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Transcranial Magnetic Stimulation in Succinic Semialdehyde Dehydrogenase Deficiency: A Measure of Maturational Trajectory of Cortical Excitability

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Abstract

Background: Succinic semialdehyde dehydrogenase deficiency (SSADHD) is a disorder of GABA degradation with use-dependent downregulation of postsynaptic $GABA_{A/B}$ receptors. We aim to measure the resulting cortical excitation: inhibition ratio using transcranial magnetic stimulation. **Methods:** In this single-center observational study, 18 subjects with SSADHD and 8 healthy controls underwent transcranial magnetic stimulation. Resting motor threshold, cortical silent period, and long-interval intracortical inhibition were measured in both groups. Resting motor threshold in focal epilepsy patients from an institutional transcranial magnetic stimulation database were also included. **Results:** SSADHD subjects had higher resting motor threshold than healthy controls but lower relative to focal epilepsy patients. Resting motor threshold decreased with age in all groups. Cortical silent period was longer in SSADHD subjects than in healthy controls. No difference was detected in long-interval intracortical inhibition between the 2 groups. **Conclusion:** Findings suggest abnormal corticospinal tract physiology in SSADHD, but with preserved developmental trajectory for corticospinal tract maturation. Defining features of these transcranial magnetic stimulation metrics in SSADHD will be better elucidated through this ongoing longitudinal study.

Keywords

Succinic semialdehyde dehydrogenase deficiency (SSADHD), transcranial magnetic stimulation (TMS), cortical excitability, excitation: inhibition ratio, maturational trajectory, resting motor threshold (rMT), cortical silent period (CSP), long interval intracortical inhibtion (LICI)

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Background

Succinic semialdehyde dehydrogenase deficiency (SSADHD) is a rare metabolic disorder of the γ-aminobutyrate aminotransferase (GABA) degradation pathway characterized by a predominantly static encephalopathy, and core features of hypotonia, ataxia, and expressive language deficits. In rodent SSADHD models, the resulting accumulation of GABA and 4-hydroxybutyric acid (GHB) in the central nervous system has been shown to downregulate post-synaptic $GABA_A$- and $GABA_B$-receptor expression.[1-5,] [^{11}C]Flumazenil PET studies in human subjects with SSADHD showed reduced benzodiazepine receptor binding, further supporting the hypothesis of $GABA_A$-receptor downregulation and/or dysfunction of $GABA_A$ receptors.[6] Approximately half of patients with SSADHD develop epilepsy.[7] These findings further support the hypothesis that excess GABA in the central nervous system of patients with SSADHD results in downregulation of GABA receptors and paradoxical net cortical hyperexcitability.

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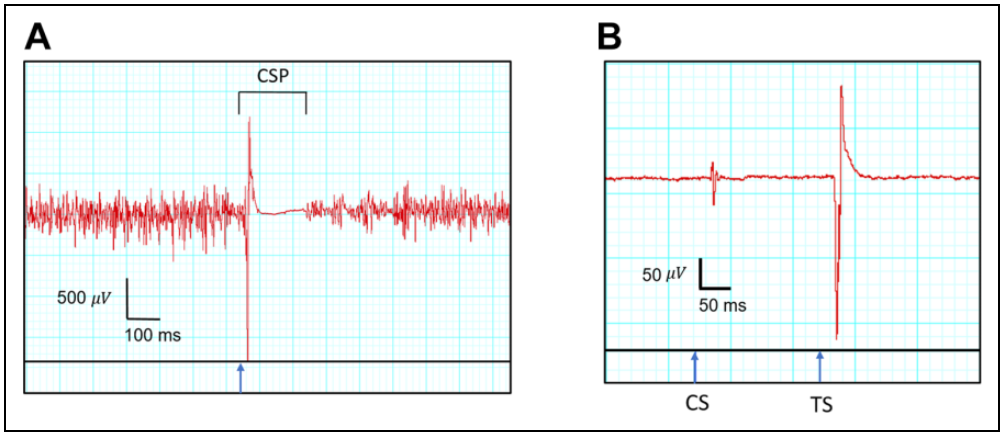

Figure 1. TMS-derived metrics. Tracings show APB activity over time recorded by a surface EMG electrode from a healthy control. Arrows indicate the time of stimulation. (A) CSP is the duration from time of stimulation to time of return of voluntary muscle contraction as depicted by surface EMG. The participant is asked to voluntarily activate the target muscle prior to stimulation. Shown in red is EMG activity followed by the MEP resultant from TMS pulse. (B) LICI is represented as a ratio of the MEP amplitude resultant from the test stimulus (TS) to the MEP amplitude resultant from the conditioning stimulus (CS) at suprathreshold intensity. The 2 MEPs resultant from the conditioning and test stimuli are depicted in red. APB, abductor pollicis brevis; CSP, cortical silent period; EMG, electromyograph; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; TMS, transcranial magnetic stimulation.

Reduction in GABA-mediated cortical inhibition can be measured using transcranial magnetic stimulation (TMS).

Transcranial Magnetic Stimulation Basics

Transcranial magnetic stimulation is a noninvasive form of focal cortical stimulation in which an external magnet induces an intracranial electrical field over the stimulated region used to interrogate or modulate states of cortical excitation or inhibition. When delivered over the motor cortex, transcranial magnetic stimulation elicits a motor evoked potential that can be recorded by surface electromyogram electrodes in the contralateral limb (Figure 1). Thus, transcranial magnetic stimulation coupled with electromyography (transcranial magnetic stimulation–electromyography) uniquely enables generation of "input-output" curves, in vivo and in humans, from which a range of cortical excitability and plasticity measures can be derived.

A range of metrics that may provide both insight into the vulnerability for seizures and also into the mechanism of disease can be derived by transcranial magnetic stimulation delivered to the motor cortex. Resting motor threshold and cortical silent period are derived using single-pulse transcranial magnetic stimulation. Resting motor threshold is most often operationally defined as minimal stimulation intensity needed to produce a motor evoked potential >50 μV from an intrinsic hand muscle in at least 50% of trials. It is measured as a percentage of total machine output (MO). The resting motor threshold reflects voltage-gated sodium channel–mediated cortical excitation, as it is increased following administration of voltage-gated sodium channel blockers.[8-14] Cortical silent period is a period of suppressed electromyograph activity until voluntary muscle activity returns following delivery of a suprathreshold stimulus that reflects $GABA_A$- and $GABA_B$-mediated inhibition.[15-19] A range of E:I ratio measures can also be obtained with paired-pulse transcranial magnetic stimulation protocols where each test stimulus is preceded by a conditioning stimulus to the same motor cortex site. Long-interval intracortical inhibition, for example, reflects $GABA_B$-mediated local inhibition and likely $GABA_A$-mediated network inhibition.[17,18,20,21] To obtain long-interval intracortical inhibition, conditioning stimulus and test stimulus are delivered at an interstimulus interval of 50-300 ms, with the degree of inhibition represented as a ratio of the second motor evoked potential amplitude (resulting from test stimulus) to the first motor evoked potential amplitude (resulting from conditioning stimulus).

These metrics can be modulated by agents that alter the GABAergic or glutamatergic tone and can be measured to detect either abnormalities in disease or restoration by treatment.

Prior transcranial magnetic stimulation studies in SSADHD:

The use of transcranial magnetic stimulation paradigms to elucidate pathophysiology of SSADHD was first reported by Reis et al[22] in 2012. In their study of 7 subjects with SSADHD, a figure-of-8 coil was placed over the left motor cortex "hot spot" for the first dorsal interosseous muscle for all transcranial magnetic stimulation–electromyograph paradigms. Cortical silent period was calculated as an average over 20 trials following stimulation at 150% resting motor threshold during active muscle contraction. Long-interval intracortical inhibition was elicited using 150% resting motor threshold for both conditioning stimulus and test stimulus at an interstimulus interval of 150 ms, and averaged over 15 trials randomly interspersed with control single test stimuli, delivered 4-8 seconds apart. Resting motor threshold was higher in SSADHD subjects (age: 10-27 years) than in their parents or in adult controls, but not significantly different from age-matched "young" control

subjects. Cortical silent period was shorter in SSADHD subjects compared to all other comparison groups. Long-interval intracortical inhibition was "virtually absent," with 101.16% ± 8.7% of the test motor evoked potential in subjects with SSADHD, and thus significantly impaired relative to the comparison groups.

Despite differences in protocols (including coil type and placement and stimulation parameters), Schreiber et al[23] corroborated Reis et al's[22] findings in a separate study in 2016 while studying the effects of taurine supplementation as a potential therapeutic in SSADHD. Seven patients (age: 12-33 years) underwent transcranial magnetic stimulation using a round coil placed over the motor "hot spot" for the FDI muscle prior to initiation of taurine. Ten trials each at a stimulation intensity of 110%, 120%, 130%, and 140% resting motor threshold were used to elicit cortical silent period. Long-interval intracortical inhibition protocol consisted of 120% resting motor threshold stimulus intensity for both stimuli, with an interstimulus interval of 100 ms, for a total of 10 trials. Although there was no control group, the cortical silent period was short (128 ms at 140% resting motor threshold) and long-interval intracortical inhibition was minimal.

The above-mentioned studies support the feasibility of and potential role for transcranial magnetic stimulation–derived biomarkers as metrics of disease severity and, perhaps, as measures of target engagement by therapeutics. Accordingly, we aim to quantify transcranial magnetic stimulation measures of cortical excitatory and inhibitory tone in a larger population of patients with SSADHD and compare them to age-matched healthy controls. This work is part of an observational natural history study in which recruitment is ongoing. Interim data analysis was presented at the SSADHD Virtual Conference in July 2020 and is summarized below.

Methods

Participants with SSADHD were enrolled as part of the Natural History Study of Patients with SSADHD (ClinicalTrials.gov Identifier: NCT03758521). Diagnostic confirmation of disease by genetic (biallelic pathogenic variants in ALDH5A1) and metabolic (elevated urine GHB levels) evaluation was performed by study physicians. Participants younger than 2 years or with any contraindication to transcranial magnetic stimulation (eg, metal hardware not known to be transcranial magnetic stimulation–compatible) were excluded from the study. Healthy controls with neurotypical development and no history of neurologic disorder or brain injury who were within 2 years of the age of one of our participants were also recruited. Unfortunately, age-matched controls for the 3 participants 3-4 years of age were unable to be recruited during this time frame. Specifically, for comparisons of the resting motor threshold, data obtained as part of routine clinical care (as part of a presurgical evaluation) from age-matched patients with focal epilepsy, also within 2 years of the age of one of our participants with SSADHD, from the Boston Children's Hospital transcranial magnetic stimulation laboratory database were also included as an additional comparison group. No patient with focal epilepsy existed in our database to age-match the 27- and 39-year-old participants. Measuring the cortical silent period and long-interval intracortical inhibition is not part of the standard clinical transcranial magnetic stimulation evaluation completed for these patients.

Transcranial Magnetic Stimulation

Neuronavigated transcranial magnetic stimulation requires use of an anatomic magnetic resonance imaging (MRI) scan to be used in conjunction with transcranial magnetic stimulation. Coregistration was performed against each participant's T1-weighted MRI sequence that was converted to a 3D head surface and brain reconstruction using Nexstim 4.3.1 software (Nexstim, Finland). For healthy controls, if an MRI was not obtained, an anonymized brain MRI with comparable head circumference available in the transcranial magnetic stimulation lab repository was used for coregistration. Surface electromyogram electrodes were placed on 6 bilateral and symmetric locations of each participant's body: (1) thumb (over the abductor pollicis brevis), (2) shoulder (over the deltoid), and (3) leg (over the tibialis anterior). An additional grounding electrode was placed on the underside of the right forearm. Single-pulse transcranial magnetic stimulation and paired-pulse transcranial magnetic stimulation protocols were performed using a figure-of-8 cooled magnetic coil positioned over the abductor pollicis brevis hotspot in either hemisphere identified for each participant.

Single-Pulse Transcranial Magnetic Stimulation

The motor hotspot was identified for abductor pollicis brevis and deltoid muscles in each hemisphere. Resting motor threshold was obtained by determining the minimum machine output required to elicit a motor evoked potential 50 μV from the target muscle at rest in >50% of trials of stimulation over the designated hotspot. If resting motor threshold was greater than maximum machine output (100% MO), resting motor threshold was recorded as 100%. To measure the cortical silent period, a suprathreshold stimulus at 120% resting motor threshold up to a maximum of 100% MO was delivered over the motor hotspot of the target muscle, with the target muscle in a controlled preactivated state. Cortical silent period was calculated as the duration from the time of stimulation to return of spontaneous muscle activity as depicted by electromyography (Figure 1). To control for variability in degree of prestimulus abductor pollicis brevis activation, during post hoc analysis of cortical silent period data, the root mean square of voltages in the 100 ms prior to the resultant motor evoked potential was calculated. Maintaining a consistent level of abductor pollicis brevis muscle contraction for cortical silent period measurements is challenging in the pediatric population, and use of a handheld dynamometer was not feasible or practical in this study. Therefore, cortical silent period duration from trials with root mean square of voltages between 50 and 150 in the 100 ms prior to the motor evoked potential were included.

Paired-Pulse Transcranial Magnetic Stimulation

To elicit long-interval intracortical inhibition, each conditioning stimulus was followed 200 ms later by the test stimulus, both at 150% resting motor threshold up to a maximum of 100% MO, over the site corresponding to peak motor evoked potential activation for the target muscle (Figure 1). Long-interval intracortical inhibition is expressed as a log transformation of the ratio of the peak-to-peak motor evoked potential amplitude resultant from each test stimulus divided by the peak-to-peak motor evoked potential amplitude

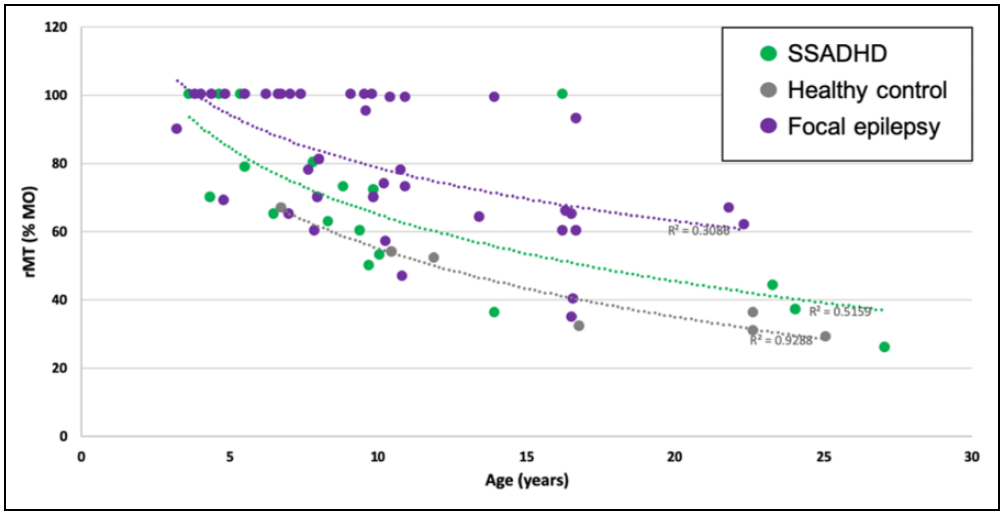

Figure 2. Average rMT for abductor pollicis brevis as a function of age per group. The dotted lines represent the logarithmic trendlines per group. rMT, resting motor threshold.

resultant from the preceding conditioning stimulus, averaged per muscle group.

Statistical Analysis

Data were analyzed by SPSS version 26. Frequency tables were generated for resting motor threshold, cortical silent period, and long-interval intracortical inhibition per cohort, as well as per subgroup of participants with SSADHD with and without epilepsy. Paired Student *t* test was used to compare right and left abductor pollicis brevis resting motor threshold within each cohort. One-way analysis of variance with Bonferroni correction was performed to compare abductor pollicis brevis resting motor threshold in subjects with SSADHD, age-matched healthy controls, and in the affected hemisphere of age-matched patients with focal epilepsy from the single-center database. Independent samples *t* test was performed to evaluate for differences between abductor pollicis brevis cortical silent period and long-interval intracortical inhibition in SSADHD participants and healthy controls. All analyses were performed with significance thresholded at 5% and *P* value <.05 deemed statically significant.

Results

Participants

Of the 19 subjects with SSADHD enrolled in the study who underwent transcranial magnetic stimulation, 18 were included in the analysis. One participant was excluded because of technical challenges eliciting the transcranial magnetic stimulation metrics described above. Median age of subjects with SSADHD was 9.1 years (range: 3.6-27.1 years, mean 11.0 years). Five (28%) of the 18 participants with SSADHD had epilepsy, 4 of whom were on antiseizure medications. Eight age-matched healthy controls were recruited, but the healthy control age-matched to the excluded SSADHD patient was not included in data analysis. The median age of healthy controls was 16.8 years (range: 6.8-25.1 years). The median age of the 44 age-matched patients with focal epilepsy was 9.5 years (range: 3.2-22.3 years), all of whom were on at least 1 antiseizure medication.

Resting Motor Threshold

Resting motor threshold was measured in all participants. There were no left-right differences in abductor pollicis brevis resting motor threshold within the SSADHD cohort or healthy controls, so right abductor pollicis brevis resting motor threshold measurements were used for comparison between groups. In all 3 groups, resting motor threshold declined with age (Figure 2). Average abductor pollicis brevis resting motor threshold in subjects with SSADHD was higher than that of healthy controls (67% ± 23% vs 43% ± 15% MO, $P = .02$). When constrained to the subgroup without epilepsy, average resting motor threshold in patients with SSADHD was still higher (73% ±19%) than in age-matched controls ($P = .002$). However, patients with focal epilepsy had a higher mean resting motor threshold in the affected hemisphere (81% ± 19%) than subjects with SSADHD ($P = .02$) (Figure 3). Even when comparing the resting motor threshold only in those subjects with SSADHD and epilepsy to those age-matched with focal epilepsy, the resting motor threshold was greater in the focal epilepsy cohort (81% ± 19% vs 52% ± 29%, $P = .04$). A comparison of the resting motor threshold in SSADHD participants with and without epilepsy was underpowered to identify a significant difference between groups (52% ± 29% vs 73% ± 19%, $P = .08$).

Cortical Silent Period

The abductor pollicis brevis cortical silent period was elicited in 5 SSADHD subjects and 6 healthy controls. The mean

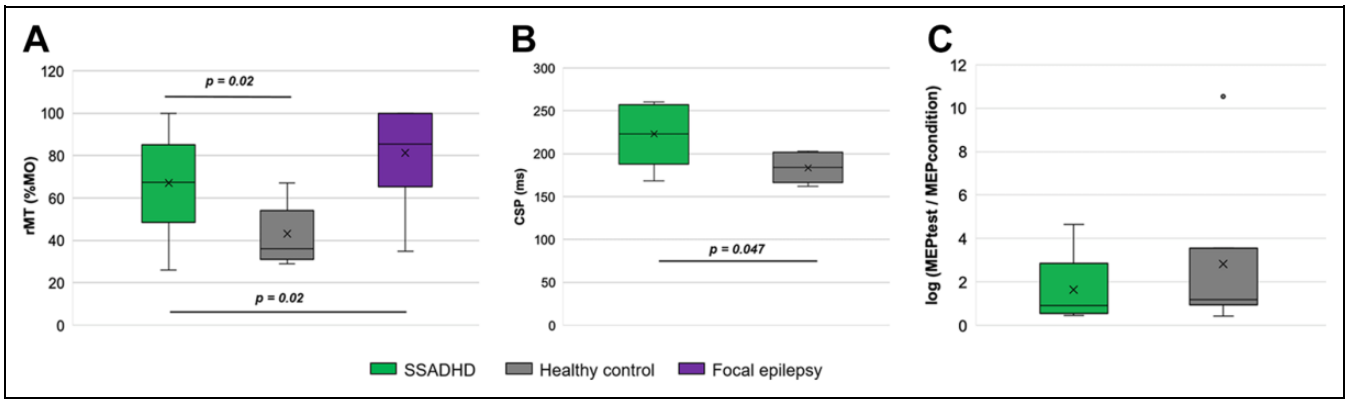

Figure 3. Boxplots illustrating transcranial magnetic stimulation metrics in subjects with SSADHD, healthy controls, and focal epilepsy. "X" represents the mean value, with height of each box representing the 25th and 75th quartiles. (A) Significant differences in resting motor threshold were found between subjects with SSADHD and healthy controls, and independently with patients with focal epilepsy. (B) Cortical silent period was also significantly longer in subjects with SSADHD than in healthy controls. (c) No difference in LICI was detected between the 2 groups, however. Log ratios >1 = facilitation; <1 = inhibition. LICI, long-interval intracortical inhibition; rMT, resting motor threshold; SSADHD, succinic semialdehyde dehydrogenase deficiency.

cortical silent period duration in SSADHD subjects was longer than that in healthy controls (222.8 $\pm$ 37.4 vs 183.7 $\pm$ 17.5 ms, $P = .047$) as shown in Figure 3.

Long-Interval Intracortical Inhibition

Abductor pollicis brevis long-interval intracortical inhibition was elicited in 6 SSADHD subjects and all 7 healthy controls. No significant difference was present between long-interval intracortical inhibition of the 2 groups ($P = .46$; Figure 3). In both groups, a mean paradoxical faciliatory response was elicited. However, at the individual level, 3 of 6 subjects with SSADHD demonstrated an inhibitory response (ratio < 1), whereas only 1 of 7 healthy controls had a net inhibitory response (Figure 4).

Discussion

This cohort is the largest one to date of subjects with SSADHD in whom transcranial magnetic stimulation has been performed. In contrast to prior studies, the age range of subjects in this study is broader, which allows for evaluation of age-dependent findings in cortical excitability and inhibition. A decline in the resting motor threshold, evidence of a maturational trajectory, is well established in typically developing individuals, in the unaffected hemisphere of patients with focal epilepsy, and in the less affected hemisphere of patients with hemiplegic cerebral palsy.[24-27] Based on this cross-sectional analysis, subjects with SSADHD still also retain this maturational trajectory, which we interpret as an encouraging sign that at least this aspect of cortical excitability remains under normal developmental control. However, to assess whether the rate of maturation or the time to full maturation is similar to that seen in healthy controls, resting motor threshold in a larger sample size over a broader age range needs to be determined. Maturational trajectory will also be evaluated prospectively with repeated resting motor threshold measurements per subject over the course of Natural History Study of Patients with SSADHD. Per subject resting motor threshold trajectory in conjunction with clinical history may also shed light on the clinical significance of the maturational trajectory in people with SSADHD.

The overall higher average resting motor threshold in the SSADHD group, compared with healthy controls, reflects a decrease in cortical excitability that, by pharmacologic studies, is contingent in large part on the voltage-gated sodium channel tone. Given the propensity of epilepsy in SSADHD, the high resting motor threshold may be a compensatory response akin to the high resting motor threshold seen in the hemisphere that is ipsilateral to the seizure focus in patients with focal epilepsy.[28] The elevated resting motor threshold was not specific to SSADHD subjects with epilepsy, but could support the known increased risk of seizures in this patient population.

Although resting motor threshold findings were similar to what was reported in prior transcranial magnetic stimulation studies in SSADHD patients, notable differences were present in our cortical silent period and long-interval intracortical inhibition data compared with published data. The prolonged cortical silent period in SSADHD subjects in our cohort suggests enhanced GABA-mediated inhibition at either $GABA_A$ or $GABA_B$ or both receptor subtypes. In contrast, Reis et al[22] and Schreiber et al[23] both found shortened cortical silent period in this population, which was concordant with rodent models and flumazenil-PET studies suggesting downregulation of postsynaptic $GABA_A$ and $GABA_B$ receptors. Absence of difference in long-interval intracortical inhibition response between SSADHD subjects and healthy controls also differs from prior reports.

Such discrepancies may be due to differences in transcranial magnetic stimulation protocols. A longer interstimulus interval duration could result in less of an inhibitory effect of the conditioning stimulus on the second motor evoked potential.[29] The

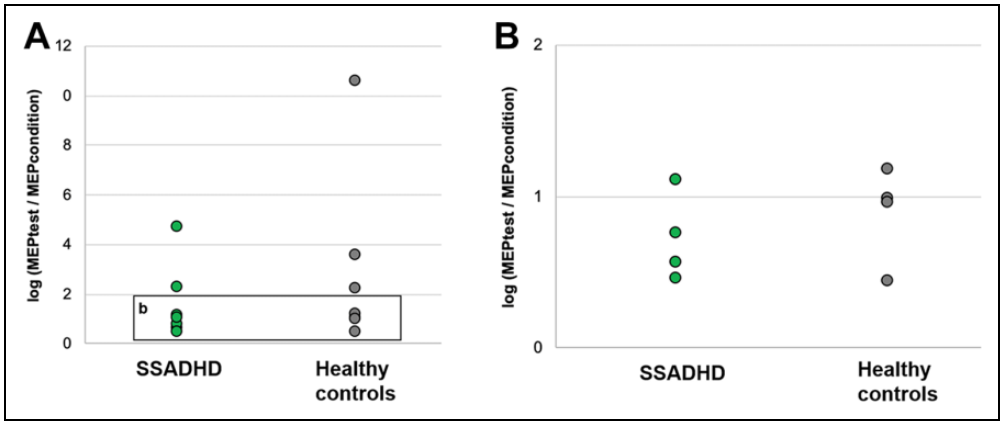

Figure 4. LICI scatter plot. Log ratios >1 indicate cortical facilitation; ratios <1 indicate cortical inhibition. (A) Average LICI per participant varied from inhibition net to facilitation in both SSADHD and health controls. (B) Magnified view of a subset of LICI ratios show 3 of 6 subjects with SSADHD and 1 of 7 healthy controls demonstrated net inhibition. LICI, long-interval intracortical inhibition; SSADHD, succinic semialdehyde dehydrogenase deficiency.

suprathreshold stimulation intensity of 150% resting motor threshold may have resulted in stimulation of a greater density of neurons more reliably, also resulting in a decreased inhibitory response.[30] The combination of these 2 parameters in our long-interval intracortical inhibition protocol may have contributed to the trend toward facilitation in both subjects with SSADHD and healthy controls. The variance was smaller in the SSADHD population, with 50% demonstrating net inhibitory long-interval intracortical inhibition. A dedicated study to determine optimal long-interval intracortical inhibition protocol parameters to reliably obtain expected inhibitory response in healthy control subjects is needed to then further refine stimulation parameters for long-interval intracortical inhibition in people with SSADHD.

However, the discrepancy between our cortical silent period findings and those previously reported are difficult to reconcile. Based on these findings we also cannot distinguish between the role that $GABA_A$ and $GABA_B$-mediated inhibition may play in SSADHD. Further studies using murine SSADHD models to correlate transcranial magnetic stimulation data with immunohistochemical and electrophysiologic data will be useful to better elucidate this inconsistency.[5,31,32]

Limitations of this study include the small, heterogeneous sample size of subjects with SSADHD in whom cortical silent period and long-interval intracortical inhibition measurements were able to be obtained. However, this cohort of SSADHD participants is the largest one in whom resting motor threshold has been measured. Recruitment of additional subjects is ongoing. In addition, stimulation intensity to obtain long-interval intracortical inhibition and cortical silent period in SSADHD subjects with high resting motor threshold was less than 150% resting motor threshold when that value exceeded 100% MO. Increasing the sample size and future methods that use a low suprathreshold intensity for long-interval intracortical inhibition and cortical silent period to provide uniformity across subjects will be considered. Unique brain MRIs were not available for each participant (though anonymized brain MRI of a subject with similar head circumference stored in the transcranial magnetic stimulation lab repository was used as needed).

Conclusion

Threshold for cortical excitability is higher in participants with SSADHD than in age-matched healthy controls but lower than in the epileptic (and nonepileptic) hemisphere of patients with focal epilepsy, the significance of which remains uncertain. However, preserved corticospinal tract maturational trajectory suggests that aspects of neurodevelopment are maintained. The discordant cortical silent period measurements recorded thus far in SSADHD participants compared to prior published results may be due to differences in stimulation parameters or differences in the age of participants. The longer cortical silent period is, however, consistent with a hyper-GABAergic state that could result from the excess central nervous system GABA. Animal models that can correlate cortical silent period measurements with in vivo alterations in $GABA_{A/B}$ expression or function may be helpful. The absence of differences in long-interval intracortical inhibition between SSADHD participants and healthy controls thus far remains preliminary and may be due to suboptimal stimulation parameters and small sample size.

These interim transcranial magnetic stimulation results from the ongoing observational study in participants with SSADHD presented at the Virtual SSADHD Conference in July 2020 and at the Virtual Joint International Child Neurology Conference and Child Neurology Society Meeting in October 2020. Continued recruitment and repeat transcranial magnetic stimulation testing at different time points will provide an opportunity to better define the maturational trajectory in SSADHD and confirm intrasubject test-retest reliability, in addition to correlating transcranial magnetic stimulation metrics with metabolite levels being collected in the biorepository of the natural history study. Ultimately, we may be able to identify transcranial

magnetic stimulation–derived metrics of disease severity that may also serve as biomarkers of therapeutic target engagement.

Author Contributions

All authors contributed to the conception of the study. MT, JL, PLP, and AR designed the study. MT and AR drafted the manuscript. MT, JL, and AR contributed to acquisition, analysis, and interpretation. HK contributed to acquisition; MD contributed to acquisition and analysis; and PLP contributed to interpretation. All authors critically revised the manuscript for important intellectual content, gave final approval, and agreed to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the Boston Children's Hospital Institutional Review Board (IRB-P00029917).

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