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Lasting effects of repeated rTMS application in focal hand dystonia

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Abstract

Purpose—Focal hand dystonia (FHD) is a rare but potentially devastating disorder involving involuntary muscle spasms and abnormal posturing that impairs functional hand use. Increased cortical excitability and lack of inhibitory mechanisms have been associated with these symptoms. This study investigated the short- and long-term effects of repeated administrations of repetitive-transcranial magnetic stimulation (rTMS) on cortical excitability and handwriting performance.

Methods—Six subjects with FHD and nine healthy controls were studied. All subjects with FHD received rTMS (1Hz) to the premotor cortex (PMC) for five consecutive days; of those, three subjects received five days of sham rTMS completed ten days prior to real treatment. Healthy subjects received one real rTMS session. Cortical silent period (CSP) and measures of handwriting performance were compared before and after treatment and at ten-day post-treatment follow-up.

Results—At baseline, significant differences in CSP and pen pressure were observed between subjects with FHD and healthy controls. Differences in CSP and pen velocity between subjects in real and sham rTMS groups were observed across treatment sessions and maintained at follow-up.

Conclusions—After five days of rTMS to PMC, reduced cortical excitability and improved handwriting performance were observed and maintained at least ten days following treatment in subjects with FHD. These preliminary results support further investigation of the therapeutic potential of rTMS in FHD.

Keywords

Writer's cramp; handwriting analysis; transcranial magnetic stimulation; rehabilitation; cortical excitability

1. Introduction

Focal hand dystonia (FHD) is a disorder characterized by involuntary contraction and co-contraction of muscles of the hand causing abnormal posturing and reduced fine motor control (Sheehy & Marsden, 1982). Writer's cramp and musician's dystonia are two

prevalent types of task-specific FHD involving repetitive, highly stereotyped movements (Rosenkranz et al., 2005). In addition to the outward physical manifestations of FHD, patients also show evidence of altered brain activity and organization (Bara-Jimenez et al., 1998; Elbert et al., 1998; Meunier et al., 2001). The prevalence of primary dystonia is estimated to be 732/100,000 people and is “an underestimated public health concern” (Muller et al., 2002). Currently, there exists no fully successful treatment intervention to address this disorder.

The development of FHD may be due to a lack of synaptic inhibition throughout the central nervous system (for review: Berardelli et al., 1998)). It is this lack of inhibition, normally present in healthy individuals, that may lead to cortical disorganization evidenced by abnormal somatotopy in the hand region of the primary motor cortex (Bara-Jimenez et al., 1998; Candia et al., 2003; Elbert et al., 1998) and impaired sensorimotor integration (Abbruzzese & Berardelli, 2003; Tinazzi et al., 1999). It has been hypothesized that abnormal sensorimotor associations formed during skilled movement practice, paired with a failure to weaken former associations, may lead to maladaptive changes in the cortical organization and function seen in FHD (Quartarone et al., 2003; Quartarone et al., 2005; Quartarone et al., 2006).

Supporting this idea, Quartarone and colleagues (2003) found significantly greater cortical silent period (CSP) values in healthy subjects compared to subjects with FHD indicating inhibitory circuitry. The authors concluded that the mechanisms that facilitate the excitability of the corticospinal outputs to the affected limb were abnormally reactive in subjects with FHD causing a wider spread of excitation beyond the somatotopically specific area of stimulation.

Relatedly, Siebner and colleagues (Siebner et al., 2003) applied low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) over the premotor cortex (PMC) in subjects with dystonia and healthy subjects to examine the after-effect on patterns of regional neuronal activity. Low frequency rTMS (1 Hz) has been shown to produce inhibitory effects on neuronal excitability (Chen et al., 1997) and rTMS to PMC led to a reduction in regional neural activity for at least one hour after the end of stimulation. Importantly, the changes in activity were more pronounced in subjects with FHD than in healthy subjects, suggesting that premotor neurons were more susceptible to input, or in a different resting state, in FHD (Quartarone et al., 2006).

Given the assumption of decreased inhibition in FHD, techniques that *facilitate* inhibition have a potential role in the treatment of the disorder. This was investigated by Murase and colleagues (Murase et al., 2005) in nine subjects with writer’s cramp. Using low-frequency rTMS (0.2 Hz), the authors compared CSP and hand-writing performance before and after rTMS applied to the M1, SMA, PMC, and sham stimulation. Subjective ratings by the subjects with FHD revealed PMC was the most affected by stimulation, with 78% reporting improvement. Quantitative changes were also greatest with PMC stimulation, including decreases in pen pressure and significant prolongation of the TMS-induced CSP. Other work has shown that one treatment of low-frequency rTMS over M1 during active ‘nonsense’ scribbling (Siebner et al., 1999) or at rest (Siebner et al., 1999) produced objective

improvements in hand-writing and subjective symptom improvements lasting for about one day.

These results are encouraging but have not demonstrated lasting changes. In line with treatment approaches using rTMS in other neurologic disorders (Khedr et al., 2005; Khedr et al., 2005; Lefaucheur et al., 2004; Miniussi et al., 2005), we performed a five-day rTMS treatment on subjects with FHD. Our purpose of this preliminary inquiry was to determine the short- and long-term effectiveness of five consecutive days of rTMS on cortical excitability, handwriting parameters, and subjective symptom report in subjects with FHD.

2. Methods

2.1. Subjects

A total of six subjects with a diagnosis of FHD (age: 46.5 ± 12.4 y) (Table 1) were studied. Of the six, three were randomly assigned to first receive sham stimulation. Subjects were recruited from local clinics and posted advertisements. Two subjects demonstrated clinical characteristics consistent with simple writer's cramp (task specific dystonia) and one subject presented with dystonic writer's cramp (dystonic symptoms with other hand tasks in addition to hand-writing). The clinical history and physical exam of the other three subjects was consistent with musician's dystonia with additional symptoms during writing. All symptoms primarily affected the dominant arm (four right-hand dominant, two left-hand). Exclusion criteria were: (1) any neurologic condition other than FHD, (2) medication for dystonia, (3) botulinum toxin injection within the past six months, (4) seizure history, (5) pregnancy, (6) metal in head, or (7) implanted medical devices (Wassermann, 1998).

Nine healthy control subjects (age: 33 ± 10.5 y) were also recruited from postings. All subjects gave informed consent prior to participation. The study was approved by the University of Minnesota General Clinical Research Center and Institutional Review Board.

2.2. Study design

A single-blinded partial cross-over design with follow up was employed whereby subjects randomly assigned to the sham group first received the sham stimulation paradigm and then crossed over to the real treatment protocol following a ten day washout period. Subjects in the real treatment group received only the real rTMS protocol. Each treatment protocol consisted of five consecutive days of rTMS application to the PMC. For the sham treatment, the coil was positioned at 90 degrees from the cortex, thereby avoiding stimulation-associated biological effects (Lisanby et al., 2001). All subjects received the pre-and post-treatment testing assessments. These included functional handwriting performance, cortical excitability and subjective symptom report. Handwriting assessment occurred on day one, five and at follow-up, ten days post treatment. Cortical excitability and symptom report data were collected pre- and post-treatment each day and at follow-up. Healthy subjects received one real treatment session with handwriting and cortical excitability assessment before and after rTMS following the same protocol.

2.3. Handwriting assessment

Handwriting analysis was performed using a computerized tablet (WACOM Co., Ltd, Japan), and custom modified digitized pen (UltraPen, Kiko Software, The Netherlands) with the OASIS software package (Kiko Software, The Netherlands) used for data collection and analysis. Subjects were required to perform three loop tracing conditions: externally-paced (1) with and (2) without visual positional feedback, and (3) self-paced with feedback. The remaining condition required self-paced writing of a sentence, (4) 'My country tis of thee,' with visual feedback given. In the loop tracing conditions, subjects were instructed to follow the cursor as closely as possible while maintaining a natural limb position. For sentence writing, subjects were instructed to write in their natural style. Each condition was randomly presented and repeated three times within each testing session. Data were sampled at 215 Hz (resolution: 5,080 lpi, accuracy: $\pm 0.01''$, pressure range: 0–800 grams). Pen pressure, pen velocity, fluency, and accuracy data were the functional variables of interest. Handwriting fluency was assessed with a custom-designed MATLAB program by calculating the number of inversions in the positive x-velocity profile for each loop drawn during condition 3.

2.4. Cortical excitability assessment

Following handwriting analysis, subjects were seated comfortably in a chair and surface electrodes were affixed to the skin overlying the first dorsal interosseus muscle (FDI) of the involved hand in a belly/tendon montage. Electromyographic (EMG) signals were acquired at a sampling rate of 2560 kHz using a Cadwell Sierra EMG amplifier (Cadwell Laboratory, Washington) (sensitivity: 100 $\mu\text{V}/\text{div}$, filter: 20–2000 Hz) (Fig. 1).

To find the optimal position for activating the FDI muscle, a 70-mm figure-of-eight TMS coil connected to a Magstim 200 Rapid magnetic stimulator (Magstim Co., Whitland, Dyfed, UK) was used. The coil was positioned with the handle directed posterolaterally 45° to the mid-sagittal line of the head over the approximate location of maximal sensitivity for FDI muscle activation (hotspot). Single-pulse magnetic stimuli were delivered manually at approximately 0.1 Hz starting at an intensity of 55% of maximum stimulator output. The intensity level was adjusted until a motor evoked potential (MEP) was elicited. Coil position was systematically moved 1cm anterior, posterior, medial and lateral to the presupposed hotspot until maximal MEP was observed. This location was used to determine the resting motor threshold (rMT), defined as the minimum intensity required to elicit MEP amplitude $>50 \mu\text{V}$ peak-to-peak in at least 3 of 5 trials in the resting target muscle (Rossini et al., 1999). The rMT was then used to determine stimulus intensity for MEP and CSP assessment. Stimulator output intensity was set to 120% of rMT for MEP and CSP assessment to prevent stimulation spread to neighboring cortical regions (Murase et al., 2005).

At rest, MEP data was collected for 5 single pulse stimulations applied at 0.1Hz (gain: 200–500 $\mu\text{V}/\text{div}$, filter: 20–2000 Hz). For CSP recording, subjects performed an isometric contraction of the FDI against a strain gauge coupled to a load cell. Force was transduced into an electrical signal displayed on an oscilloscope placed in front of the subject. Subjects were asked to produce a constant 6N force marked on the screen, until instructed to relax. Stimulation was applied 3–5 s after contraction initiation and subjects were instructed to

relax 2–3 s after stimulation (Fig. 2). Ten CSP measurements were obtained with a minimum 20s rest interval between each trial.

All EMG traces were rectified off-line, and the mean MEP amplitudes were determined by averaging the peak-trough values for each trial. Mean CSP was defined as the distance between the first MEP peak and return of EMG activity equal to at least 50% of the average prestimulus voluntary activity during the 25ms epoch preceding the stimulation (Murase et al., 2005).

2.5. Subjective symptom and safety assessment

Each visit, subjects rated their perceived symptom change using a seven point Likert scale (–3 = significant worsening, 0 = no change, 3 = significant improvement) (Siebner, Tormos et al., 1999). Scores were collected at the beginning of subsequent treatments to assess 24 hr effect and after treatment on day 1 to evaluate immediate treatment effect. To monitor for unintended stimulation effects, an adverse events questionnaire and memory test (HVLT-R) were administered prior to, and after, each session, as well as follow-up.

2.6. rTMS treatment

In each treatment session, subjects received 900 monophasic stimuli applied to the contralateral PMC. Stimulus amplitude was set at 90% rMT and administered at 1 Hz using a hand-held figure-eight coil. The stimulation site for PMC was defined as 2 cm anterior and 1cm medial to the previously defined hotspot for FDI activation. This site was chosen based on localization from a previous PET study (Fink et al., 1997; Schluter et al., 1998) and a previous FHD treatment study (Murase et al., 2005). In the sham treatment, the coil was held orthogonally to the head to prevent biological effects of stimulation delivery to the head (Lisanby et al., 2001).

2.7. Statistical analysis

Handwriting parameters (pressure, velocity, accuracy, fluency) and measures of cortical excitability (rMT, MEP, CSP) were analyzed in two stages. All data were assessed for normality and homogeneity of variance (Levene's test). First, day 1 differences between healthy and FHD groups were evaluated. An independent t-test was conducted between healthy and dystonia subjects for baseline differences in cortical excitability. A repeated-measures ANOVA was then performed with session (pre- and post-rTMS) as the main factor within subjects and group (real vs. sham vs. healthy control) as the main factor between subjects for each excitability measure. In the handwriting analysis, additional main factors between subjects of condition and trial were included in the analysis of handwriting pressure, velocity, and accuracy (the sentence writing condition was not included in accuracy assessment) and fluency measurement only involved condition 3.

Second, differences between real and sham treatment groups were investigated. A univariate two-way ANOVA was conducted with treatment day (1–5) and group (real vs. sham) as the main factors between subjects for each cortical excitability measure. This analysis was repeated to include follow-up assessment data if a treatment effect was observed. Day 5 data for one subject in the sham group was not analyzed to due instrumentation malfunction

during data collection. A repeated-measures ANOVA with main factors between subjects of trial and condition were included for each handwriting measure analyzed across testing sessions (pre-/post-stimulation on days 1 and 5). This analysis was repeated if a treatment effect was observed to include follow-up assessment. A repeated-measures ANCOVA was conducted for pen velocity with prestimulation day 1 values as the covariate to account for group differences at baseline. Two-tailed post-hoc t-tests for paired samples with Bonferroni correction were performed as necessary (corrected $p < 0.01$).

3. Results

3.1. Cortical excitability

Each measure of cortical excitability, rMT, MEP and CSP, was normally distributed across groups. There were no significant differences in rMT or MEP values in any statistical analyses. Baseline differences in CSP between healthy controls and subjects with FHD were observed, $t(16) = 3.39$, $p = 0.004$ (Fig. 3). There was no difference between real and sham stimulation groups prior to treatment initiation. After one rTMS application, there was no change in CSP within group or between groups. Across treatment sessions, a main effect of group for CSP was observed with those in the real treatment group exhibiting significant CSP prolongation in comparison to the sham control group, ($F(1, 75) = 10.64$, $p = 0.002$) and maintained at follow-up ($F(1, 82) = 10.95$, $p = 0.001$) (Fig. 4, Table 2).

3.2. Handwriting performance

All handwriting measures, except pen velocity, were normally distributed for all groups. Pen velocity was analyzed separately for the sentence condition. Before the first rTMS stimulation application, there was no significant difference in pen pressure, loop tracing error or fluency between real and sham stimulation groups (Fig. 3). There was a difference between the FHD groups in baseline pen velocity ($t(79) = -2.046$, $p = 0.04$) (Fig. 5). Subjects with FHD demonstrated greater pen pressure ($t(226) = -5.152$, $p < 0.0005$) compared to healthy subjects. Tracing error and pen velocity were not different between healthy subjects and subjects with FHD in either loop tracing or sentence writing conditions prior to rTMS application (Fig. 3).

After one rTMS treatment, no significant change in handwriting performance was demonstrated. Across five days of treatment, there was a significant increase in pen velocity during loop tracing in subjects with dystonia in comparison to subjects receiving the sham stimulation, (Wilks' $\lambda = 0.886$, $F(3, 64) = 2.747$, $p = 0.05$) which was maintained at follow-up (Wilks' $\lambda = 0.796$, $F(4, 61) = 3.906$, $p = 0.007$) (Fig. 5). When accounting for baseline differences in pen velocity, significant differences in pen velocity were still observed at the end of treatment (Wilks' $\lambda = 0.914$, $F(2, 68) = 3.210$, $p = 0.05$) and at follow-up (Wilks' $\lambda = 0.840$, $F(3, 65) = 4.140$, $p = 0.01$). No difference was observed across sessions for pen pressure, tracing error, or fluency. Handwriting measurements are represented for each subject across testing sessions (Table 2).

3.3. Self-report and memory performance

Five subjects reported transient symptom improvement (4 mild, 1 moderate) during the week of treatment (Table 2). One subject reported no change with repeated rTMS and two subjects reported transient symptom worsening lasting less than one day. In the sham stimulation group, one subject reported improvement; the remaining subjects reported no change. At ten day follow-up, two subjects in the real rTMS group and one subject in the sham group reported symptom improvement (Table 2).

No changes in memory performance or serious adverse effects due to stimulation were observed in any subject. Mild side effects were reported in the real rTMS group and included: confusion ($n = 1$) and fatigue ($n = 1$), both lasting less than one day.

4. Discussion

The results of this preliminary investigation demonstrate that cortical excitability and handwriting performance can be modulated by five consecutive days of rTMS and show that effects persist for at least ten days after treatment in subjects with FHD. Contrary to other reports, changes in cortical excitability and handwriting performance were not observed after one treatment. Subjects with FHD demonstrated a significantly reduced CSP as well as increased pen pressure during loop tracing and sentence writing in comparison to healthy controls prior to rTMS. Changes in cortical excitability and pen velocity were observed, yet, subjects did not report profound subjective symptom improvement.

Previous investigation of one rTMS application in subjects with FHD has demonstrated significant changes in cortical excitability, handwriting performance and symptom report lasting up to one day (Murase et al., 2005; Siebner, Auer et al., 1999; Siebner et al., 2003; Siebner, Tormos et al., 1999). The differences in this finding may be due to differences in stimulation protocol or clinical characteristics of subjects recruited. Variations in previously published protocols include: intensity (85–90% rMT), frequency (0.2–1 Hz), site of stimulation (PMC, M1), stimulus waveform (monophasic, biphasic) and length of stimulation (15–30 minutes) (Murase et al., 2005; Siebner, Auer et al., 1999; Siebner et al., 2003; Siebner, Tormos et al., 1999). This variability makes comparing results across studies difficult, but can serve as important information for the future development of optimal treatment parameters.

The differences demonstrated between subjects with FHD and healthy subjects in CSP prior to rTMS are in agreement with previous research (Quartarone et al., 2003; Siebner, Auer et al., 1999; Siebner, Tormos et al., 1999) supporting the theory of decreased cortical inhibition being a defining characteristic of FHD. Reduced excitability of inhibitory circuits involved in sensory input processing and movement production may disrupt the balance between excitation and inhibition, such that subjects with FHD are unable to properly modulate cortical excitation in response to changing environmental stimuli (Quartarone et al., 2005). The mechanism of low-frequency rTMS modulates neuronal excitability and may restore normal plasticity within the sensorimotor system (Filipovic et al., 2004; Murase et al., 2005; Siebner, Auer et al., 1999). It has yet to be determined if this technique can remediate the underlying neural impairments leading to permanent functional improvement (Quartarone et

al., 2005; Quartarone et al., 2006; Siebner et al., 2003). Though there was not a clear clinical improvement reported from the subjects, present findings are encouraging, however, that a long term effect with functional changes may be possible.

The present study recruited subjects with FHD who all possessed symptoms during writing but differed in degree of task-specificity. Consistent with the heterogeneity of this disorder, our subject population was diverse in that subjects who also had symptoms consistent with musician's dystonia were not excluded. As mentioned previously, with only one low-frequency rTMS application, others have found robust effects in subjects with FHD (Murase et al., 2005; Siebner, Auer et al., 1999; Siebner et al., 2003; Siebner, Tormos et al., 1999). These studies recruited subjects with only simple and/or dystonic writer's cramp. Our subjects demonstrate greater symptoms diversity, which may have influenced our day one findings.

Indeed, distinct pathophysiological and etiological differences between writer's cramp and musician's dystonia have been suggested (Rosenkranz et al., 2005). Rosenkranz and colleagues (2005) demonstrated abnormal sensorimotor integration when a vibratory stimulus was given to a single hand muscle in both groups of FHD, but the characteristics of the deficit were different. In musician's dystonia, sensory input strongly reduced intracortical inhibition in all hand muscles whereas in writer's cramp, cortical excitability was minimally affected by vibratory input. This may indicate distinct mechanisms of effect in the disorders.

Maladaptive plasticity in response to overtraining present in musicians and/or patients with occupational hand dystonia is suggested to be a causal factor (Byl, Merzenich, & Jenkins, 1996; Lim, Altenmuller, & Bradshaw, 2001; Quartarone et al., 2006; Rosenkranz et al., 2005). In contrast, genetic predisposition, without highly repetitive activity, may cause changes in brain organization leading to the development of writer's cramp (Berardelli et al., 1998; Ghilardi et al., 2003; Quartarone et al., 2006). Given the dependence on sensory input in the acquisition of musician's dystonia, it may be that stimulation of the PMC in this population will have a different effect when compared to writer's cramp. Qualitatively, our results suggest that subjects with musician's dystonia demonstrated greater changes in cortical excitability and handwriting performance in response to repeated rTMS administrations. This question was not a focus of this current work but warrants further inquiry to determine if differential sensitivities to rTMS exist in FHD.

The significant findings in this study are particularly encouraging given the modest sample size and heterogeneity of the population. For observed trends in the data, power analyses indicate between nine to sixteen subjects per group would be sufficient to demonstrate population effects for each outcome measure. The encouraging preliminary results of the present study lend support for a comprehensive study of the lasting effects of rTMS in FHD.

5. Conclusion

Previous research has demonstrated transient changes following rTMS, but this is the first report demonstrating lasting changes in cortical excitability and handwriting parameters in response to five days of rTMS treatment. These results are heartening and suggest further

research is warranted. More work is required to determine the most effective method to induce maximum symptom change including: stimulus location and parameters, larger sample sizes to account for patient diversity and allow for subgroup stratification, and combined interventions. Such a comprehensive approach will build on this and previous work to identify the optimal parameters to maximize the utility of rTMS as a therapeutic intervention in FHD.

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Fig. 1.
rTMS set-up used for cortical excitability assessment and treatment.

Fig. 2.

Top: Force trace during CSP measurement. Box highlights the increased force production due to superimposed rTMS excitation and the resulting decreased force during CSP before voluntary force return. Bottom: Rectified EMG trace demonstrating CSP.

Fig. 3. Mean CSP, tracing error, pen pressure, pen velocity and fluency before rTMS application across groups ($\pm$ SE). Significant differences between healthy and both patient groups in CSP and pen pressure are observed, * $p = 0.004$, ** $p < 0.0005$.

Fig. 4.

A) CSP change across assessments between subjects receiving real versus sham rTMS ($\pm$ SE). B) CSP change across treatment day ($\pm$ SE). Significant silent period prolongation after five-day rTMS treatment application is observed and maintained at follow-up, $p = 0.002$, $**p = 0.001$.

Fig. 5.

Change in pen velocity during loop tracing conditions across treatment day and follow-up assessment ($\pm$ SE). Pen velocity increases across five-day rTMS treatment application are observed in the treatment group compared to the sham group, maintained at follow-up, $*p = 0.05$, $**p = 0.007$. Differences between groups at baseline with sham group subjects demonstrating higher velocities prior to rTMS, $\#p = 0.04$.

Table 1

Subject demographics and clinical characteristics

Case	Group	Sex	Age	Handedness	Duration of sx (y)	Diagnosis	Clinical pattern	Botox Hx
1	real	M	41	R	13	MD R	2nd/3rd digit spasm during typing and classical guitar playing	N
2	sham	M	34	L	3	WC B	writing/typing L2-4, R 4th and 5th abnormal posturing	Y, 2yr prior
3	real	M	61	R	6	WC R	writing, digits 2-4 spasm/abnormal posturing	Y, 1yr prior
4	sham	M	43	L	8	MD L	L 2nd digit flexion playing piano	N
5	real	M	37	R	9	MD B	4th and 5th digit spasm L>R during guitar, piano and keyboarding	N
6	sham	F	63	R	20	WC R	R 3rd digit flexion during writing and typing	Y, 6mo prior

Healthy Controls			
Case	Sex	Age	Handedness
1	M	26	R
2	F	28	R
3	M	25	R
4	M	57	R
5	F	36	L
6	M	36	R
7	F	28	R
8	M	38	L
9	M	23	R

Table 2

CSP, tracing error, pen pressure, pen velocity and fluency for each subject across treatments and at follow-up assessment

Subject	Measurement	Day 1		Day 2		Day 3		Day 4		Day 5		Follow Up
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
H01	CSP (ms)	138.30	*	157.76	158.61	144.42	146.37	127.02	140.44	151.36	155.53	138.68
	pen error (au)	12.17	12.06							12.13	12.25	12.32
	pen pressure (g)	181.78	161.90							182.41	172.23	157.23
	pen velocity (m/s)	2.32	2.51							2.13	2.19	2.11
	fluency (inv/loop)	9.19	7.48							6.49	4.38	4.89
H02	sxs change (-3 to +3)		+1	0		0		0		0		+1
	CSP (ms)	113.75	123.44	122.81	125.42	121.88	120.94	130.85	130.42	127.61	117.43	122.30
	pen error (au)	12.21	12.25							11.92	11.92	11.56
	pen pressure (g)	134.23	143.03							146.81	128.81	156.03
	pen velocity (m/s)	3.09	2.94							2.85	2.68	3.13
H03	fluency (inv/loop)	3.44	4.69							4.75	4.17	3.33
	sxs change (-3 to +3)		+1	+1		-1.5		0		0		-2.5
	CSP (ms)	121.98	136.97	123.40	121.72	130.53	131.78	132.17	122.97	122.38	128.44	124.80
	pen error (au)	12.35	12.51							12.35	12.48	12.33
	pen pressure (g)	105.39	100.19							95.17	96.83	92.79
H04	pen velocity (m/s)	3.43	4.21							3.73	3.33	3.49
	fluency (inv/loop)	3.72	3.19							3.17	3.86	3.47
	sxs change (-3 to +3)		0	0		0		0		0		0
	CSP (ms)	115.28	117.74	89.62	91.42	93.73	89.90	94.61	86.70	102.69	107.60	112.20
	pen error (au)	11.70	11.69							11.46	11.66	10.91
H05	pen pressure (g)	151.68	154.24							114.21	121.94	124.58
	pen velocity (m/s)	2.41	2.69							2.95	2.76	2.80
	fluency (inv/loop)	5.48	4.50							3.94	4.33	4.64
	sxs change (-3 to +3)		+1	+1		+1		+2		+2		+1
	CSP (ms)	131.12	128.19	137.12	150.15	170.27	163.88	*	*	165.56	159.71	146.21
	pen error (au)	11.65	11.73							11.72	11.74	11.73
	pen pressure (g)	158.27	156.45							142.01	147.28	151.36

Subject	Measurement	Day 1		Day 2		Day 3		Day 4		Day 5		Follow Up
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
H06	pen velocity (m/s)	2.26	2.36					2.44	2.57	2.44	2.57	2.52
	fluency (inv/loop)	4.61	2.94					3.81	2.89	3.81	2.89	3.47
	sxs change (-3 to +3)		+0.5	0		-1		+0.5				0
	CSP (ms)	76.92	77.49	96.63	100.82	82.17	82.77	86.81	90.56	83.38	88.49	90.97
	pen error (au)	12.42	12.69							12.22	12.78	12.31
	pen pressure (g)	135.70	122.01							138.08	122.73	129.08
	pen velocity (m/s)	2.66	2.58					2.45	2.66			2.57
	fluency (inv/loop)	4.97	4.28					4.33	4.67			4.33
	sxs change (-3 to +3)		0	+1		+1		0				0
	CSP (ms)	120.00	134.43	112.75	105.99	114.95	125.58	121.91	116.69	**	**	123.59
L01	pen error (au)	11.46	12.04							12.10	**	12.35
	pen pressure (g)	110.60	129.99							125.89	**	105.39
	pen velocity (m/s)	3.46	2.85							2.84	**	3.43
	fluency (inv/loop)	3.28	4.00							3.94	**	3.72
	sxs change (-3 to +3)		0	0		0		0		0		0
	CSP (ms)	119.04	110.06	97.11	90.44	97.73	81.12	107.76	105.38	108.09	99.71	119.54
	pen error (au)	11.60	11.75							11.53	11.60	11.80
	pen pressure (g)	174.25	163.01							132.85	149.25	142.28
	pen velocity (m/s)	2.44	2.46							2.56	2.48	2.41
	fluency (inv/loop)	5.11	5.14							4.69	5.76	4.67
L03	sxs change (-3 to +3)		+2	0		0		0		+1		+1
	CSP (ms)	92.70	83.42	100.70	115.56	74.37	74.14	84.01	76.56	107.79	100.97	76.92
	pen error (au)	12.54	12.73							12.85	13.23	12.42
	pen pressure (g)	136.66	146.29							145.78	132.98	137.95
	pen velocity (m/s)	2.40	2.61							2.66	2.54	2.52
	fluency (inv/loop)	5.33	3.42							5.25	3.28	5.00
	sxs change (-3 to +3)		0	0		0		0		0		0

H=high (real) stimulation, L=low (sham) stimulation, CSP=cortical silent period, sxs=symptoms ms=milliseconds, au=arbitrary units, g=grams, m/s=meters per second, inv/loop=inversions per loop drawn

* denotes missing data due to corrupted file.

** denotes missing data due to instrumentation malfunction

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