follow specific periodic patterns. Such a pattern is measured as frequency and its unit measure is Hz which indicates the number of occurrences of a repeating event (cycles or periods) per unit time. For example, a signal that changes every 20 s has a frequency of 0.05 Hz and a signal that changes every second has a frequency of 1 Hz.

Mathematical operations measure the degree to which specific periodic patterns exist in any time series (i.e., data collected over time), such as RT data collected in this study. Fast Fourier transform (FFT) decomposes a signal into its frequency components and provides a measure of the magnitude of each component (power spectrum). However, Fourier transformation does not contain information about changes in this pattern over time, i.e., it assumes that the time series is stationary (i.e., stable mean and variance over time). In contrast, the continuous wavelet transform (CWT) maps the time series to a function of time and frequency, whose squared magnitude, the scalogram [30,32] decomposes variability over both time and frequency. The scalogram is generally conceptualized as the decomposition of energy [27]. The Morlet wavelet is a continuous function used to create a family of wavelets generated by scaling (compressing and dilating) and translating a mother wavelet over time [3].

Prior to conducting frequency analyses we tested for stationarity of our RT data. Specifically, we compared the first and second halves of each task with respect to mean RT and RT-SD, using pairwise comparison t-tests with an alpha level of 0.05. Time-on-task effects were observed for two of the four tasks: mean RT during the first half of the 0B task was significantly longer than during the second half ($p=0.039$), while RT SD during the second half of 1B was significantly larger than during the first half ($p=0.004$). For this

reason and for consistency with our earlier work [8] we used the Morlet wavelet transform for frequency analyses.

Spectral Measures

For each task, the interstimulus interval (the time from the onset of one stimulus to the onset of the next one; t) was jittered between 1750, 2000 and 2250 ms with a mean of 2000 ms, which is what we used as our sampling rate. This simplification only minimally reduces our frequency resolution above 0.22 Hz per the Nyquist theorem. Accordingly, we only examined frequencies up to 0.20 Hz. Since we excluded the first two trials of each task, we analyzed 98 trials at $t-2$ s intervals. According to the Nyquist theorem, the lowest frequency for which the power spectrum can be reliably estimated is ~ 0.01 Hz ($1/(n \cdot t/2) = 1/98$). Thus, the frequency interval that we examined ranged from 0.01 to 0.20 Hz. Our primary analyses focused on LFO, ranging from 0.01 to 0.1 Hz [25]. For exploratory analyses, we selected three frequency bands defined by applying the approach described by Penttonen and Buzsáki [26]. These were Slow-5 (range 0.01-0.027 Hz [periods 37-101 s]), Slow-4 (0.027-0.073 Hz [14-37 s]) and Slow-3 (0.073-0.20 Hz [5-14 s]).

To compute the energy of LFO and the three specific frequency bands, the MWT (half-length 12), implemented in the Matlab (The MathWorks, Natick, Massachusetts) Time-Frequency Toolbox (<http://tftb.nongnu.org>) was applied to each subject's logarithmic transformed residuals of RT time series using the `tfrscal` function.

Statistical Analyses

We examined the relationship of LFO during the four TEC tasks to the three global DSM-IV CPRS subscales (*DSM-IV: Inattentive*, *DSM-IV: Hyperactive-Impulsive* and *DSM-IV: Total*) and the two CPRS primary subscales most related to the core symptoms of ADHD (*Cognitive Problems/Inattention* and *Hyperactivity*). First, we asked whether the LFO alone contributed significantly to explaining variability in parent ratings, after adjusting for age and sex. To address this question, we fitted a regression model in which LFO during each task was used as a predictor for each selected subscale. The statistical software R [28], allowed us to adjust by age and sex by including them in the set of predictors when we fitted the regression model. Second, we asked whether LFO contributed to explaining variability in the subscales after adjusting for RT CV in addition to age and sex. This question was addressed by using the likelihood ratio test to compare two models: for each subscale, we fitted a first model containing age, sex and RT-CV as predictors and a second model that also contained LFO as a predictor. The likelihood ratio test computed a p-value for each comparison, offering information about the contribution of LFO and clarifying whether LFO significantly increased the proportion of explained variance.

We then explored whether the energy of the time-frequency representations of the Slow-5, Slow-4 and Slow-3 bands contributed to explaining the variance of the rating subscales. To address this question, we fitted a regression model for each of the five subscales as a function of each slow energy spectrum, adjusting by age and sex. As previously, we calculated this contribution separately for all slow bands during each of the tasks.

To account for correlations in the outcomes of children from the same family, models for correlated data were used. Specifically, we performed mixed effects models analyses applying the function *lmer* in R [28] for all the aforementioned analyses. To account for multiple comparisons, we applied Bonferroni corrections. For each task, the significance of the relationship with the five CPRS subscales was judged at level $\alpha = 0.05/5 = 0.01$.

RESULTS

Group and Tasks Characteristics

The sample consisted of mostly Latino children ($n = 88$; 90%), 6% Caucasian ($n = 6$), 2% Black ($n = 2$) and 2% Asian ($n = 2$). According to parent clinical questionnaires, 47 children (48%) had a history of psychological or medical difficulties. Among them, 25 children (26%) had a prior diagnosis of ADHD. Parents also reported history of learning difficulties ($n=25$), language delay ($n=20$), audition problems ($n=4$), emotional difficulties ($n=16$), behavior difficulties ($n=29$) and other medical conditions ($n=20$). Eleven children (11%) were taking stimulants (7 methylphenidate and 4 amphetamines) that were withheld on the day of testing; four children (4%) were reported to be receiving neuroleptics. For our results, T scores for the CPRS ranged from 40 to 90. Mean T scores for the CPRS global DSM-IV subscales varied from 55 to 61 (SD from 12 to 14).

Table 1 shows the RT-CV, RT mean, accuracy, and rates of omission and directional and commission errors, as they were detailed elsewhere [14]. Mean RT across the tasks ranged from 457.1 to 528.6 ms (SD from 104.6 to 153.2) and RT-CV varied from 0.29 to 0.32 (SD from 0.08 to 0.10); between-task differences were not significant. Accuracy ranged from 82% to 88% (SD 11% to 12%) and omissions ranged between 1% and 2% (SD 2% to 4%).

Spectral Measures Explaining Parent Ratings

During the 0BI, 1B and 1BI tasks, RT LFO explained significant proportions of the variance for all the rating subscales ($p<0.01$), with $100 \times R^2$ ranging from 5% to 17%. RT LFO during 0B explained a significant proportion of the variance (6%) in two rating subscales ($p<0.01$): *Cognitive Problems/Inattention* and *DSM-IV: Hyperactive-Impulsive*. RT LFO during the 0BI task showed the tightest relationship with the subscales, explaining 10% (in *DSM-IV: Total*) to 17% (in *Cognitive Problems/Inattention*) of the variance in ratings (see Table 2). We then modeled RT-CV as a predictor of each rating subscale. As shown in Table 3, RT-CV during the 0BI task explained significant proportions of the variance in the five rating subscales (ranging from 7% to 11%; $p<0.01$) and RT-CV during the 1B task significantly explained the variance in three of the rating subscales (*Cognitive Problems/Inattention*, *Hyperactivity* and *DSM-IV: Hyperactive-Impulsive*). RT-CV either during 0B or 1BI was not significantly related to any rating subscale. Likelihood ratio tests showed that RT LFO during the 0BI task was a significant predictor of the *Cognitive Problems/Inattention* subscale even after adjusting for 0BI RT-CV, with the percent explained variance in this scale increasing from 11% to 17%. For the 1BI task, adding RT LFO as a predictor increased significantly the proportion of variance explained by RT-CV in three rating subscales (*Cognitive Problems/Inattention*, *Hyperactivity* and *DSM-IV: Hyperactive-Impulsive*). This means that RT LFO carries information about the scales beyond what is contained in RT-CV. None of the subscales was better explained by the additional contribution of RT LFO during 0B or 1B.

Table 4 shows the percentage variance in the rating subscales explained by each of the slow frequency bands (Slow-3, Slow-4 and Slow-5), adjusting for age and sex and accounting for correlations among family members. The energy of the Slow-3 spectrum during all the TEC tasks (separately) explained significant proportions of the variance in all five rating subscales, ranging from 4% to 12%. The Slow-4 spectrum during 0BI explained significant proportions of the variance in all the rating subscales, varying from 9% to 16%. The Slow-4 spectrum during 1B explained significant proportions of the variance in four rating subscales (all but *DSM-IV: Inattentive*), varying between 5% and 7%; Slow-4 during 1B significantly explained three rating subscales, ranging from 4% to 7%. The Slow-4 spectrum during 1BI was not significantly related to any rating subscale. The Slow-5 spectrum during 0BI and

during 1BI explained significant proportions of the variance in all the rating subscales, ranging from 7% to 13%. The Slow-5 spectrum during 1B explained three rating subscales (from 4% to 7%), whereas this spectrum during 0B was not significantly related to any rating subscale.

Post-hoc analyses: relationship between RT LFO and task performance

We calculated the proportion of variance explained by RT LFO in accuracy (number of correct responses), number of omissions, number of directional errors (incorrect responses in go-trials), and number of commission errors (responses to no-go trials in the two tasks that included inhibition). Interestingly, all these task performance measures were significantly explained by RT LFO during all tasks.

DISCUSSION

The primary objective of this study was to assess whether analyses of spectral measures, such as RT LFO, provide further information in explaining parent ratings of ADHD than RT-CV alone. As hypothesized, we found that the RT LFO in all four computer tasks significantly explained ratings of Conners subscales in a moderately large convenience sample of mostly Latino children. We also found that adding RT LFO as a predictor significantly increased the proportions of variance explained in subscales of both inattention and hyperactivity/impulsivity, beyond the effects of RT-CV in several instances.

Our results are consistent with a prior report that spectral measures provide additional information beyond time domain analyses in characterizing categorically diagnosed ADHD [8]. In the present study, this relationship was also observed across a dimensional spectrum of symptom severity. Further, in contrast with prior studies [4,8,17,18] that used only one task paradigm with durations ranging from 5.5 to 18 min, here we used a battery of brief (~ 3 min 20 s) cognitive tasks designed to assess aspects of executive function. RT LFO during the simple choice reaction time task (0B) explained only two ADHD subscales in contrast to LFO on the remaining more complex tasks that explained all five subscales. Adding RT LFO to RT-CV during the 0BI and 1BI tasks significantly increased the proportion of explained variance for the Cognitive Problems/Inattention subscale; RT LFO during 1BI also significantly increased the proportion of explained variance for the two Hyperactivity subscales. Further research would analyze why the inclusion of an inhibitory component in the executive task had a larger effect on the proportion of parent ratings explained by RT LFO. We could hypothesize this is due to a relationship between abilities of inhibition and attention. Because the tasks were presented in a fixed rather than counterbalanced order, we cannot disentangle the extent to which cognitive load may interact with RT LFO. Although future studies are needed to clarify this point, our results suggest that the relation between RT LFO and ADHD symptoms can be observed in a range of tasks including a brief simple-choice RT task. These results contrast with the lack of a relationship between ADHD diagnosis and RT variability reported by Geurts et al. despite the use of three analytical methods that included FFT in large samples of children with ADHD and typically developing controls [13]. One possible explanation for this divergence is that FFT, which assumes stationarity of time series, may have missed time-varying fluctuations characteristic of LFO that we noted even in our brief tasks. Additionally, the ADHD subjects in the Geurts et al. study were carefully diagnosed and relatively free of comorbid conditions; our subjects were explicitly not diagnosed and were selected to provide a naturalistic range of symptom severities. These factors may also have contributed to the differences in our results.

Exploratory analyses on specific frequency bands within and above the LFO frequency range indicate that all the low frequency bands examined were strongly related to the ADHD rating scales. Slow-3 showed the most pervasive results, explaining all five rating subscales

across all four tasks. Slow-4 and Slow-5 were almost as strongly related, each with significant relationships across three tasks (all but 1BI for Slow-4 and 0B for Slow-5). These findings contrast with Di Martino et al. [8], who showed Slow-4 to be more related to variability than Slow-3 and Slow-5.

In general we did not discern prominent differences among the specific slow frequency bands – all were strongly related to Conners ratings and to performance measures such as error rates. To a first approximation, this resembles the finding of Monto et al. that all six electroencephalographic frequency bands were nested within LFO and equivalently related to fluctuations in sensory detection [25].

One of the limitations of the study is that we used a variable inter-trial interval, jittered between 1750, 2000 and 2250 ms which we approximated with the mean of 2000 ms as our sampling rate. This only minimally reduced our frequency resolution above 0.22 Hz, so we excluded frequencies over 0.20 Hz. Another limitation is the lack of diagnostic interviews. The study was designed with a dimensional approach, with a main focus on continuous ratings of ADHD features and avoiding dichotomized classifications of the disorder. An advantage of our approach was that the brevity of the tasks made it feasible to conduct the study in a busy clinical setting in which we were able to recruit a clinic-based sample of mainly Latino children, who tend to be underrepresented in research studies [1].

The potential link to pathophysiological mechanisms possibly implicated in ADHD rests on the observation that similar slow fluctuations observed with brain fMRI might account for intermittent lapses of attention [2,10]. Spontaneous low frequency oscillations appear to regulate reciprocal relationships between anti-correlated networks in the brain, task positive networks and task negative networks [9,11,12]. The default network is a resting state network synchronized by spontaneous low-frequency oscillations [7] which is argued to represent a physiological baseline, showing greater activity at rest than during the performance of goal-directed tasks [29]. This circuit includes the medial and lateral parietal, the medial prefrontal cortex and the precuneus and posterior cingulate cortex. Failure to modulate activity in the default network may underlie intermittent lapses of attention [19]. Data from fMRI studies demonstrate that LFO are related to behavioral trial-to-trial variability [33] and variations in EEG [25].

In conclusion, RT LFO explain a significant proportion of the variation found in the parent ratings of ADHD symptoms. This finding suggests that frequency analyses might be a suitable methodology to find links between behavioral performance and underlying physiological processes.

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References

1. Bauermeister JJ, Canino G, Bravo M, Ramirez R, Jensen PS, Chavez L, Martinez-Taboas A, Ribera J, Alegria M, Garcia P. Stimulant and psychosocial treatment of ADHD in Latino/Hispanic children. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2003; 42:851–855. [PubMed: 12819445]
2. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*. 1995; 34:537–541. [PubMed: 8524021]

3. Bruce LM, Cheridat A, Burns M. Wavelets: getting perspective. *IEEE Potentials*. 2003; 22:24–31.
4. Castellanos FX, Sonuga-Barke EJS, Scheres A, Di Martino A, Hyde C, Walters JR. Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. *Biological Psychiatry*. 2005; 57:1416–1423. [PubMed: 15950016]
5. Castellanos FX, Tannock R. Neuroscience of attention-deficit hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience*. 2002; 3:617–628.
6. Conners, CK. Conners' Rating Scales-Revised User's Manual. Multi-Health Systems, Inc.; North Tonawanda, NY: 1997.
7. DeLuca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage*. 2006; 29:1359–1367. [PubMed: 16260155]
8. Di Martino A, Ghaffari M, Curchack J, Reiss P, Hyde C, Vannucci M, Petkova E, Klein DF, Castellanos FX. Decomposing intra-subject variability in children with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2008; 64:607–614. [PubMed: 18423424]
9. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van E, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:9673–9678. [PubMed: 15976020]
10. Fox MD, Snyder AZ, Vincent JL, Raichle ME. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron*. 2007; 56:171–184. [PubMed: 17920023]
11. Fransson P. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping*. 2005; 26:15–29. [PubMed: 15852468]
12. Fransson P. How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia*. 2006 Ref Type: In Press.
13. Geurts HM, Grasman RPPP, Verte S, Oosterlaan J, Roeyers H, van Karmen SM, Sergeant JA. Intra-individual variability in ADHD, autism spectrum disorders and Tourette's syndrome. *Neuropsychologia*. 2008; 46:3030–3041. [PubMed: 18619477]
14. Gómez-Guerrero L, Domínguez Martín C, Mairena MA, Di Martino A, Wang J, Mendelsohn AL, Dreyer BP, Isquith PK, Gioia G, Petkova E, Castellanos FX. Response time variability is related to parent ratings of inattention, hyperactivity and executive function. *Journal of Attention Disorders*. 2011; 15(7):572–82. [PubMed: 20686098]
15. Hervey AS, Epstein JN, Curry JF, Tonev S, Eugene AL, Keith CC, Hinshaw SP, Swanson JM, Hechtman L. Reaction time distribution analysis of neuropsychological performance in an ADHD sample. *Child Neuropsychology*. 2006; 12:125–140. [PubMed: 16754533]
16. Isquith, PK.; Roth, RM.; Gioia, GA. Tasks of Executive Control (TEC). Psychological Assessment Resources, Inc.; Lutz, FL: 2009.
17. Johnson KA, Kelly SP, Bellgrove MA, Barry E, Cox M, Gill M, Robertson IH. Response variability in attention deficit hyperactivity disorder: evidence for neuropsychological heterogeneity. *Neuropsychologia*. 2007; 45:630–638. [PubMed: 17157885]
18. Johnson KA, Robertson IH, Kelly SP, Silk TJ, Barry E, Daibhis A, Watchorn A, Keavey M, Fitzgerald M, Gallagher L, Gill M, Bellgrove MA. Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. *Neuropsychologia*. 2007; 45:2234–2245. [PubMed: 17433378]
19. Kelly AMC, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. *Neuroimage*. 2008; 39:527–537. [PubMed: 17919929]
20. Klein C, Wendling K, Huettner P, Ruder H, Peper M. Intra-subject variability in attention-deficit hyperactivity disorder (ADHD). *Biological Psychiatry*. 2006; 60:1088–1097. [PubMed: 16806097]
21. Kollins SH, Anastopoulos AD, Lachiewicz AM, Fitzgerald D, Morrissey-Kane E, Garrett ME, Keatts SL, Ashley-Koch AE. SNPs in dopamine D2 receptor gene (DRD2) and norepinephrine transporter gene (NET) are associated with continuous performance task (CPT) phenotypes in ADHD children and their families. *Am J Med Genet B Neuropsychiatr Genet*. 2008; 147B:1580–1588. [PubMed: 18821566]

22. Kuntsi J, Stevenson J. Psychological mechanisms in hyperactivity: II The role of genetic factors. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2001; 42:211–219.
23. Leth-Steensen C, Elbaz ZK, Douglas VI. Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. *Acta Psychologica (Amsterdam)*. 2000; 104:167–190.
24. Levy F, Hay DA, McStephen M, Wood C, Waldman I. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36:737–744. [PubMed: 9183127]
25. Monto S, Palva S, Voipio J, Palva JM. Very slow EEG fluctuations predict the dynamics of stimulus detection and oscillation amplitudes in humans. *J Neurosci*. 2008; 28:8268–8272. [PubMed: 18701689]
26. Penttonen M, Buzsaki G. Natural logarithmic relationship between brain oscillators. *Thalamus & Related Systems*. 2003; 2:145–152.
27. Percival, DB.; Walden, AT. *Wavelet Methods for Time Series Analysis*. Cambridge University Press; Cambridge: 2000.
28. R Development Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: 2003.
29. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*. 2001; 98:676–682. [PubMed: 11209064]
30. Rioul O, Flandrin P. Time-Scale Energy Distributions: A General Class Extending Wavelet Transforms. *IEEE Transactions on Signal Processing*. 1992; 40:1746–1757.
31. Rommelse NN, Altink ME, Oosterlaan J, Beem L, Buschgens CJ, Buitelaar J, Sergeant JA. Speed, variability, and timing of motor output in ADHD: which measures are useful for endophenotypic research? *Behavior Genetics*. 2008; 38:121–132. [PubMed: 18071893]
32. Vidakovic, B. *Statistical Modeling by Wavelets*. Wiley, New York: 1999.
33. Weissman DH, Roberts KC, Visscher KM, Woldorff MG. The neural bases of momentary lapses in attention. *Nature Neuroscience*. 2006; 9:971–978.

Figure 1. Low frequency oscillations beyond coefficient of variation

OB: Zero-Back or simple choice response task with a designated target; OBI: Zero-Back with an inhibitory component; 1B: 1-Back; 1BI: 1-Back with an inhibitory component. The graphic represents the percentage variance explained ($100 \times R^2$) in Conners' Parent Rating Scale subscales by Response Time Coefficient of Variation (RTCV) alone (BLUE) and by RTCV and low frequency oscillations (LFO; RED) during OB, OBI, 1B and 1BI, after adjusting for age and sex and accounting for correlations between family members ($p < 0.01$). Striped columns represent non-significant values.

Figure 2. Three non-overlapping low frequency bands predicting parent ratings of ADHD symptoms

OB: Zero-Back or simple choice response task with a designated target; OBI: Zero-Back with an inhibitory component; 1B: 1-Back; 1BI: 1-Back with an inhibitory component; Slow-3: 0.073-0.20 Hz; Slow-4: 0.027-0.073 Hz; Slow-5: 0.01-0.027. The graphic represents the percentage variance explained ($100 \times R^2$) in Conners' Parent Rating Scale subscales by each slow spectrum in OB, OBI, 1B and 1BI, after adjusting for age and sex and accounting for correlations between family members ($p < 0.01$).

Table 1

Task Performance

	MRT (ms) <i>M</i> (SD)	RTCV <i>M</i> (SD)	Percentage Accuracy <i>M</i> (SD)	Percentage Omissions <i>M</i> (SD)	Percentage Directional Errors <i>M</i> (SD)
0B	457.1 (104.6)	0.29 (0.08)	87% (12%)	1% (2%)	11% (10%)
0BI	496.8 (113.4)	0.29 (0.10)	88% (11%)	2% (4%)	10% (8%)
1B	509.6 (151.3)	0.30 (0.09)	84% (11%)	2% (2%)	14% (9%)
1BI	528.6 (153.2)	0.32 (0.10)	82% (12%)	2% (2%)	14% (8%)

0B: Zero-Back or simple choice response task with a designated target; 0BI: Zero-Back with an inhibitory component; 1B: 1-Back; 1BI: 1-Back with an inhibitory component.; MRT: mean response time on go trials; RTCV: response time coefficient of variation.

Adapted from Gómez-Guerrero et al. (2011)

Table 2

Percentage variance explained ($100 \times R^2$) in CPRS rating subscales by low frequency oscillations during 0B, 0BI, 1B and 1BI, after adjusting for age and sex and accounting for correlations between family members.

	0B	0BI	1B	1BI
Cognitive Problems/Inattention	6 * (p=0.005)	17 * (p=0.0000015)	9 * (p=0.00034)	8 * (p=0.0010)
Hyperactivity	3 (p=0.0271)	12 * (p=0.0000597)	6 * (p=0.0017)	7 * (p=0.00038)
DSM-IV: Inattentive	3 (p=0.0352)	12 * (p=0.000027)	5 * (p=0.0059)	6 * (p=0.0022)
DSM-IV: Hyperactive-Impulsive	6 * (p=0.0067)	13 * (p=0.000054)	7 * (p=0.0021)	10 * (p=0.00022)
DSM-IV: Total	3 (p=0.0339)	10 * (p=0.000054)	5 * (p=0.0027)	6 * (p=0.0012)

CPRS: Conners' Parent Rating Scale-Revised: Long Version; 0B: Zero-Back or simple choice response task with a designated target; 0BI: Zero-Back with an inhibitory component; 1B: 1-Back; 1BI: 1-Back with an inhibitory component.

* p<0.01.

Table 3

Percentage variance explained ($100 \times R^2$) in CPRS rating subscales by Response Time Coefficient of Variation (RTCV) alone and by RTCV and low frequency oscillations (LFO) during 0B, 0BI, 1B and 1BI, after adjusting for age and sex and accounting for correlations between family members.

	0B			0BI			1B			1BI		
	RTCV	RTCV +LFO	RTCV	RTCV	RTCV +LFO	RTCV	RTCV	RTCV +LFO	RTCV	RTCV	RTCV +LFO	RTCV
Cognitive Problems/Inattention	3	6	11 [*]	17 [*]	7 [*]	9 [*]	2	9 [*]	2	9 [*]	9 [*]	9 [*]
Hyperactivity	1	3	7 [*]	12 [*]	5 [*]	6 [*]	3	6 [*]	3	8 [*]	8 [*]	8 [*]
DSM-IV: Inattentive	1	3	9 [*]	12 [*]	2	5	3	5	3	7	7	7
DSM-IV: Hyperactive-Impulsive	2	6	7 [*]	13 [*]	7 [*]	8 [*]	4	8 [*]	4	10 [*]	10 [*]	10 [*]
DSM-IV: Total	1	3	7 [*]	10 [*]	4 [*]	5 [*]	3	5 [*]	3	6	6	6

CPRS: Conners' Parent Rating Scale-Revised; Long Version; 0B: Zero-Back or simple choice response task with a designated target; 0BI: Zero-Back with an inhibitory component; 1B: 1-Back with an inhibitory component. **Bold:** Adding low frequency energy as a predictor significantly increases variance explained in subscales by RTCV, age and sex ($p < 0.01$)

* $p < 0.01$

Table 4

Percentage variance explained ($100 \times R^2$) in CPRS rating subscales by each slow spectrum in 0B, 0BI, 1B and 1BI, after adjusting for age and sex and accounting for correlations between family members.

	SLOW-3 SPECTRUM				SLOW-4 SPECTRUM				SLOW-5 SPECTRUM			
	0B	0BI	1B	1BI	0B	0BI	1B	1BI	0B	0BI	1B	1BI
Cognitive Problems/Inattention	8*	12*	8*	9*	7*	16*	7*	4*	4*	13*	7*	8*
Hyperactivity	6*	10*	7*	7*	5*	9*	5*	4*	2*	10*	4*	8*
DSM-IV: Inattentive	5*	9*	6*	7*	4*	12*	5*	3*	2*	8*	3*	7*
DSM-IV: Hyperactive-Impulsive	7*	11*	9*	7*	7*	11*	6*	6*	4*	11*	4*	10*
DSM-IV: Total	4*	8*	6*	5*	4*	9*	4*	3*	1*	8*	4*	7*

CPRS: Conners' Parent Rating Scale-Revised; Long Version; 0B: Zero-Back or simple choice response task with a designated target; 0BI: Zero-Back with an inhibitory component; 1B: 1-Back; 1BI: 1-Back with an inhibitory component.

* $p < 0.01$.