Varieties of Attention-Deficit/Hyperactivity Disorder-Related Intra-Individual Variability

F. Xavier Castellanos, Edmund J.S. Sonuga-Barke, Anouk Scheres, Adriana Di Martino, Christopher Hyde, and Judith R. Walters

Intra-individual variability in behavior and functioning is ubiquitous among children with attention-deficit/hyperactivity disorder (ADHD), but it has not been systematically examined or integrated within causal models. This article seeks to provide a conceptual, methodologic, and analytic framework as a foundation for future research. We first identify five key research questions and methodologic issues. For illustration, we examine the periodic structure of Eriksen Flanker task reaction time (RT) data obtained from 24 boys with ADHD and 18 age-matched comparison boys. Reaction time variability in ADHD differed quantitatively from control subjects, particularly at a modal frequency around .05 Hz (cycle length approximately 20 sec). These oscillations in RT were unaffected by double-blind placebo and were suppressed by double-blind methylphenidate. Together with converging lines of basic and clinical evidence, these secondary data analyses support the speculative hypothesis that the increased power of multisecond oscillations in ADHD RT data, and by inference, in attentional performance, represents a catecholaminergic deficit in the ability to appropriately modulate such oscillations in neuronal activity. These results highlight the importance of retaining time-series data and quantitatively examining intra-subject measures of variability as a putative endophenotype for ADHD.

Key Words: Attention-deficit/hyperactivity disorder, time-series analyses, fast Fourier transform, endophenotypes, reaction time, variability, Morlet wavelet

The contributions to this special issue of *Biological Psychiatry* demonstrate the accelerating progress in our understanding of the behaviorally defined phenotype designated as attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association 1994). The imperative to develop causal models that will link genetic variations (and specific environmental factors) to functional differences in cellular biology, physiology, and behavior (see Sonuga-Barke 2005 [this issue]), have led to the search for intermediate phenotypes, also called endophenotypes (Almasy and Blangero 2001; Castellanos and Tannock 2002; Slaats-Willemse et al 2003). Endophenotypes are simply quantifiable or dimensional constructs that index the risk of manifesting a disorder and that are linked to "deeper" conceptual levels than that of symptoms or symptom-based diagnoses (Castellanos and Tannock 2002). Importantly, although estimates of endophenotype heritability allow genetic and nongenetic contributions to be partitioned, endophenotypes are not required to be heritable. Candidate endophenotypes in ADHD include inhibitory-based executive deficits associated with frontal–striatal dysfunction (Nigg et al 2005) delay-related motivational processes linked to limbic–ventral striatal circuits (Sagvolden et al, in press; Sonuga-Barke 2002, 2003); cerebellar-based timing deficits (Toplak et al 2003); and posterior parietal noradrenergic orienting deficits e.g., (van Leeuwen et al 1998). Given the likely pathophysiologic heterogeneity of ADHD, these candidate endophenotypes are not mutually exclusive; they could each be playing substantial roles in different clusters within the "ADHD population."

Although all behavior and related indices of performance fluctuate from moment to moment to some degree, the common observation that such fluctuations are larger and more common in children with ADHD led to the recent suggestion that increased intra-individual response variability might represent a ubiquitous and etiologically important characteristic (Castellanos and Tannock 2002). Until recently, such ADHD-related variability (ARV) has been almost entirely ignored (but see Douglas 1999; Leth-Steensen et al 2000; Kuntsi and Stevenson 2001; Ridderinkhof et al, in press; Sergeant 1988). Furthermore, the form and function of ARV and its role within causal models of ADHD pathophysiology have not been examined systematically. Castellanos and Tannock (2002) called for a systematic analysis of ARV as the dependent variable of primary interest rather than being conflated with measurement noise or experimental error. The aim of this article is to provide a conceptual framework for such analyses, identify key research questions, and to highlight qualitative and quantitative methodologic distinctions, which we illustrate in a secondary data analysis. We conclude with a neurobiologically plausible, though speculative, proposal concerning one type of ARV that is derived from in vivo single-neuron recordings and their modulation by dopaminergic agents.

The analysis undertaken here is delimited in terms of 1) whether the variability is intra-individual or inter-individual; 2) its time frame; and 3) its functional domain. First, heterogeneity is the rule in ADHD, and groups of ADHD children demonstrate high degrees of between-subject variation in performance almost irrespective of task or setting (Nigg et al 2005). Such group heterogeneity suggests the existence of potentially independent multiple pathways to the disorder. Nevertheless, it is important to draw a distinction between such intersubject variation and the form of intra-individual variability that is our focus here.

Second, although children with ADHD display temporal fluctuations over multiple time scales, for practical measurement-related as well as ecologic reasons, the moment-to-moment changes that are our primary interest in this article consist of fluctuations measured in multiples of seconds rather than hours (King et al 1998; Porrino et al 1983; Puig-Antich et al 1978), on

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the one hand, or milliseconds (Basar et al 1999a, 1999b; Heinrich et al 2001; Kolev et al 1999; Yordanova et al 1996, 1997, 2001), on the other. Finally, although ARV can be noted at a behavioral level, the analyses we propose cross behavioral, cardiovascular, and neurophysiologic domains. The requirement for measures with good temporal resolution restricts us to indices that can be accurately recorded in time-series, such as reaction times (RTs), and physiologic variables, such as heart rate variability (Borger and Van der Meere 2000; Borger et al 1999), cerebral blood oxygenation levels (Biswal et al 1997a; Hampson et al 2002; Mayhew et al 1996; Obrig et al 2000), or cerebral arterial velocities (Diehl et al 1998; Hirth et al 1997).

Conceptual Issues and Foundational Research Questions

In this section, we draw a number of conceptual distinctions regarding ARV that lead us to frame a program of basic research around five key questions.

How Robust Is the Association Between ADHD and Response Variability?

The first question concerns the strength of the association between ADHD and variability associated with moment-to-moment fluctuations. Neuropsychologic analyses of ADHD have traditionally focused on indices of response accuracy or efficiency (e.g., errors, RTs). Such studies report variability only at the group level and thus confound intra-individual and inter-individual variability. Some investigators are beginning to report intra-individual measures of variability (Kuntsi et al 2001; Leth-Steensen et al 2000; Scheres et al 2001a, 2001b). Even in these (for an interesting exception, see Ridderinkhof et al, in press), such variability is handled by collapsing across time intervals, yielding a single-point estimate of deviation around the mean (SD) for each subject. Group comparisons of variability are then based on group means of individual SD. Thus, although RT studies in ADHD are nearly too numerous to count, the question of the robustness of the association between ADHD and variability has yet to be addressed quantitatively.

Is ARV Random Noise or a Dynamic–Periodic Phenomenon?

Although single-point estimates of overall variability (e.g., SD) allow us to assert the importance of ARV, they provide little insight into its possible place within causal models. First, when applied specifically to RTs, such an approach fails to recognize the non-Gaussian nature of RT data (Leth-Steensen et al 2000). It also fails to capture any temporally dynamic patterning of fluctuations that might exist. The simplest interpretation of ARV is that it reflects greater entropy or randomness of behavior associated with global dysregulation. Such an account fits models of ADHD that emphasize breakdown of executive control (Barkley 1997). If it transpires that ARV is essentially random with no temporal regularity, nothing would be gained from more sophisticated analyses. However, dynamic biological systems rarely exhibit absolute randomness or its polar opposite, absolutely regular periodicity (Carney et al 2001; Kleiger et al 1987). Biological systems invariably convolve random or stochastic elements with quasi-systematic periodic fluctuations across multiple time frames (Auffray et al 2003). If this is the case in ADHD, then it is likely that a full characterization of variability will require both quantitative estimates of such variability and estimates of those parameters that define its periodic structure and the way that such periodicities change over time.

Does ARV Vary Dynamically as a Function of Context, Task, and State?

Moment-by-moment fluctuations characteristic of biological processes are fundamentally dynamic in that their quantity and quality of patterning and periodicity are highly sensitive to contextual factors (Stein and Kleiger 1999). Significant factors in this regard include the context within which the organism is working (e.g., rewards) (Sonuga-Barke 2003), the tasks being performed (e.g., sustained attention or vigilance) (Swaab-Barneveld et al 2000), and the internal physiologic and/or cognitive state (e.g., agitated, tired) (Borger and Van der Meere 2000; Leung et al 2000). For this reason, an analysis of the dynamic properties of ARV requires an examination of the extent to which it is both modifiable and modified by changes in contextual factors. Indeed, ARV might be distinctive not only in terms of amount or degree and its temporal structure and periodicity but also in terms of its relationship to other factors within the environment, as demonstrated by the frequently documented observation that the performance of children with ADHD is highly context dependent (Corkum and Siegel 1993). To address this issue, we need to study the quantitative and qualitative characteristics of ARV in different settings and in association with diverse physiologic states. An analysis of this sort starts to move us from an account of the form of ARV to an exploration of its role within broader psychologic functions. These functions are likely to be expressed at different levels of analysis. For example, variability plays the key role in the maintenance of adaptive functioning by providing the basis for a range of behavioral repertoires that are then amenable to selection pressures (Machado 1992). Such variability needs to be appropriately constrained, however, if it is not to impinge on and undermine day-to-day functioning.

Is ARV Unique to ADHD or Shared with Other Brain Pathologies?

Increased levels of response variability seem to be characteristic of a range of conditions other than ADHD, including mental retardation, traumatic brain injury, and epilepsy e.g., (Segalowitz et al 1997; Stuss et al 1989). Thus, gross variability might represent a nonspecific characteristic of brain pathology without value to the process of identifying endophenotypes for ADHD. Alternatively, ARV might be distinctive at a number of levels. First, children with ADHD could show either more or less increased variability than other groups. Second, children with ADHD could have different periodic or temporal structure in their patterns of variability. Third, ARV could be the result of distinctive processes that generate and/or maintain oscillations across multiple levels of physiology and function. Given the provisional nature of current nosology and the arbitrary nature of the boundaries between disorders, the sorts of variability we are discussing might be related to pathophysiologic processes cutting across diagnostic boundaries. For example, such an analysis could provide a framework for linking the presence of ADHD symptoms in many individuals within the autism spectrum (e.g., Althaus et al 1999) to emerging genetic results (Smalley et al 2002). Likewise, complex, and likely chaotic, temporal characteristics of motor and vocal tics in Tourette's disorder have been described (Peterson and Leckman 1998), as has their potential link to oscillations of neuronal activity in motor networks (Walters et al 2001).

Does ARV Reflect Processes Causally Related to ADHD?

By definition, endophenotypes should mediate causal pathways between putative originating causes and behavioral traits or

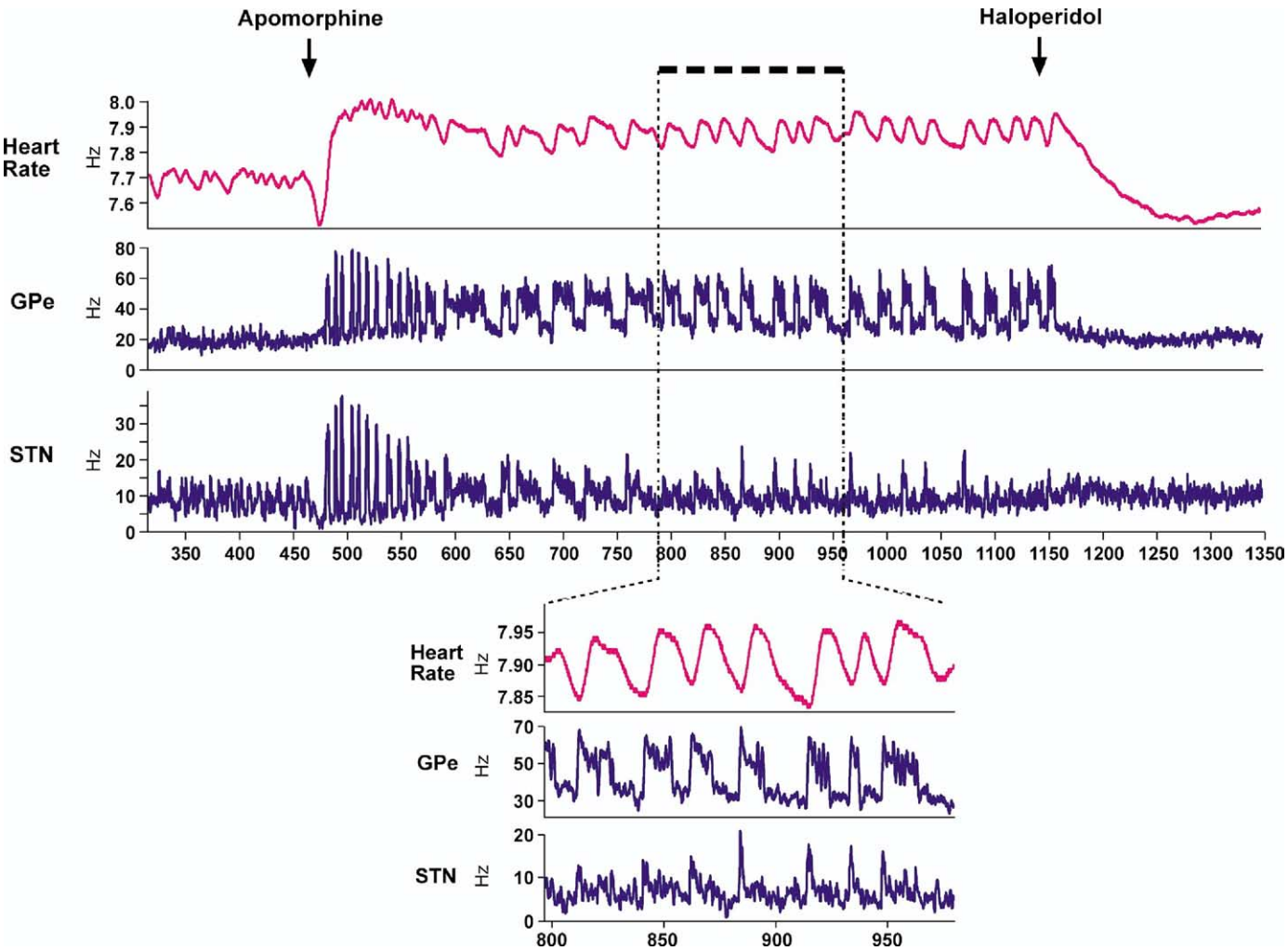

Figure 1. Multisecond oscillations in heart rate variability correlate with multisecond oscillations in firing rate of rodent globus pallidus (GPe) and subthalamic (STN) neurons. Single-unit activity of the GPe and STN neurons was recorded extracellularly from awake, locally anesthetized and immobilized rats (Ruskin et al 2003), and heart rate was determined from simultaneously recorded electrocardiographic activity. Robust multisecond oscillations in heart rate variability and firing rate of these basal ganglia nuclei are induced following administration of the direct dopamine agonist apomorphine (.32 mg/kg, IV). Oscillations have a period of approximately 10 sec. The dopamine antagonist haloperidol (.2 mg/kg, IV) eliminated the periodic oscillatory activity. X-axis units are in seconds. Unpublished observations, P.L. Tierney, D.A. Bergstrom, and J.R. Walters.

symptoms. Even if ARV can be effectively characterized in terms of its dynamic temporal structure and its functional characteristics, we are left with the question as to whether it reflects specific neurobiologically definable processes that are causally related to the behaviors of ADHD, or whether ARV simply reflects an epiphenomenal alternative manifestation of such symptoms. Castellanos and Tannock (2002) argued that some of the distinctive elements of ARV might be grounded in the neurobiology of the cerebellum and linked to timing (Ivry 1997; Toplak et al 2003) and motor control deficits (Denckla et al 1985; Middleton and Strick 2000). Alternatively, response variability might result from deficits in state regulation (Sergeant et al 2003). In both cases, it remains to be seen whether ARV is a cause or a consequence of psychologic or physiologic processes. The heritability of ARV has not been examined explicitly, but the heritability of RT variability has been documented in contrast to other cognitive constructs (Kuntsi and Stevenson 2001).

The most convincing evidence for a fundamental role for ARV in the pathophysiology of ADHD would come if similarly distinctive patterns of variability in terms of magnitude, temporal structure, and dynamic responsiveness could be detected across processes operating at multiple levels within the child. For instance, in the awake, locally anesthetized but paralyzed rat, Walters and colleagues have observed synchronized phase-locked fluctuations in single-neuron recordings in basal ganglia, local field potentials, skull-electrode recorded electroencephalogram, and heart rate variability, all of which are exquisitely affected by systemic dopaminergic manipulations (see Figure 1); see also (Allers et al 2002; Ruskin et al 2001a, 2001b, 2003; Walters et al 2001).

Issues of Measurement and Analysis

In the previous section, we proposed questions that provide the framework for a program of research into ARV; however, a prerequisite is the development of methods to quantify and characterize important features of variability. This raises issues of data capture, data characterization, and the use of inferential statistical methods to determine the extent to which children with

ADHD differ from typically developing children. In this section, we address each of these conditions in turn.

Data Capture

The first imperative is to capture and preserve time-series information from individual performance data. Although such data are readily available, they are rarely retained or examined in their original trial-by-trial formats. Second, although measures of inter-individual variability can be derived from many types of tasks, temporal task parameters (e.g., intertrial interval [ITI], length of testing blocks or runs) constrain the frequencies that can be investigated. In the absence of strong hypotheses regarding possible frequencies of interest, near-continuous measures are preferable. In such cases, the sampling or digitization rate sets the upper bound on resolution of frequencies. In hypothesis-driven studies, the temporal structure of the task and the response requirements must be designed so as to be sensitive to the appropriate range of frequencies of interest. When discrete trial designs are used, the Nyquist frequency of twice the ITI sets the upper frequency that can be studied, and the lower limit is set by the continuous duration of each observation block. Thus a 3-sec ITI allows resolution of frequencies up to .17 Hz (6 sec per cycle); a 180-sec block of 60 such trials corresponds to a lower frequency resolution limit of .011 Hz (90 sec per cycle). Given these constraints, long task durations sampled frequently yield greater statistical power for detecting periodicities as long as they do not lead to excessive loss of data from boredom or exhaustion.

Data Characterization

Raw time-series data should always be plotted directly and examined visually. Such an initial qualitative inspection provides an overall impression of fluctuations and facilitates the detection of outliers, data-entry errors, and impossible responses but does not provide quantitative analysis, which requires transforming the raw data. A common method is the fast Fourier transform (FFT), which extracts the relative strength (power) of each of the sampled frequencies present throughout an entire time-series interval (Bracewell 1989; Houtveen and Molenaar 2001) like the way a prism decomposes light into its constituent colors (Hubbard 1998, p. 10). Wavelet-based analyses can optimize time resolution across all examined frequencies, providing a means of assessing the evolution of periodic activity over time (Blinowska and Durka 1997; Dickhaus and Heinrich 1996; Heinrich et al 1999; Houtveen and Molenaar 2001; Ruttimann et al 1998). The wavelet transform compresses or dilates a model "mother" wavelet to characterize the magnitude of correlation between a signal and a set of wavelets over a range of frequency scales (Bruce et al 2003; Dickhaus and Heinrich 1996).

Statistical Analysis

Several core questions are raised by analysis of ARV. First, do children with ADHD show more variability than typically developing children? This can be established by a simple comparison of group mean variability. Second, does ARV contain patterns of specific periodicity? The null hypothesis in time-series data—that there is no systematic or periodic temporal structure beyond what would be expected by chance—can be tested by comparing relative peak amplitudes (Kaneoke and Vitek 1996) or by comparing areas under the curve within defined frequency bands through FFT. Third, does the pattern of variability differ in strength and structure of periodicity in between-subject or between-group comparisons? Such contrasts can also be performed by examining the mean area under the curve for defined portions of the FFT curve and then performing standard statistical tests.

An Illustrative Comparison: From Standard Deviations to Fourier Analyses

Supported by overwhelming evidence that, as a group, children with ADHD consistently exhibit deficits in multiple versions of the continuous performance task (Corkum and Siegel 1993), early accounts of the neuropsychology of ADHD posited a central deficit of sustained attention or vigilance, which worsens as test sessions are prolonged (Sykes et al 1971). The straightforward prediction in ADHD was that performance relative to comparison subjects should also worsen over time, but this was not observed in carefully performed experiments (e.g., Van der Meere and Sergeant 1988), which instead detected roughly comparable between-group differences from the earliest testing blocks. This apparent falsification of a theoretic prediction led to alternative formulations, focusing primarily on deficits of inhibitory function or state regulation as central to the neuropsychology of ADHD (Barkley 1997; Sergeant 2000).

By contrast, we assert below that deficits in sustained attention are not simply synonymous with fatigue and that they can be straightforwardly detected with current approaches. To illustrate the process of time-based analysis, we are using data that were collected as part of the doctoral dissertation of one of the authors in The Netherlands (AS) (for extensive description of the sample and methods of this ethically approved and conducted study, see Scheres et al 2003, 2004; note that these focused on the Flanker incongruency effect and did not report RT per se). Briefly, in an arrow version of an Eriksen Flanker task (Ridderinkhof et al 1997), subjects responded by pressing the corresponding right or left response key, depending on the right or left direction of a target arrow. On neutral trials, the target arrow was flanked by two rectangles on either side; on congruent trials, five arrows were presented, all pointing in the same direction as the target; and on incongruent trials, the flanking arrows pointed in the direction opposite to that of the target arrow. The present secondary analyses were obtained from up to 24 boys with ADHD, ranging in age from 6 to 12 years (mean ± SD, 8.7 ± 1.7 years), who were tested in up to five conditions (baseline $n = 22$, double-blind crossover placebo $n = 23$), and low (5 mg, $n = 24$), medium (10 mg, $n = 24$), and high (15 mg [20 mg if weight >25 kg], $n = 23$) doses of immediate-release methylphenidate, along with a healthy comparison group composed of 18 boys (aged 9.6 ± 1.8 years; $p > .10$) as determined from parent and teacher ratings. These secondary analyses were conducted with data sets stripped of all protected health information, as approved by the institutional review board of New York University School of Medicine.

The Eriksen Flanker task was administered in six blocks of 180 sec each. A total of 803 blocks of RT data were analyzed (108 blocks from 18 control subjects and 695 blocks from 22–24 ADHD participants; data from one block were corrupted). Reaction times in each block were converted to evenly spaced time-series data, detrended to remove low-frequency (<.03 Hz) noise, and analyzed with FFT (with a 7-point Tukey-Hamming window). The specific FFT results analyzed were the frequency of the largest oscillations (i.e., the frequency of the highest peak in the FFT per 180-sec block) and the power of the oscillation (i.e., the area under the FFT curve for specific frequency bands).

This analysis addressed four questions, as follows.

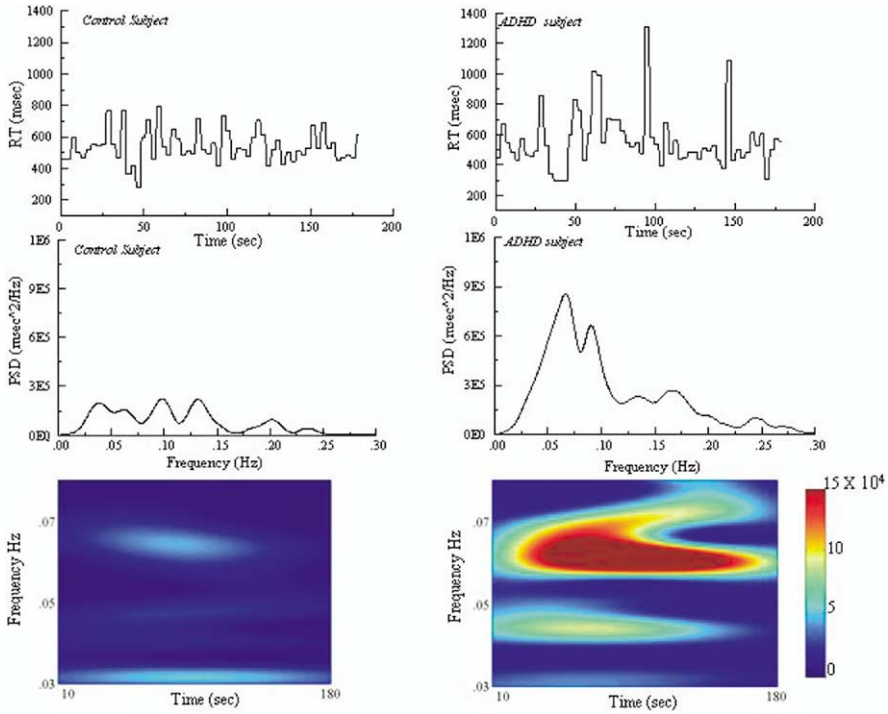

Figure 2. Top panels: Time-series (reaction time [RT] plotted against elapsed time) for two representative individuals during the second of six blocks of the Eriksen Flanker task. The control subject (left panels) shows less power in RT oscillations compared with the unmedicated subject with attention-deficit/hyperactivity disorder (ADHD) during baseline (right panels). Middle panels: Power spectral plots (fast Fourier transforms) of the same data, showing that the most prominent RT oscillations (the highest power spectral density [PSD]) were centered at a frequency of .05 Hz. Bottom panels: Morlet wavelet analyses produced with the Matlab 6.5 Time-Frequency Toolbox (The MathWorks, Natick, Massachusetts) with wavelet half-length set at 37 with 150 frequencies (scales) sampled in the frequency band between .03 Hz and .079 Hz. The color bar expresses the distribution of energy of the signal in the time-scale plane, as power per frequency unit. The increased power of the oscillation at a modal frequency of .06 Hz in the boy with ADHD is clearly visible.

Is RT Variability Random or Do RTs Oscillate at a Specific Frequency?

Mean RT and its SD were calculated for each block of 60 trials (one outlier was capped) for the two groups at baseline. Although the groups did not differ significantly in average RT [$t(38) = 1.39$; $p = .17$], boys with ADHD had significantly greater overall RT variability than comparison subjects [$t(38) = 2.65$; $p = .01$; two outliers (identified with SPSS Tukey Exploratory Data Analysis; SPSS, Chicago, Illinois) for values >3.3 SD] were "capped," that is, set equal to the next highest or lowest value to minimize spurious correlations (Seguin et al 1995; Tabachnick and Fidell 1996, p. 69). (See Figure 2 for smoothed RT and the corresponding FFT and wavelet analyses for representative blocks of data from a control boy and a boy with ADHD.)

The FFT analysis indicated that RT in the Eriksen Flanker task oscillated at similar specific frequencies in both groups. The most commonly encountered oscillations in the control group FFT were at .05 Hz and .075 Hz (44% and 33%, respectively), whereas 69% of the baseline or placebo blocks from the ADHD group manifested oscillations centered at .05 Hz. The mean frequencies in the two groups were indistinguishable (.069 ± .02 Hz and .067 ± .02 Hz for the control and ADHD groups, respectively, not significant). Within the patient group, the frequency of the main oscillation per block was statistically unaffected by medication.

On the basis of this confirmation of an underlying oscillation in RT in both groups centered between .05 and .075 Hz, the amplitude of oscillations in the .02–.07-Hz band (the area under the curve within this frequency band) was used as the dependent variable in subsequent analyses. Seven extreme outliers (2.9% of the entire data set) were capped.

Do ADHD Children Differ from Control Subjects in Specific RT Oscillations?

The power of RT oscillations centered at .05 Hz was 50% greater for the ADHD group compared with control subjects [$t(38) = 2.54$; $p = .01$; see Figure 3].

Does Methylphenidate Affect RT Variability and Oscillations?

Within the ADHD group, RT were significantly faster after any dose of medication [repeated-measures analysis of variance: $F(23,1) = 66.94$; $p = .0005$; two outliers were capped]. Reaction times were significantly less variable after any dose of medication [repeated-measures analysis of variance: $F(23,1) = 31.98$; $p < .0005$; one outlier was capped]. The power of oscillations in the .05-Hz band was also significantly reduced after any dose of methylphenidate [$F(23,1) = 10.17$; $p = .004$], as is shown in Figure 3.

Does Time on Task Affect RT Oscillations?

Reaction time oscillations were not linearly affected by increasing time on task. Regression of power for the .05-Hz band against block yielded standardized β coefficients of .059 and .069 for the control and ADHD groups, respectively (not significant). Thus, the power of these oscillations in RT was relatively constant over all six blocks in both groups, as was the overall between-group difference.

Implications of Quantitative Analyses of Variability in ADHD

Before considering the results of our analyses, we must first acknowledge that the form of the Eriksen Flanker task used here

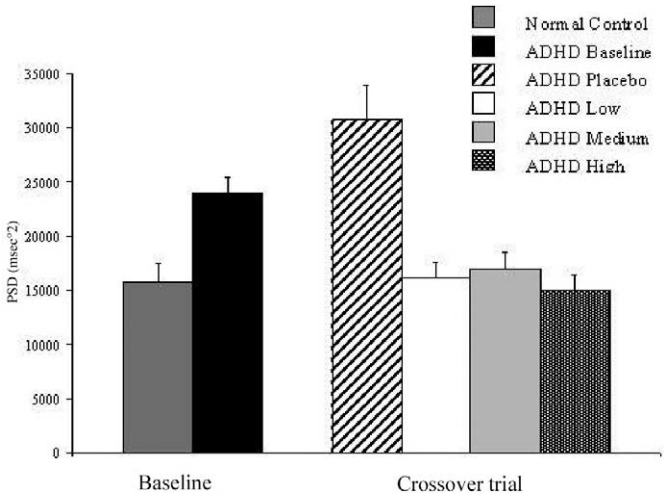

Figure 3. The area under the fast Fourier power spectra was integrated for the .02–.07-Hz band for each of the five conditions for the attention-deficit/hyperactivity disorder (ADHD) group and for the normal comparison boys during baseline. The mean spectral density for control boys is shown at the far left, next to the value for boys with ADHD during unmedicated baseline ($p = .01$). From left to right, the next four bars depict spectral density for the ADHD groups receiving placebo and low, medium, and high doses of methylphenidate, administered in a randomized, double-blind, crossover fashion (see Scheres et al 2003). The reaction time oscillations were markedly reduced to an equivalent degree by all doses of methylphenidate ($p = .0005$) and were equivalent to those of the control boys. PSD, power spectral density.

could itself entrain oscillations based on the rhythmic presentation of trials every 3 sec (i.e., at .33 Hz). The main RT oscillation we encountered reflected a cycle length approximately seven times the ITI, and harmonics from such a presumed artifact were not observed. This possibility could be definitively excluded in the future by varying the ITI for this and other cognitive tasks. Less likely is the possibility that the oscillation in RT reflected a rhythmic presentation of incongruent and congruent flanking stimuli. Although the presence of incongruent flankers consistently results in longer RT than neutral or congruent flankers (Scheres et al 2003), stimulus presentation in the present data set was fully randomized for each session, as verified by visual inspection.

Thus, the analyses illustrated above confirm that children with ADHD manifest greater overall variability, which can be simply appreciated by comparing SD. By examining FFT and wavelet analyses, however, we found that increased variability was also higher within a specific spectral band centered around .05 Hz. The potential importance of this observation depends on whether it reflects causally relevant underlying physiologic processes.

The converging evidence in support of such a conclusion emanates from a wide range of sources. Similar multisecond oscillations in blood pressure were first described more than a century ago (Mayer 1876; thus called Mayer waves or vasomotor oscillations) and have been noted in multiple species and with various methods (e.g., Golanov et al 1994; Haxhiu et al 1989; Vern et al 1998). We were motivated to examine this phenomenon by the observation of similar fluctuations in basal ganglia neuronal activity from awake, locally anesthetized, paralyzed rats. These fluctuations are exquisitely modulated by low doses of systemically administered dopaminergic agonists and uptake blockers, including methylphenidate and dextroamphetamine (Ruskin et al 2001a, 2001b, 2003; also see Figure 1). Similar multisecond oscillations in electroencephalogram and behavioral activity with periods of 15–30 sec were observed over a 6-hour period in each of six chair-restrained squirrel monkeys (Ehlers and Foote 1984), and similar, albeit somewhat slower, oscillations were confirmed in basal ganglia recordings obtained in awake, chair-restrained rhesus macaques (Wichmann et al 2002). The same apparent phenomenon of spontaneous low-frequency oscillations has been repeatedly recorded in human cerebral hemodynamic response functions observed with functional magnetic resonance imaging (Biswal et al 1995, 1997b; Hampson et al 2002; Lowe et al 2000) or near-infrared spectroscopy (Obrig et al 2000). Such oscillations, however, are typically ignored because they are routinely filtered out in the first phase of processing of physiologic data by high-pass filtering at .1 Hz.

Such low-frequency fluctuations in cerebral hemodynamic, electrophysiologic, neuronal, or behavioral parameters have not been previously studied in subjects with ADHD; however, increased spectral power corresponding to similar multisecond oscillations (<.1 Hz) in heart rate variability have been detected in children with ADHD (Beauchaine et al 2000; Borger and Van der Meere 2000) and in children with autism spectrum disorders combined with ADHD symptoms (Althaus et al 1999). Increased spectral power of multisecond oscillations in heart rate variability was also found to be a sensitive indicator of driver fatigue in adults (Egelund 1982). We acknowledge that the linkages among similar oscillations in cardiovascular parameters, such as heart rate variability, cerebral hemodynamics, and cognitive/behavioral performance, remain hypothetical, but the synchronization of rat heart rate oscillations and neuronal activity in motor networks depicted in Figure 1 suggests that examining such relationships in humans would be worthwhile. Additionally, the observation of dopaminergic modulation of cerebral cortical microcirculation (Krimer et al 1998) might provide a unifying mechanism through which central dopaminergic influences might simultaneously impinge on vascular, neuronal, and behavioral domains (Iadecola 1998). Thus, the analyses presented above, together with the literature reviewed, lead us to formulate the hypothesis that a catecholaminergic deficiency in the ability to appropriately modulate very-low-frequency fluctuations in neuronal activity represents one of the fundamental causes of transient but relatively frequent lapses in attention (2–4 times per minute), which underlie such behavioral symptoms as difficulty sustaining attention, forgetfulness, disorganization, and careless errors. Future studies should include simultaneous quantification of physiologic measures, such as heart rate variability and regional cerebral hemodynamic fluctuations, along with a range of measures of attentional efficiency, such as time-series RT and accuracy data. Such multidimensional data sets should in turn enhance the statistical power of molecular genetic studies by providing insights into underlying physiologic processes that are assumed to be more directly affected by variations in genetic endowment.

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