ORIGINAL ARTICLE

Unraveling the Nature of Hyperactivity in Children With Attention-Deficit/Hyperactivity Disorder

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Context: Seated hyperactivity is a defining feature of the combined and predominantly hyperactive-impulsive subtypes of attention-deficit/hyperactivity disorder (ADHD), but its underlying nature is unknown.

Objective: To determine whether hyperactivity is a consequence of an impaired ability to inhibit activity to low levels or to maintain positional stability.

Design: Case-control study.

Setting: Academic research center and school.

Participants: Sixty-two boys 9 to 12 years of age (of 73 screened), recruited from the community by advertisement, who met *DSM-IV* criteria for ADHD combined subtype on structured interview. Sixty-two controls were selected by matching for age and sex from a community sample of 1168 subjects in 3 participating school districts. Pupils with Conners' Teacher Rating Scores Revised within ±1 SD of the mean for age were eligible for randomized matching.

Intervention: Infrared motion analysis of head-marker movements (50 Hz) during performance of a 15-minute cognitive control task. Subjects with ADHD were tested at least 18 hours following their last dose of methylphenidate and again 120 minutes after a 0.4-mg/kg probe dose.

Main Outcome Measures: Inhibitory control (spike and basal amplitude) and head-marker stability (approximate entropy, Lyapunov, and spectral exponents).

Results: Inhibitory control measures were 2-fold higher in subjects with ADHD (d' = 0.63-0.95). Group differences in head-marker stability were even greater (d' = 2.20-4.71; receiver operating characteristic area = 0.956-1.0). Methylphenidate restored inhibitory ability to control levels but only partially corrected stability deficits, which still distinguished subjects with ADHD from controls (receiver operating characteristic area = 0.722-0.995).

Conclusions: Children with ADHD have a deficient ability to inhibit activity to low levels and unstable control of head-marker position characterized by deterministic chaos (sensitivity to initial conditions). These deficits differed in degree of correctability by methylphenidate, suggesting that they may be mediated by different neural circuits (eg, corticostriatal vs cerebrovestibular).

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood, conservatively estimated to affect 3% to 9% of school-aged children.[1-3] Attention-deficit/hyperactivity disorder is characterized by a triad of symptoms involving deficits in attention, impulse control, and hyperactivity.[4,5]

Hyperactivity is a discernible sign (rather than symptom) of the disorder, and a variety of instruments have been used to confirm its presence.[5,6] The most successful early studies used actigraphs and found that children with ADHD were about 30% more active than normal controls, particularly during academic activities[7] or during performance of laboratory-based attention tasks.[8,9] Increased motor activity was also present during sleep.[7] However, children with ADHD were no more active than controls when allowed to play.[7] These studies provide the fundamental insight that hyperactivity in children with ADHD may manifest most clearly as a diminished ability to inhibit activity to low levels (eg, to sit or lie still).[6,7]

A more detailed understanding of seated hyperactivity was obtained using infrared motion analysis.[10] This study revealed that children with ADHD performing an attention test spent 66% less time immobile than normal children, moved their head 3.4 times as far, covered a 3.8 times greater area, and had a movement pattern that was more linear and less spatially complex.[10]

Nevertheless, there is still a great deal to be learned about ADHD hyperactivity, and this knowledge may provide fundamental insight into the nature of the disorder. For example, an impaired ability to

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inhibit activity can result from at least 3 different mechanisms. First, children with ADHD may not be able to inhibit their activity to the same low level as controls. Second, they may be able to briefly inhibit their activity to very low levels but may not be able to sustain this degree of suppression for long. This may culminate in frequent spikes or bursts of activity. Third, they may be able to inhibit as well, and for as long, but when inhibitory control falters, and break-through movements occur, they may be of much greater amplitude.

Another critical point is that while motion analysis confirmed an inhibitory deficit, it showed that a reduction in spatial complexity was a more reliable discriminative metric.[10] Children with ADHD had many large, essentially linear, side-to-side movements, which is indicative of sway, a possible sign of postural instability. A few recent studies found that individuals with ADHD have a relatively minor but significant degree of impaired postural control when standing,[11,12] which can be improved by methylphenidate treatment.[13] Hence, it is possible that one reason children with ADHD fidget is that they have less ability to maintain control of posture or head position. However, to the best of our knowledge, this has not been assessed in children with ADHD while seated.

Understanding the nature of hyperactivity may tie together diverse neurobiological findings. For example, postural or positional instability in ADHD may be the result of cerebellar abnormalities.[14-17] On the other hand, an impaired ability to inhibit activity may stem from dysfunction in frontal-striatal inhibitory networks.[18-21] It is possible that some children with ADHD have a deficit in inhibitory control, while others have an impaired regulation of posture or position. These may represent distinct endophenotypes.

The primary purpose of the present study was to analyze the microstructure of head movements on a millisecond time scale to test specific hypotheses regarding capacity of hyperactive children with ADHD to inhibit motor activity and to maintain positional control of a head marker, reflecting the relative position of their head while viewing a computerized attention test. The second goal was to ascertain whether inhibitory deficits or positional control deficits had greater power to discriminate children with ADHD from more typical children. The final goal was to evaluate the effects of methylphenidate to ascertain if deficits in these domains were equally ameliorated by treatment.

METHODS

SUBJECTS

Data were analyzed from a study approved and monitored by the McLean Hospital institutional review board. The ADHD sample consisted of 62 boys between 9 and 12 years of age who met *DSM-IV*[22] criteria for ADHD combined subtype. Subjects were recruited from the general population via newspaper advertisement for hyperactive boys who were currently or previously treated with methylphenidate, because the protocol called for them to receive a moderately large probe dose of immediate-release methylphenidate. This was easier to justify in subjects known to tolerate methylphenidate. Parental written consent and child verbal assent were obtained. Most of the children enrolled were receiving treatment with immediate-release methylphenidate (92%), and the remaining children had a history of treatment. Seventy-three boys went through the screening procedures, which included structured interviews for *DSM-IV* Axis I disorders using the Schedule for Affective Disorder and Schizophrenia for School-Age Children, Epidemiologic Version[23] and parent ratings on the Conners' Hyperactivity Index[24] and Achenbach Child Behavior Checklist.[25] Children with ADHD could not have any current major mood disorder, psychosis, tic disorder, major anxiety disorder, or mental retardation. Children with oppositional defiant disorder, or reported learning disorders, could participate. Eleven subjects were excluded from further participation. Eight children had too few symptoms to meet criteria for combined subtype. One subject was disqualified for drug use, another was disqualified for current antidepressant treatment of night terrors, and one withdrew before the probe dose. These 62 subjects with ADHD combined subtype had a mean (SD) age of 11.0 (1.1) years. There were 19 boys with comorbid oppositional defiant disorder, 2 with current dysthymia, 4 with learning disorders, and 3 with past major depression or past anxiety disorders. Subjects with ADHD had an average Abbreviated Conners' Hyperactivity Index[24] score of 19 (any score >15 is indicative of hyperactivity) and mean scores of 20 and 29 for Internalizing and Externalizing Problems on the Child Behavior Checklist.[25] Sixty of these subjects were previously included in a study examining fluctuations in attentional state,[26] and 48 were included in a study on pharmacokinetic-pharmacodynamic response to methylphenidate treatment.[27]

For comparison, we analyzed data from a representative nonclinical contrast group. This group consisted of 62 typically developing male students, randomly selected from a sample of 1168 subjects (6-14 years of age) tested at local public schools using teacher ratings and the same attention and motion analysis equipment.[10,26] This study was approved by the McLean Hospital institutional review board and school administrators. Parents provided written consent and children gave verbal assent. Subjects selected for analysis were male and matched 1:1 with the subjects with ADHD by age to the nearest month (mean [SD] age, 11.0 [1.0] years). The selection criterion was a Conners' teacher rating[28] within ±1 SD of the mean of peers their own age and sex (ie, T score <60) to help exclude subjects with potential ADHD.

PROTOCOL

Children with ADHD were tested prior to and 120 minutes following a probe dose of 0.4-mg/kg methylphenidate. Contrast subjects only received a single test. Each child sat on a chair without back support, adjusted so that they were seated comfortably with both feet on the floor with knees bent at a right angle. Children were instructed to place their feet on the floor but were able to freely move their legs during the task. The attention test was presented on a computer screen on an adjustable-height school desk, set so that screen height was positioned at eye level. Subjects were instructed to press a space bar every time they saw a target. Their hand rested on the desk with fingers poised directly above the bar. Children were instructed to press when they saw an 8-sided star and not to press when a 5-sided star appeared (50% target density). Stars were presented briefly (200 milliseconds), at random screen positions, every 2 seconds. During this 15-minute task, an infrared motion analysis system tracked and recorded the vertical and horizontal position of a small reflective marker worn on a headband (0.04-mm resolution).[10]

DATA ANALYSIS

Horizontal and vertical head-marker positions were smoothed to filter out camera noise using a 5-point moving average. Dis-

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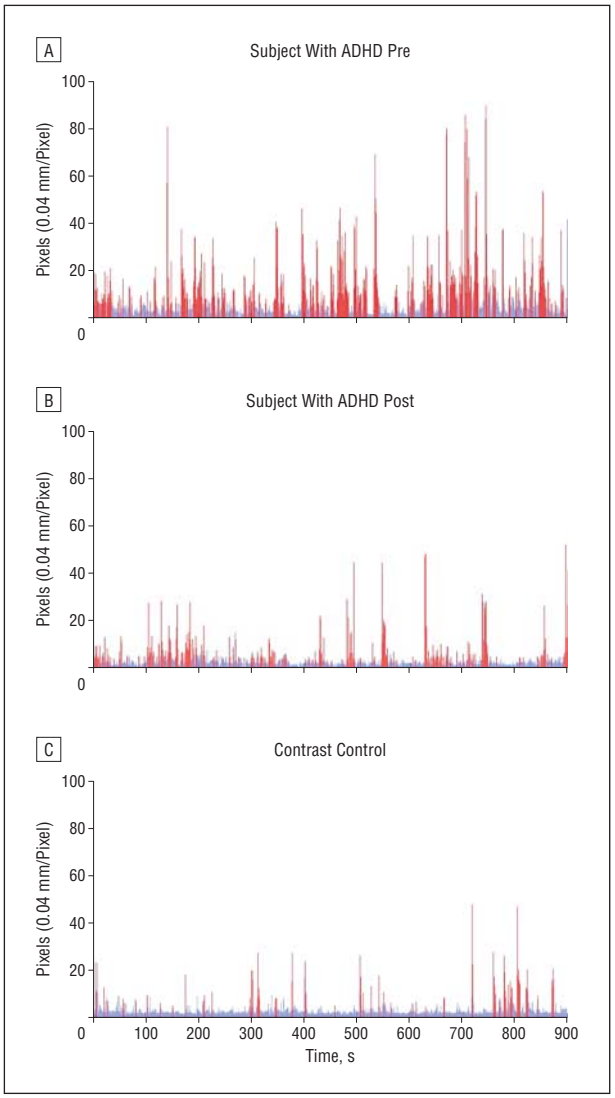

Figure 1. Head position time series indicating absolute change in pixel distance between successive measures captured at 50 Hz during a 15-minute cognitive control task for a typical subject with attention-deficit/hyperactivity disorder (ADHD) before (Pre) (A) and 120 minutes after (Post) (B) methylphenidate administration and a representative subject from the contrast control group (C). Red and blue regions indicate spike and baseline activity, respectively. The data are averaged each second for visual purposes.

tance between successive marker positions was calculated, providing a 45 000-point time series of distance moved every 20 milliseconds throughout the 15-minute test.

The head movement time series was characterized by low basal levels of activity punctuated by much higher–amplitude spikes (**Figure 1**). Basal and spike signals were discriminated using Max-Pass, which is a robust technique for detecting spontaneous neural spikes embedded in background.[29] Briefly, this technique calculates a statistically optimal baseline as the line through which the signal makes the maximal number of positive and negative excursions. Median average deviation (MAD) is calculated from excursions below the line, and a threshold is set a certain number of MAD units above baseline to optimally distinguish spikes.[29] A conservative 8-MAD criterion was used, given the high amplitude of spikes. A 4-MAD criterion produced nearly identical results.

Because the use of Max-Pass for analysis of velocity time series is novel, we also calculated basal and spike amplitudes using cluster analysis. This technique is frequently used in electrophysiology to classify spikes from different neurons[30] and can be used to detect spikes.[31] For each data set, K-means cluster analyses were performed to delineate a high-amplitude cluster that contained between 1% and 10% of the total number of data points. This "high-amplitude/low-frequency-of-occurrence" cluster identified spikes and provided their number and mean amplitude.

The following nonlinear techniques were used to characterize the predictability, persistence, and stability of activity, because abnormalities in these parameters provide the strongest evidence for postural or positional instability. Approximate entropy (ApEn) was quantified as a measure of predictability or regularity of head-marker movements. This method is related to Kolmogorov entropy and revised to be applicable to finite, noisy biological time series.[32,33] Approximate entropy was calculated using Matlab code (http://www.macalester.edu/~kaplan/hrv/doc/). Highly irregular and unpredictable time series have large ApEn values. Two parameters are assigned for these calculations. We set run length $m = 2$ and the filter factor $r = 20\%$ of the standard deviation, as previously recommended.[33]

Persistence of marker movements was estimated by the spectral exponent (β), based on the general linear relation between log-power spectral density and log frequency observed in human physical activity.[34-37] The spectral exponent is the negative slope of this relation (ie, $1/f^{\beta}$). Time series with large β are more persistent. Coarse-graining spectral analysis[38] was used to separate periodic from nonperiodic components of biological signals. There was a strong 2-second (0.5-Hz) periodicity in marker movements corresponding to the interstimulus interval. Coarse-graining spectral analysis was able to extract this component to provide an accurate estimation of β.

The maximal Lyapunov exponent (MLE) was used as a local stability measure. This technique examines the dynamic characteristics of the time series by embedding them into state space. Lyapunov exponents quantify the rate of separation over time of very close points in the state space. Thus, MLE quantifies the effect of perturbations in a dynamical system, as well as its dependence on initial conditions (degree of deterministic chaos). Elevated MLE provides strong evidence for postural or positional instability.[39] The MLE was calculated using TISEAN (http://www.mpipks-dresden.mpg.de/~tisean/TISEAN_2.1/index.html). Embedding parameter dimensions (m) and time delay (τ) were chosen using the time-delayed mutual information and false nearest neighborhood methods, respectively.[40,41] To verify whether the time series was deterministic in nature, the method of "surrogation" was applied, which compares surrogate data with the original data.[42] Surrogate data were generated from the original time series by spectrally balanced randomization (reshuffling), which removes potentially deterministic (nonlinear) structure from the series but preserves mean, variance, and power spectra. For each original time series, 19 surrogates were generated and differences between actual and surrogates were assessed using the procedures of Theiler et al.[43] Because low-pass filtering can introduce spurious Lyapunov exponents,[44] MLE analyses were performed on time series preprocessed using nonlinear filtering.[39,45] Evidence for deterministic chaos was also verified using the correlation dimension method followed by surrogation.[46]

STATISTICAL ANALYSES

Differences between contrast controls and subjects with ADHD before and 120 minutes after administration of methylphenidate were assessed using between-subject analysis of variance. Methylphenidate effects were assessed using repeated-measures analysis of variance. Effect size differences related to diagnosis and methylphenidate administration were indicated

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Table 1. Mean (SD) for Subjects With ADHD and Contrast Controls

Measure	Mean (SD)			Pre vs Contrast		Pre vs Post		Post vs Contrast	
	Pre	Post	Contrast	$F_{1,122}$	*P* Value	$F_{1,61}$	*P* Value	$F_{1,122}$	*P* Value
Spike percentage	13.9 (7.35)	9.10 (8.01)	8.30 (4.83)	25.4	<.001	15.2	<.001	0.45	.50
Spike amplitude	37.7 (26.7)	18.0 (12.1)	19.3 (7.57)	27.4	<.001	34.4	<.001	0.49	.48
Baseline amplitude	4.40 (5.33)	1.61 (1.53)	2.01 (1.04)	12.0	<.001	16.6	<.001	2.84	.09
Approximate entropy	0.35 (0.11)	0.60 (0.34)	0.81 (0.28)	147.7	<.001	33.4	<.001	14.4	<.001
Spectral exponent	2.74 (0.26)	2.29 (0.47)	1.68 (0.29)	437.8	<.001	56.9	<.001	73.9	<.001
Maximal Lyapunov exponent	0.0555 (0.013)	0.0415 (0.014)	0.0087 (0.005)	676.3	<.001	47.2	<.001	287.8	<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; Contrast, contrast control; Pre, subjects with ADHD before methylphenidate administration; Post, subjects with ADHD 120 minutes after methylphenidate administration.

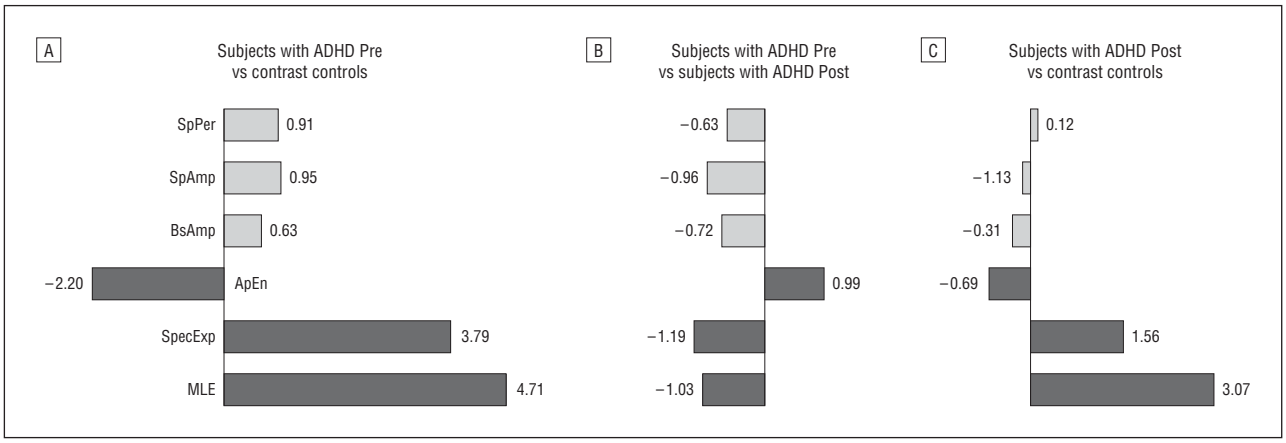

Figure 2. Cohen *d′* effect size for percentage of spike (SpPer), spike amplitude (SpAmp), baseline amplitude (BsAmp), approximate entropy (ApEn), spectral exponent (SpecExp), and maximal Lyapunov exponent (MLE) between attention-deficit/hyperactivity disorder (ADHD) groups before (Pre) and 120 minutes after (Post) methylphenidate administration and the contrast control group. A, Subjects with ADHD Pre vs contrast controls. B, Subjects with ADHD Pre vs subjects with ADHD Post. C, Subjects with ADHD Post vs contrast controls.

by the Cohen *d*. Discriminative differences between subjects with ADHD and contrast controls were calculated using receiver operating characteristic (ROC) analysis.[47] The interrelationship and independence of the assessed parameters were evaluated using principal component analysis. Statistical tests were performed in SPSS (SPSS Inc, Chicago, Illinois).

RESULTS

Subjects with ADHD had baseline and spike amplitudes that were 2.2- and 2.0-fold greater than controls, respectively (**Table 1**). They also had a 68% greater number of spikes. Effect size differences between subjects with ADHD before methylphenidate administration and contrast subjects ranged from 0.6 (baseline amplitude) to 1.0 (spike amplitude) (**Figure 2**). Spike amplitude discriminated subjects with ADHD from controls with modest accuracy (ROC area = 0.799) (**Figure 3**).

Inhibitory control was markedly enhanced by methylphenidate administration. Baseline and spike amplitudes were reduced by 63% and 52%, respectively (both $P < .001$) (Table 1), yielding effect sizes of about 0.7 to 1.0. Number of spikes was reduced by 35% ($P < .001$). Overall, baseline and spike amplitudes and spike numbers were suppressed to at or below contrast control levels (Figure 2).

Cluster analysis confirmed that subjects with ADHD had baseline and spike amplitudes that were 2.2- and 1.9-fold greater than controls, that spike amplitude discriminated subjects with ADHD from controls with moderate accuracy (ROC area = 0.822), and that methylphenidate administration reduced baseline and spike amplitudes to at or below control levels.

Subjects with ADHD prior to taking medication and contrast controls differed dramatically in stability, predictability, and persistence of movements. The MLE was 6.4-fold greater in subjects with ADHD. Eighty-four percent (52 of 62) of subjects with ADHD showed evidence for a nonlinear deterministic component in their movement time series based on surrogation ($z = -27.04$; $P < .001$, group values vs surrogates). In contrast, there was no evidence of a deterministic component in any of the contrast controls (zero of 62). The movement pattern of subjects with ADHD was much more persistent (1.6-fold greater β) and predictable (57% lower ApEn). These differences were associated with very large effect sizes (2.2-4.7) (Figure 2). Further, there was virtually no overlap between subjects with ADHD and contrast subjects on MLE (ROC area = 1.0) and β (ROC area = 0.991) (Figure 3). Nonlinear analysis revealed much stronger differences between subjects with ADHD and controls than traditional linear measures. For instance, mean activity levels differed between groups ($F_{1,121} = 35.10$; $P < .001$; $d' = 1.07$; ROC = 0.857), but effect size and ROC measures were much greater for β and MLE.

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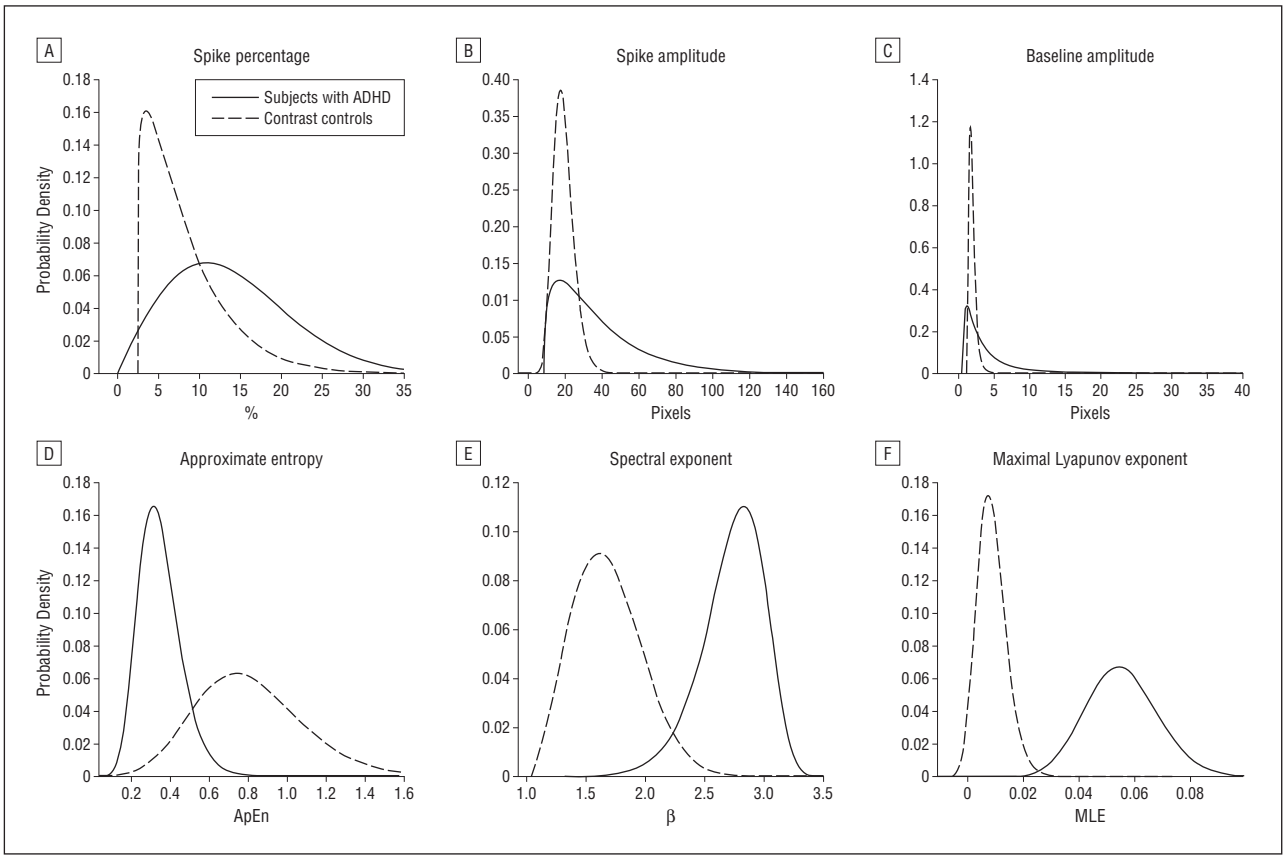

Figure 3. Probability density curves for subjects with attention-deficit/hyperactivity disorder (ADHD) before methylphenidate administration vs contrast controls. The distribution of scores for all subjects in a group were fit to normal, log-normal, γ, or Weibull distributions to reveal the theoretical degree of overlap for the populations and the shapes of the curves. The Figure shows the best-fitting probability density curve for each group. Goodness of fit for each series of quasi-normal curves was evaluated by Kolmogorov-Smirnov tests.

Table 2. Principal Component Analysis With Varimax Rotation

	Rotated Component Matrix Components		
Measure	**1**	**2**	**3**
Approximate entropy	–0.897	–0.059	–0.205
Spectral exponent	0.764	0.391	0.184
Maximal Lyapunov exponent	0.889	0.283	0.291
Basal amplitude	0.115	0.975	0.018
Spike amplitude	0.319	0.906	–0.068
Spike number	0.344	–0.054	0.936

ApEn, β, and MLE were significantly affected by probe-dose methylphenidate, with effect sizes that ranged from 1.0 to 1.2 (all $P<.001$) (Figure 2). The percentage of subjects with ADHD with evidence for a deterministic chaotic component fell from 84% to 66% (41 of 62) ($z=-17.66$; $P<.001$, group vs surrogates).

However, while methylphenidate exerted strong statistical effects on these measures, they remained quite different from controls (all $P\leq.001$). This was particularly true for MLE, which was 4.8-fold higher in subjects with ADHD after methylphenidate administration ($d'=3.1$). The ROC analysis confirmed that discriminative differences persisted between subjects with ADHD 120 minutes after methylphenidate administration and contrast subjects on β (ROC area=0.850) and MLE (ROC area=0.995). Multivariate analysis of variance indicated that measure of inhibition (baseline and spike amplitude) and positional stability (β and MLE) were affected quite differently by methylphenidate (methylphenidate × measurement type, $F_{1,60}=64.49$; $P<.001$). Methylphenidate produced a mean (SD) 58.3% (39.9%) within-subject reduction in composite inhibitory measures, but only a mean (SD) 16.6% (19.2%) reduction in composite measures of positional stability.

Confirmation of a deterministic component to head position was evaluated by assessing the presence of a plateau on a dimension plot across a wide range of length scales. Altogether, 56 of 62 subjects with ADHD before methylphenidate administration, 62 of 62 subjects with ADHD 120 minutes after methylphenidate administration, and zero of 62 contrast subjects showed evidence for a deterministic component using this approach. The mean (SD) correlation dimension for the subjects with ADHD was 2.46 (0.37).

Principal component analysis with varimax rotation indicated that these 6 activity measures segregated into 3 orthogonal components that explained 91.1% of the variance (**Table 2**). The first component was strongly influenced by the 3 measures of positional stability (ApEn, β, and MLE) and accounted for 40.2% of the variance (eigenvalue 2.4). The second component was influ-

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enced by the 2 measures of inhibitory amplitude and accounted for 33.5% of the variance (eigenvalue 2.0), while the third component was based on the number of spikes (17.4% variance; eigenvalue 1.0).

The second component (inhibitory amplitude) correlated best with performance on the cognitive control task (11 of 13 performance measures correlated with a significant degree). Some of the most significant parameters to correlate with inhibitory amplitude were variability in response latency, errors of omission, and errors of commission (Spearman rank order correlation [r_s] = 0.464, 0.377, and 0.317, respectively; all $P < .001$). The first component (marker stability) correlated with variability in response latency (r_s=0.225; P=.002) and errors of omission (r_s=0.187; P=.01). The third component (spike number) only correlated significantly with correct response latency (r_s=0.181; $P < .02$). Errors of commission (an index of insufficient behavioral response inhibition) correlated significantly with spike (r_s=0.361; $P < .001$) and basal amplitude (r_s=0.321; $P < .001$) but did not correlate significantly with β or MLE.

Differences in motor activity were not due to differences in attention task performance. First, subjects with ADHD performed with the same level of accuracy as controls (mean [SD], 83.1% [10.6%] vs 84.8% [11.2%]; $F_{1,121}$=0.74; $P > .38$). Second, motor activity measures differed much more dramatically between subjects with ADHD and controls than any of the attention measures (eg, maximal ROC difference on attention measures=0.694; $F_{1,121}$=8.24; P=.005; d'=0.52, variability in response latency). Finally, covarying motor activity measures by the significant attention parameters did not have any discernible effect on the significance of any of the motor activity differences.

Finally, group differences in activity were not an artifact of fatigue due to the long test session. Subjects with ADHD and controls differed markedly in MLE during the first 5 minutes of the test ($F_{1,120}$=237.5; $P < .001$; d'=2.8; ROC=0.970). Similarly, group differences in basal and spike amplitude and spike number were essentially identical whether we analyzed the first 5 minutes or the entire 15 minutes. Methylphenidate also exerted comparable effects on the first 5 minutes of the test, such that 120 minutes after methylphenidate administration inhibitory measures did not differ from controls, while 120 minutes after methylphenidate administration nonlinear measures remained distinctly different.

COMMENT

Seated activity of children with ADHD was characterized by an impaired ability to (1) inhibit activity to low levels, (2) maintain suppression, and (3) stabilize head-marker position. This latter problem may be a consequence of postural instability affecting the head and trunk and/or a problem with head positioning involving movements around the atlanto-occipital joint or cervical spine. Recent studies have shown that individuals with ADHD have problems with postural control while standing.[11,12] However, differences between subjects with ADHD and controls in these studies were minor,[11,12] and the linear analytic methods applied were not capable of characterizing the dynamics of postural stability.[39,48] Postural control and head positioning are characterized by strong nonlinearities due to the elastic and damping properties of muscles as well as nonlinear feedback control in the nervous system.[49] The head is stabilized in space by sensory inputs, vestibular and cervicocollic reflexes, and the cervical musculoskeletal system.[50] Since these systems interact through feedback loops, and form a multilink network, small changes in one can have remarkable and unpredictable effects throughout the network.

Between 84% and 90% of children with ADHD prior to taking medication (depending on analytical method), but none of the contrast controls, had evidence for a significant MLE. This result indicates that fluctuations in positioning of the head marker were not randomly derived but showed sensitivity to initial conditions (ie, slight differences in initial values can result in large or unpredictable differences, aka the "butterfly effect"). To our knowledge, this is the first report showing that children with ADHD have movement patterns that are deterministic and chaotic in nature.

Methylphenidate significantly affected all measures in the subjects with ADHD. However, while problems with inhibitory suppression fully resolved after methylphenidate administration, instability persisted, and most subjects with ADHD continued to show evidence of deterministic chaos. Rocchi et al[51] reported that drugs affecting dopaminergic systems (eg, levodopa) actually increased postural sway in patients with Parkinson disease.

Functional magnetic resonance imaging studies have shown that dysfunctions in portions of the frontal cortex and striatum underlie inhibitory deficits in ADHD.[18-21] Stimulant drugs partially correct patterns of frontal[52] and striatal hypoactivation.[53] Teicher et al[54] reported significant elevations of T2 relaxation time in the putamen of boys with ADHD, suggestive of diminished blood flow and neuronal activity. Methylphenidate reduced T2 relaxation time (increased blood flow) in the putamen of objectively hyperactive children with ADHD. Mostofsky and Simmonds[21] and Simmonds et al[55] found that activity within a portion of the frontal cortex known as the presupplementary motor area correlated with measures of response selection, response inhibition, and variability in response latency. These performance measures correlated most strongly with measures of motor inhibition.

In contrast, the most consistent structural abnormality in ADHD is a reduction in cerebellar vermal size.[14-17] The vermis plays a crucial role in head motion, eye movements, and postural control[56-58] by receiving and processing vestibular and proprioceptive inputs necessary for these functions.[57,59-61] Lesions of the spinocerebellar (upper vermal and intermediate) part of the anterior lobe result in spontaneous anterior-posterior body sway.[56] Lesions of the lower (vestibulocerebellar) vermis produce postural ataxia of the head and trunk while sitting, standing, and walking.[56] The posterior inferior vermis (lobules VIII, IX, and X) has been found to be the portion of the vermis most significantly affected in ADHD in some studies[14,15,62] but not in others.[17] Cerebellar cortical neurons in lobules IX and X transform head-centered vestibular afferent information into earth-referenced self-

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motion and spatial orientation signals necessary for orientation, navigation, and positioning.[63]

The vermis is also responsive to methylphenidate, though its metabolic/hemodynamic response may be opposite to that observed in the basal ganglia.[64] Methylphenidate increased T2 relaxation time (decreased blood flow) in this region in hyperactive children with ADHD[65] while exerting the opposite effect on the putamen.[54] Thus, postural and/or positional instability in ADHD may be related to abnormalities in the vermis that are not ameliorated by methylphenidate. We suspect that partial improvement in positional stability following methylphenidate administration maybe an indirect result of an improved degree of inhibitory suppression. If children with ADHD make smaller-amplitude head movements while taking methylphenidate, they may tax their positional control mechanisms to a lesser degree and exhibit an improved degree of stability. Interestingly, long-term stimulant treatment may help to normalize the development of the posterior inferior vermis.[62] Alternatively, the more persistent and predictable pattern of marker movements in subjects with ADHD (increased β, decreased ApEn) could stem from premotor system dysfunction diminishing the ability to generate more specific and appropriate movements in response to postural change.

This study suggests that hyperactivity and fidgeting in ADHD is a complex neurointegrative problem. It is not simply "exuberance" or the upper end of a normal distribution.[66] The distributions of MLE and β in children with ADHD and contrast subjects were mutually distinct and essentially nonoverlapping (Figure 3).

There are several implications of these findings. First, elevated MLE and β may be strong biobehavioral markers for ADHD hyperactivity in children. It remains to be seen if these parameters are elevated in other disorders that enter into the differential diagnosis. We suspect that deterministic chaos in head movements could be a sign of ADHD hyperactivity that normal individuals would be unable to fake.

Second, it is conceivable that inhibitory suppression measures may provide a window into the functional capacity of frontostriatal inhibitory control circuits, while nonlinear measures of positional stability may provide a window into the functional activity of the cerebellar vermis. The ability to assess functional capacity of brain regions in this way may eventually enable us to predict which treatments will be most useful.

There are several limitations of this study. First, we included only 9- to 12-year-old boys and only selected subjects with ADHD with the combined subtype. Comparable investigations need to be conducted in girls, adolescents, and adults. Further, all of the subjects with ADHD had received treatment with methylphenidate. It will be important to ascertain if untreated subjects with ADHD show the same abnormalities. Subjects with ADHD in this study had conventional movement measures (number of position changes, total displacement, area, and spatial complexity) that were highly comparable with those observed in unmedicated subjects.[10] Subjects with ADHD were tested twice (before and 120 minutes after methylphenidate administration) and controls were only tested once, raising the possibility that improvement was a practice effect. This was not the case; test-retest measures are highly concordant (unbiased estimates of reliability range from 0.92-0.97) and motor activity shows no improvement while subjects are taking placebo.[27] Contrast controls were not evaluated using structured interviews but were only screened by teacher ratings to help exclude subjects with ADHD. Rigorously screened controls with no personal or family history of psychiatric disorders tested in the laboratory typically show even lower degrees of activity and better performance on the cognitive control task.[26] It is not possible to tell in this study whether instability in head-marker position resulted from postural instability or from a more specific problem in head positioning. We previously found that subjects with ADHD differed to the same degree from controls in conventional movement measures whether markers were located on the head, back, shoulder, or elbow,[10] suggesting that postural factors may be particularly important.

The application of chaos theory to complex biological systems has been widely pursued in the past few decades.[67-69] However, the interpretation of results has been the subject of much debate. This is largely due to the inherent nature of biological data, which can only provide a time series of finite length mixed with noise.

Critical issues involved in demonstrating the existence of chaotic behavior include data size, sampling rate, and existence of noise.[46] No accepted standard has emerged for minimal number of points, or sampling rate, as this depends largely on the underlying dynamics.[46] One previous study calculating MLE on heart rate variability used 20 000 points,[70] while another study calculating MLE, correlation dimension, and Kolmogorov entropy of cerebral blood flow velocity used 5 to 10 minutes of data with a sampling rate of 60 Hz.[71] An article calculating MLE for postural displacement used 100 seconds of data sampled at 100 Hz.[39] Our time series with 45 000 data points collected over 15 minutes is larger than most previously published series but collected at a slightly slower sampling rate (50 Hz). Nevertheless, this series should be quite adequate for calculating MLE.

Noise is another critical concern. A previous study pointed out that low-pass filtering can introduce spurious Lyapunov exponents.[44] Hence, MLE was analyzed following nonlinear filtering. Results were also verified using the correlation dimension method.[46]

These findings suggest that ADHD hyperactivity is a complex phenomenon that appears to stem from deficits in regulatory systems that differ in degree of correctability by methylphenidate. It will be particularly interesting if future studies link the deficit in inhibitory suppression to frontostriatal circuits and the problems with positional stability to the cerebellar vermis.

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BioBehavioral Diagnostic Company (BioBDx). Dr Teicher is the inventor on a number of patents related to this technology and has the potential to receive a portion of the royalties that might be paid to McLean from the use of Quotient, in compliance with guidelines established by Harvard Medical School to minimize conflict of interest in clinical research. Dr Teicher has no equity interest in BioBDx and holds no management position. Dr Teicher has been reimbursed by BioBDx for travel expenses incurred to present results of research on Quotient, has received funding in the past from BioBDx for new research relating to Quotient, and receives consulting fees that fall within the de minimis guidelines established by Harvard Medical School and Partners Health Care. Dr Teicher also received recent research support, as a component of a National Institute of Mental Health Small Business Innovation Research award, from Ambulatory Monitoring Inc to investigate use of a feedback actigraph in treatment of children with ADHD. He previously received ADHD-related research funding from Copley Pharmaceuticals and OPTAx Systems Inc; the later also paid consulting fees. Dr Ohashi is a coinventor on a submitted patent application regarding Quotient technology and could receive a portion of royalties paid to McLean. A portion of her salary has been paid through research funding to Dr Teicher's program. She holds no position with BioBDx and receives no consulting fees. Drs Vitaliano and Polcari have no conflicts to declare.

The collection of data analyzed in this study was funded through Copley Pharmaceuticals and OPTAx Systems Inc. The aim of the Copley-funded study was to assess the pharmacodynamics of different methylphenidate time-release preparations in children with ADHD. Data analyzed in this report came from the initial screening stage of that study. The aim of the OPTAx Systems study was to provide normative data on changes in activity and attention parameters of healthy schoolchildren during development. Data from both studies were combined and new mathematical techniques were applied to their analysis. Copley Pharmaceuticals was sold to Teva Pharmaceuticals, who abandoned interest in the project. OPTAx Systems Inc went out of business. Rights to the technology reverted to McLean Hospital and were licensed to BioBDx.

Role of the Sponsors: The commercial sponsors of the data collection had no role in the analysis and reporting of the results or writing of the article, nor did BioBDx. None of the measures provided in this report are currently available on the commercial version of the Quotient ADHD system.

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