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Transcranial Magnetic Stimulation Measures in Attention-Deficit/Hyperactivity Disorder

STEVE W WU, MD^{*}, DONALD L GILBERT, MD, MS^{*}, NASRIN SHAHANA, MBBS^{*}, DAVID A HUDDLESTON, BA^{*}, and STEWART H MOSTOFSKY, MD[†]

^{*}Division of Neurology, Cincinnati Children's Hospital Medical Center and University of Cincinnati School of Medicine, Cincinnati, Ohio, USA

[†]Departments of Neurology and Psychiatry, Laboratory for Neurocognitive and Imaging Research, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Children affected by Attention-Deficit/Hyperactivity Disorder have diminished intra-hemispheric inhibition (Short Interval Cortical Inhibition) as measured by Transcranial Magnetic Stimulation. This study's objective is to determine whether inter-hemispheric inhibition (Ipsilateral Silent Period Latency) correlates with clinical behavioral rating and motor control deficits of affected children. In 114 8–12 year old, right-handed children (age/sex-matched, 50 affected, 64 controls), we performed comprehensive assessments of behavior, motor skills and cognition. Using Transcranial Magnetic Stimulation, we reliably elicited Ipsilateral Silent Period in 54 children (23 affected) - all were on average older than those who had unobtainable measures. Mean Ipsilateral Silent Period latency was 5 milliseconds longer in the affected group ($p=0.007$). Longer latencies correlated with more severe behavioral symptom scores ($r=0.38$, $p=0.007$), particularly hyperactivity ($r=0.39$, $p=0.006$), as well as with worse motor ratings on the Physical and Neurological Examination for Soft Signs ($r=0.27$, $p=0.05$). Longer latency also correlated with Short Interval Cortical Inhibition ($r=0.36$, $p=0.008$). In conclusion, longer Ipsilateral Silent Period latencies suggest interhemispheric inhibitory signaling is slower in affected children. The deficit in this inhibitory measure may underlie developmental, behavioral and motor impairments in children with Attention-Deficit/Hyperactivity Disorder.

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Correspondence: Steve W Wu, MD, Division of Neurology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue MLC 2015, Cincinnati, OH 45229-3039, USA, 513-636-4222, 513-636-1888 fax, steve.wu@cchmc.org.

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INTRODUCTION

Maturation of motor and behavioral control are fundamental processes that occur in parallel throughout childhood. The fine motor control required to manipulate tools and instruments includes development of independent hand and finger use. Relative delay or dysmaturation of the circuitry permitting motor control results in subtle motor deficits in repetitive and sequential movements, accuracy in rhythm, and suppression of motor overflow [1]. An expanding body of research shows that these particular motor skills are significantly impaired in children with Attention-Deficit/Hyperactivity Disorder (ADHD) relative to typically developing peers [1–4]. The temporal association between development of motor and behavioral control and the consistent statistical associations between deficits in motor skills and ADHD [3–5] suggest that the developing motor system may provide a useful window into neurobiological mechanisms of behavioral control.

A broad aim of our research program has been to identify easily obtained, quantitative, robust, brain-based markers of behavioral and motor function in children with ADHD. To this end, we recently described, in a large and well characterized, matched sample of 104 8–12 year old ADHD children and typically developing controls, physiological findings in motor cortex that may function as a biomarker of ADHD [6]. We used transcranial magnetic stimulation (TMS) in the motor cortex to measure depolarization motor thresholds, paired pulse facilitation, and two measures of intracortical inhibition: short interval cortical inhibition (SICI) and the cortical silent period. The most profound difference was in SICI, which was on average 40% reduced in the ADHD group [6]. Furthermore, SICI correlated robustly with parent rated ADHD severity and moderately with measures of motor skill impairment [6], rated using the Physical and Neurological Examination for Soft Signs (PANESS) [2,3]. However, as expected in evaluating a behaviorally defined disorder with pathophysiological heterogeneity, there was overlap between ADHD and control groups.

The objective of the present study was to investigate in similar detail the relationships between ADHD, motor development, SICI and a less studied measure of physiological inhibition in the motor system, the Ipsilateral Silent Period (ISP). The ISP is a period of relative inhibition in ongoing electromyographic activity after stimulation of the cortex ipsilateral to the target muscle [7]. The ISP may involve both intra-hemispheric and inter-hemispheric inhibitory circuits [7–12] and is altered in persons with lesions of the corpus callosum [9,13].

The ISP may be of particular value as a quantitative physiological measure, given that both qualitative observations and quantitative measures demonstrate that children with ADHD have increased overflow movements, a motor sign believed to reflect impaired inter-hemispheric inhibitory control [2,3,5]. Two research groups previously evaluated ISP and found that children with ADHD had longer ISP latencies [14,15]. However, both of these studies included relatively small sample sizes, totaling twenty-four [15] and twenty-six [14] children (ADHD and control), and could not powerfully assess relationships with other physiological markers, behavioral severity, or maturation of motor control. Furthermore, in addition to the inter-hemispheric mechanism, SICI-like intra-hemispheric inhibitory input has also been implicated in the generation of ISP [11]. We therefore hypothesize that, compared to controls, ADHD children would have longer ISP latencies and that these latencies would correlate with both ADHD symptom severity and motor development scores, particularly motor overflow, evaluated with the PANESS.

MATERIALS AND METHODS

Participants

This is a 1:1, age and sex-matched, case-control study of motor development, motor cortex physiology, and behavioral symptoms in 8–12 year old, right-handed children with ADHD children vs. typically developing controls.

Participants were recruited from 2006 to 2011 from a variety of sources including outpatient clinics at Cincinnati Children's Hospital Medical Center and the Kennedy Krieger Institute (Baltimore, Maryland), from local chapters of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder, from local schools, pediatrician offices and services organizations (e.g., boy/girl scouts), and through fliers posted in the community. Age and sex-matched controls were recruited from email and flier advertisements posted at Cincinnati Children's Hospital Medical Center, Kennedy Krieger Institute and the surrounding communities.

Parents who responded were initially screened by phone. To be included, children had to be otherwise healthy, with no history of Psychiatric or Developmental Disorders other than ADHD. Children whose parents reported they had a history of mental retardation, seizures, traumatic brain injury or other neurological illnesses were excluded from participation. Psychostimulants, but no other medications, were allowed. For the study, stimulants were discontinued on the day prior to and the day of cognitive and TMS testing.

Standard protocol approvals, registrations, and patient consents

Permission for the study was obtained from the Cincinnati Children's Hospital Medical Center and Johns Hopkins Medicine Institutional Review Boards. Written informed consent was obtained from legal guardians and assent from children.

Clinical diagnostic and cognitive assessments

All evaluations were conducted by research personnel trained to administer psychological interviews and parent questionnaires, and all data were reviewed and diagnoses confirmed by the physician investigators. These research personnel were blinded to the neurophysiologic data.

Socioeconomic status was queried using the Hollingshead Parent History Questionnaire assessment of Socio Economic Status [16]. Right-handedness was verified using the Edinburgh Handedness Inventory [17].

All children were administered the Basic/Word Reading subtests from Wechsler Individual Achievement Test II [18] to rule out a learning disability in reading. Intellectual ability was then assessed using the Wechsler Intelligence Scale for Children-IV [19]. Children with full scale intelligence quotient (IQ) scores below 80 were excluded from participation. Children were excluded from participation if they demonstrated a statistically significant discrepancy between full scale IQ and Wechsler Individual Achievement Test II score or a Basic/Word Reading subtest score below 85.

Diagnostic status (ADHD) was established through administration of the Diagnostic Interview for Children and Adolescents-IV (DICA-IV) [20]. Children meeting criteria for diagnosis of conduct, mood, generalized anxiety, separation anxiety or obsessive-compulsive disorders on DICA-IV interview were excluded. Children with oppositional defiant disorder were not excluded from participation. Although we would much prefer to have a sample of participants with "pure" ADHD, we did not exclude children with comorbid oppositional defiant disorder due to a high rate of comorbid psychiatric diagnoses

that can lead to recruitment difficulties. While findings from past studies suggest that ADHD associated with conduct disorder may be a distinct subtype, this is not the case for ADHD associated with oppositional defiant disorder [21,22].

Parents and teachers also completed Conners' Parent and Teacher Rating Scales-Revised and the Dupaul ADHD Rating Scale-IV, home and school versions [23]. Inclusion in the ADHD group was made based on all the following criteria: (1) diagnosis of ADHD and referral for participation by community clinicians; (2) DSM-IV-TR diagnosis of ADHD based on positive scores on at least one of the parent and (when obtained) one of the teacher rating scales (i.e., T-score of 65 or higher on scale L (DSM-IV: inattentive) or M (DSM-IV: hyperactive-impulsive) on the Conners' Parent and Teacher Rating Scales-Revised), or children receiving scores of 2 or 3 on at least 6/9 items on the Inattentive or Hyperactivity/Impulsivity scales of the Dupaul ADHD Rating Scale; and (3) confirmation of ADHD diagnosis by DICA-IV psychiatric interview.

In order to meet inclusion criteria for the control group, parent and teacher reports on Conners' Parent and Teacher Rating Scales-Revised and DuPaul ADHD Rating Scale had to be below clinical cutoff scores and they could not meet diagnostic criteria for any psychiatric disorder based on DICA-IV. Like children in the ADHD group, they could not have history of neurological disorder, or be taking psychotropic medication. The same IQ, reading, and achievement discrepancy criteria were also required for inclusion.

Motor skill assessments of ADHD children and controls

Study personnel at both sites trained together for consistency and reliability of motor assessments. Motor function was assessed comprehensively using the PANESS, as recently described in a large cohort of children with ADHD children and controls [3]. The PANESS measures or rates timed movements, lateral preference, motor overflow, dysrhythmia, coordination, gait, balance, and motor persistence. The main subscale of interest in the PANESS was the motor overflow subscale as deficient control of motor overflow might be expected to correlate with reduced inter-hemispheric inhibition/ISP.

Motor Cortex Physiology

Both sites performed single and paired pulse TMS using identical devices: a Magstim 200® stimulator (Magstim Co., Whitland, Wales, UK) connected through a Bistim® module to a double 70 mm coil. The coil was placed tangential to the skull with handle backward, at 45 degrees to the midline and its center near the optimal position and orientation for producing a motor-evoked potential (MEP) in the right first dorsal interosseous muscle (FDI). Surface electromyography (EMG) was performed to capture the amplitudes of the TMS-evoked MEPs. The surface EMG signals were amplified and filtered (100/1000 Hz) (Coulbourn Instruments, Allentown, PA) before being digitized at 2 kHz and stored for analysis using Signal® software and a Micro1401 interface (Cambridge Electronic Design, Cambridge, UK). For single vs. paired pulse studies, all individual tracings were analyzed blinded and off line. More detailed descriptions of single and paired pulse measurements in this study were recently published, including methods to address motion artifact in hyperkinetic children [6].

Resting (RMT) and active depolarization motor thresholds were evaluated and defined using conventional criteria [24]. In brief, starting at a low and comfortable intensity of 20% of the stimulator's output, pulses were administered and then the stimulation intensities were increased by intervals of 10% until an MEP was identified. After adjusting the location and position of the coil to produce a reliable, well formed MEP, the intensity was decreased sequentially until an intensity was reached where 3 of 6 trials yielded no MEPs and 3 trials

evoked small MEPs (~0.1 mV amplitude MEPs in resting muscle) [25]. The RMT is expressed as a percentage of maximum intensity of the Magstim device. The active motor threshold is measured per standard method [26] and is also approached from above, decreasing the stimulus intensity until the point at which 3 of 6 trials yielded no MEP visible above background EMG activity and the other 3 evoked MEPs visible over background. TMS pulses were administered at ~5 second intervals and for the active motor threshold, the participant relaxed between trials.

The primary physiological measure of interest was the Ipsilateral Silent Period (ISP), obtained using conventional methods [7,14]. The figure-8 TMS coil was placed over right motor cortex at the optimal location for producing an MEP in the FDI of the left hand, and the EMG tracing was measured in the right hand for 100 msec prior to and 400 msec after the TMS pulse. The goal was 5 valid trials. Trials were separated by rest for at least 5 seconds. During each trial, children were instructed to squeeze maximally in each hand simultaneously by squeezing two balls between their thumbs and abducting index fingers. Proper FDI activation while squeezing was verified with visual and tactile means and was confirmed by surface electrophysiology. The children were instructed to maintain muscle contraction until told to “let go” after the completion of each trial. Trials where children released the balls or did not maintain muscle contraction were observed in real time and repeated to ensure adequate trials. Invalid trials were excluded from analysis. ISP onset and offset were defined visually, blinded to diagnosis, using the rectified average from the valid ISP trials. ISP latency is the time interval from the TMS pulse to ISP onset. ISP duration is the time interval between ISP onset and offset (Figure 1A).

The study of children with ISP posed some unique challenges, of which we had partial expectations based on prior experience with ISP measurement in children. We did anticipate that this stimulus would be noxious for some children. We always performed this measurement last, after other measures. If children wished to discontinue after the first pulse, we allowed this and did not record any data. Because the device is set at 100% stimulation and both hands (and hemispheres) are activated, there is a large and diffuse motor response elicited, including some direct spread in some children, perhaps due to smaller head size, to temporalis muscle, causing a jaw jerk. We also anticipated that even some cooperative children would not have an ISP elicitable, in part because the maximal intensity of the machine would be just at or slightly above resting motor threshold for some young participants. Silent period durations are strongly affected (lengthened) by higher intensities relative to RMT [27].

SICI was measured using standard methods [28]. In brief, 20 single pulse trials were performed with the intensity set at 15 to 30% above the RMT (test pulse) to produce an MEP of amplitude of ~ 1 mV. The paired pulse trials had a conditioning pulse intensity set at 60% of RMT because 70% of RMT conditioning pulse yielded stronger inhibition in both ADHD and control children. Based on this experience, trial and errors at other intensities and the published conditioning pulse “dose” intensity study in healthy adults [29], we determined that a slightly less efficient condition pulse would disperse the ratios in children more widely, with a higher opportunity for evaluating group differences and correlations of interest. The conditioning pulse preceded the test pulse by either 3 msec (inhibitory interval - SICI) or 10 msec (excitatory interval – Intracortical Facilitation). Trials were generated in random order, separated by 6 seconds (+/- 5%). SICI is expressed as a ratio of mean paired pulse to mean single pulse amplitudes so that, for example, a ratio of 0.55 would indicate 45% inhibition. Lower ratios indicate greater inhibition.

Statistical Analyses

Primary Analysis – sample size calculation—Diagnosis group difference in ISP latency was the primary outcome of interest. We assumed this would be normally distributed and planned a two sample t test. Estimated means and standard deviations of ISP were obtained from two prior publications in small samples of ADHD and control children [14,15]. Sample size of 30 children per group was calculated in order to have an 80% power, with alpha of 0.05, to detect a 4 msec (~10%) group difference, with estimated standard deviation of 6 msec.

Analysis of groups based on presence of clear ISP—Reproducible ISPs were difficult to obtain in children. Participation was voluntary, and ISP was obtained after all other measures due to likelihood of discomfort, as this measure is obtained at 100% of stimulator output. Discomfort at higher intensities led 15 children (10 ADHD) to discontinue/decline measurement after feeling the higher intensity TMS pulses. Even in cases where experiments were completed, a silent period was not always consistently reproducibly (clearly identified in at least 3 of 5 individual tracings). Therefore, the first analysis we performed was to identify clinical and demographic features of children in whom ISP was present vs. those in whom ISP was not identified, using Chi Square and unpaired t tests.

The loss of participants due to discomfort or high thresholds potentially created a case control sample that was less matched, thereby creating potential bias. Therefore, ADHD vs. control group differences were assessed statistically using t test and Chi Square, as appropriate. In the final analysis, the primary outcome of interest, ISP by diagnosis group, was then also regressed over Sex and any factors identified at the $p < 0.1$ level, to evaluate for confounders.

Assessment of normality—All continuous data were assessed for normality using Kolmogorov Smirnov testing. ADHD rating scales were not normative. Therefore, correlations with ADHD severity based on scales were evaluated with nonparametric (Spearman) correlations. All other analyses employed parametric statistics.

Univariate analyses: ADHD Children vs. Controls: ISP, Behavior, Motor Function, Motor Physiology, Clinical/Demographic variables—The primary dependent variable of interest for all analyses in this study was the ISP latency. ISP duration was analyzed but of secondary interest, for several reasons. First, the most robust age related effect and difference previously identified in ADHD children versus controls was in the ISP latency [15]. Second, silent period durations are likely confounded by RMT. This is because conventionally ISP is measured at maximum stimulator intensity, not indexed to RMT as in the case of cortical silent period. Therefore, for each individual the relative intensity applied during ISP measures would differ as a proportion of their RMT, so that duration might actually reflect and be confounded by RMT, rather than being related to ADHD diagnosis.

Motor and behavioral rating scales scores were treated as continuous variables. Demographics and IQ were compared across groups and clinical and experimental data were compared across the two sites using t tests and Chi Square as appropriate.

Group Comparisons—Behavior (ADHD Total scores, Inattention, Hyperactivity), Motor Physiology (Thresholds, ISP, SICI), and Motor Function (PANESS Total, PANESS subscales) were characterized (mean, standard deviation (SD)), and compared between ADHD children and controls, using t tests.

Correlations for ADHD severity, Motor Skills—Correlations of behavior with ISP latency were the primary correlations of interest. Nonparametric (Spearman) Correlations of total ADHD symptom severity as well as inattention versus hyperactive/impulsive subscales were calculated. Parametric Correlations (Pearson) were used for Motor Function (PANESS, plus motor overflow subscales) and for SICI and other TMS measures.

RESULTS

Participants

TMS motor physiology and ratings of motor function did not differ across sites (Cincinnati, Baltimore). The recruited sample included 114 children (50 ADHD). ISP data were considered evaluable in 54 (23 ADHD).

Group differences: ISP measurable vs. unmeasurable

Of the total sample, the proportions of ADHD children vs. controls ($p=0.8$) and the DuPaul ADHD Rating Scale symptom scores ($p=0.8$) did not differ in the ISP obtainable vs. unobtainable groups. Full scale IQ ($p=1.0$) and total PANESS (motor skill) scores ($p=0.7$) also did not differ.

Children in whom ISP could be clearly obtained were older on average (mean age 11.0 years, SD 1.4) than those in whom ISP was not clearly present (mean age 10.5 years, SD 1.4) ($p=0.03$). As expected, both active ($p=0.006$) and resting ($p=0.01$) motor thresholds were lower in the children in whom ISP was obtainable. The remainder of analyses was performed for only those children who had ISP identified. Their clinical and demographic features are shown in Table 1.

Primary Outcome: Ipsilateral Silent Period Latency in ADHD Children vs. Controls

Group differences in motor physiology and function are shown in Table 2. The primary TMS-evoked measure of interest, ISP latency, was significantly longer in the ADHD children compared to controls ($p=0.007$) (Figure 1B). ISP duration did not differ (Table 2) and was not included in further analyses. A post hoc, within-ADHD group analysis was performed of children currently taking versus not taking psychostimulants. ISP latency did not differ between these two groups ($p=NS$).

Multivariate: Ipsilateral Silent Period Latency in ADHD Children vs. Controls, assessing for possible confounders and interactions

Including Sex in the model, there was no primary Sex effect ($p=0.50$) or Sex*Diagnosis interaction effect ($p=0.12$) on ISP. Factors which differed between groups (Table 1) were also assessed with linear regression. Neither Hollingshead family social status ($p=0.82$), nor any of the cognitive subtests (all $p>0.5$) were associated with ISP latency.

Univariate correlations between ISP latency, age, ADHD symptom severity, and motor function

Exploratory univariate correlations of interest are shown in Table 3. As expected, ISP latency shortened with age. More severe parent-rated ADHD symptoms (both the DuPaul rating scale and the Conners' Scale) correlated with longer ISP latencies and with less TMS evoked motor cortex inhibition (higher SICI ratios). Longer ISP latencies correlated at the trend or marginally significant level with total PANESS scores, and more specifically with overflow and gait subscale ratings.

DISCUSSION

This study identified significantly longer Ipsilateral Silent Period (ISP) latencies in 8 to 12 year old children with ADHD compared to their typically developing peers. We identified this finding after very comprehensive assessments of cognition, learning, and behavior, including screening for and statistically analyzing IQ, reading ability, and socioeconomic status, in a cohort where other neurological, psychiatric, developmental, or medical problems that might act as confounders were excluded. This finding was statistically robust and builds on our prior findings that TMS can be used to identify measures in motor cortex which reflect presence of ADHD symptoms, severity of behavioral symptoms, and motor development anomalies.

The findings in our study confirm and extend those of two smaller prior studies which also found that the onset-latency of the ISP is longer in children with ADHD [14,15]. The present study's detailed motor and behavioral characterizations strongly support the validity of the prior studies. In addition, much more detailed clinical phenotyping allowed not only exclusion of potential statistical confounds, but more importantly evaluation of correlations of clinical and scientific interest. In support of this relationship, one of the research groups subsequently reported that methylphenidate shortens (towards normal) the ISP latency in children with ADHD [30].

There are three novel, correlational results in this study. First, we found a correlation of longer ISP latency and higher parent-rated ADHD symptom severity, particularly ratings of hyperactivity/impulsivity. This is similar to our previous findings that reduced short interval cortical inhibition (SICI) correlates more strongly with severity of hyperactivity/impulsivity in children with ADHD [6,31] and in children and adults with Tourette Syndrome [31–33]. This finding appears robust and consistent across two different ADHD rating scales. Second, longer ISP latency also correlated with more impaired motor development as assessed with PANESS. Third, and perhaps most interestingly, we also identified a correlation between longer (inter-hemispheric) ISP latency and reduced (intra-hemispheric) SICI.

We and others had previously identified reduced SICI as a robust marker of presence and severity of ADHD symptoms [6,33–35]. However, SICI had not been evaluated previously for correlations with other quantitative, TMS-evoked measures. Here we showed that there is a correlation between reduced SICI and prolonged ISP latency. Both of these TMS-evoked measures suggest children with ADHD have deficits in inhibitory control. Mechanistically, these two inhibitory measures have some similarities and differences. For example inter-hemispheric inhibition, as measured by ISP, clearly depends on trans-callosal pathways, which should not affect SICI. However, several groups have shown that intra-hemispheric cortical circuits can affect inter-hemispheric inhibition in similar fashion as SICI [11,36,37]. This mechanistic similarity between SICI and ISP might explain why these measures are both different in ADHD children when compared to controls.

With regard to anomalous motor development in ADHD, we were particularly interested in evaluating the relationship between previously characterized subtle signs [3,4] and ISP latencies, because inter-hemispheric signaling might underlie commonly observed increased motor overflow in ADHD. Our findings relating PANESS scores to ISP suggest that the inhibitory mechanisms underlying ISP also reflect those underlying anomalous motor development in ADHD. These findings, along with the age-correlation we identified, are broadly consistent with those of Garvey and colleagues, who also identified correlations between younger age, slower finger tapping speed, and longer ISP latencies [15]. Finger speed was not significant in our analysis; however, the comprehensive assessments in the PANESS identified several other correlated subscales. In evaluating right/left/total and

subscale differences, it is important to note that these values are ordinal and observational and thus likely to be less robust in general than global PANESS scores.

Higher motor cortex depolarization thresholds in younger children substantially reduced our final sample size. Features of our equipment including the coil configuration and thickness of insulation may have contributed to differences in the yield in our study, as we note that in our entire sample, the resting motor threshold is greater than 20% higher than reported in the prior studies [14,15,38]. As intensity strongly influences silent period duration [27], this may also explain why silent periods were shorter on average in our study and why, unlike the prior studies, we did not find significantly shorter ISP durations in the ADHD children (Table 2). Broader applicability of ISP to young children may require changes in coil design or perhaps alternate techniques which permit for a lower intensity stimulation or which index the ISP to the participant's resting motor threshold, as is most often done for studies of cortical silent period.

An additional potential limitation is effect of medication. The use of stimulant medication in our sample may be substantially higher than in European pediatric populations. Based on pharmacokinetics of stimulant medications, our washout period should be adequate. Post hoc analysis of currently treated vs. currently untreated children with ADHD has not identified any difference in TMS evoked inhibitory responses.

This case-control study was cross-sectional, and thus results must be interpreted cautiously. A longitudinal study might provide more readily interpretable insights into the relationship between age-related motor development, motor physiology, and ADHD. Longitudinal studies, perhaps combining ISP with not only SICI but also imaging studies of motor cortex volume and thickness [39–41], cortical studies of neurotransmitters [42], or callosal volume [43–45] or diffusion [46] might clarify the extent to which ISP latency differences reflect trans-synaptic vs. structural processes. Combining ISP and SICI measures with functional studies of behavioral such as reward delay aversion and response inhibition may help disentangle forms of inhibitory dysfunction and in turn help delineate meaningful long-term neurodevelopmental profiles that aid in development of more effective treatments [47].

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Figure 1. Figure 1A. Surface EMG tracing from one participant showing the rectified average of 5 Ipsilateral Silent Period (ISP) trials. As described in the methods, the participant is maintaining muscle activity throughout, shown on the y axis. The first arrow (0.00 second)

represents the TMS pulse artifact. In this case, the Ipsilateral Silent Period, a decrement of electromyographic activity, starts 38 msec (ISP latency) after the TMS pulse. The ISP duration is 19 msec.

Figure 1B Ipsilateral Silent Period (ISP) latencies in seconds, comparing children with ADHD to typically developing (TD) children. Each dot represents the ISP latency for one participant. The reference line is the mean for the entire sample.

TABLE 1

Demographics, clinical, and cognitive scores in ADHD vs. typically developing children

	Typically Developing n=31	ADHD n=23	p value
<i>Demographics</i>			
Male/Female	19/12	10/13	.19
Age in years	11.10(1.38)	10.93 (1.48)	.68
Hollingshead Family Total	51.71 (8.52)	40.80 (11.22)	.006
<i>ADHD ratings</i>			
ADHD-RS-IV; Home Version: Total Score	4.33(4.51)	35.95(9.11)	<.001
CPRS; T score Total	46.00(6.24)	79.13(12.61)	<.001
<i>Cognitive Assessments</i>			
Verbal Comprehension Index	109.80(16.94)	99.56(14.86)	.03
Perceptual Reasoning Index	107.33(12.05)	104.57(10.38)	.40
Working Memory Index	105.10(13.11)	101.09(13.3)	.29
Processing Speed Index	101.23(13.29)	93.55(11.62)	.04
Full Scale Intelligence Quotient	109(12.92)	100.57(10.81)	.02
Word Reading Index	110.06(10.75)	100(11.12)	.002

Demographic, Clinical, and Cognitive Data in final sample of children in whom ISP was reliably obtained.

ADHD-RS-IV Rating Scale, version 4, possible scores 0–54; percentiles are based on age, gender norms.

Hollingshead is a measure of socioeconomic status of the family.

ADHD = Attention-Deficit/Hyperactivity Disorder

CPRS = Conners' Parent Rating Scale (normed at T=50; scores above 70 consistent with ADHD)

TABLE 2

Motor Physiology and Motor Function in ADHD vs. typically developing Children

	Typically Developing		ADHD		p value
	Mean	SD	Mean	SD	
<i>Motor Physiology</i>					
ISP latency (msec)	40.9	6.1	45.9	6.9	0.007
ISP duration (msec)	10.5	6.2	9.0	7.0	0.41
SICI ratio	0.46	0.18	0.67	0.24	0.0007
RMT	60.9	12.5	62.2	10.4	0.61
AMT	40.0	9.9	40.8	8.2	0.47
ICF	1.05	0.17	1.16	0.18	0.02
CSP (msec)	60.2	40.4	73.0	52.0	0.34
<i>Motor Function</i>					
PANESS Total	16.6	8.6	28.6	10.1	0.0001
Overflow Right	3.0	2.8	4.7	2.4	0.02
Overflow Left	2.2	2.6	4.7	2.4	0.01
Overflow Total	6.1	5.3	9.9	5.4	0.01
Gait and Station	3.9	3.4	8.0	4.9	0.001
Timed Tasks	12.7	6.7	20.7	8.0	0.0003

ISP = Ipsilateral Silent Period

SICI = Short interval cortical inhibition; *ratio* is relative to "1.0," or no inhibition; so 0.46 indicates 54% relative inhibition and lower ratios indicate more inhibition. Msec = milliseconds

RMT = Resting Motor Threshold

AMT = Active Motor Threshold

ICF = Intracortical Facilitation ratio

CSP = Cortical Silent Period

PANESS = Physical and Neurological Examination for Soft Signs (higher scores indicate more significant delays)

Table 3

Correlations between ISP latency and Behavioral Ratings, Motor Ratings, and Motor Cortex Inhibition

	ISP latency	
	r	p value
Age	-.256	.062
<i>Behavioral Ratings</i>		
Dupaul ADHD Rating Scale	.327	.017
Inattention	.272	.049
Hyperactive/Impulsivity	.342	.012
Conners ADHD total T score	.376	.007
Inattention T score	.347	.013
Hyperactive/Impulsive T score	.385	.006
<i>Motor Ratings</i>		
PANESS Total Score	.252	.075
Overflow Total	.283	.044
Overflow Right	.305	.030
Overflow Left	.250	.077
Gait	.329	.018
Timed tasks	.154	.280
<i>Motor Cortex Physiology</i>		
RMT	.192	.168
AMT	.147	.288
SICI	.362	.008

ISP = Ipsilateral Silent Period

SICI = Short Interval Cortical Inhibition: larger ratios indicate less inhibition

RMT = Resting Motor Threshold

AMT = Active Motor Threshold

PANESS = Physical and Neurological Examination for Soft Signs (raw scores; higher scores indicate more significant delays)