Supplemental methods and results

Diagnosis of CD was established following criteria proposed by the Movement Disorders Society.[1] Five subjects implanted with Medtronic quadripolar lead electrodes at University of California, San Francisco (model 3389) and five subjects at University of Florida (model 3387) were included. Compared to before surgery participants subjectively reported they perceived moderate clinical benefits on the DBS settings (optimized). Active seizure disorder, pregnancy and metallic implants in the body were the exclusion criteria. Subjects were examined off dystonia medications

TMS Procedures

TMS was performed with a Bistim package (Magstim company, UK) attached to a figure-of-eight shaped (external wing diameter of 9 cm) coil. We placed a physical shielding over the implanted pulse generator (all 10 subjects in right side of the chest) to prevent the risk associated with damaging magnetic flux.[2]

Subjects were seated comfortably with the forearms rested in a semiprone position to enable complete relaxation of muscles. Surface EMG in a belly-tendon montage was recorded from the dominant first dorsal interosseous muscle (FDI) and the abductor pollicis brevis muscle using the Delsys system. Signals were band pass filtered (20 - 450Hz) and sampled at 5 kHz using a Power 1401 interface (Cambridge Electronic design). Electrical stimulation was applied to median nerve at the wrist at 300% of perceptual threshold, 0.2ms duration using a constant current generator (Digitimer) that produced a slight thumb twitch. Background activity was monitored in each trial.

TMS coil was placed over the dominant motor cortex scalp with the handle pointing in posterior and lateral direction and at a 45^{o} angle to the sagittal midline.[3] Since there were no interhemispheric differences in the TMS measures,[4] subjects had axial dystonia and DBS batteries were in right side, only dominant hemisphere was tested

An optimal site ('hot spot') over the scalp was determined that reliably produced motor evoked potentials in the target muscle. Resting motor threshold defined as the lowest intensity able to evoke a motor evoked potential (MEP) of 50 μV at rest in at least 5 out of 10 consecutive trials was recorded. Ten trials of SAI at 20 and 30ms interstimulus intervals (ISI), and ten of LAI at 150 and 200ms were recorded. All trials were randomly intermixed by the Signal software 5.01

A paired pulse protocol with a subthreshold conditioning pulse (the intensity was set at 80% of active motor threshold) preceding a suprathreshold test stimulus (intensity set to induce 1mV MEP) at 2 and 3ms ISI was performed for SICI. For the ICF, subthreshold conditioning pulse preceded a suprathreshold test stimulus at an ISI of 10 and 15ms. Ten trials for each ISI randomly intermixed with test stimulus MEP were delivered.

For the PAS, we paired median nerve stimulation with TMS pulse to the motor cortex at an ISI of 25ms, delivering 90 pairs over 30 minutes.[5] The median nerve stimulation parameters were similar to those used for SAI and LAI. The MEP amplitude was recorded from the abductor pollicis brevis muscle before, immediately after, 15 min and 30 min after PAS. Throughout the 30 min PAS procedure, patients were encouraged to concentrate on the APB muscle. The mean PAS (PAS_{mean}) was determined as the mean of MEPs recorded immediately, at 15 minutes and at

30 minutes after the PAS protocol whereas the maximal PAS ($PAS_{maximal}$) was determined as the maximal MEP recorded after the protocol. The mean and maximal MEPs were also expressed as the percentage change compared to MEP recorded before the PAS protocol

Data analysis

Peak-to-peak MEP amplitudes for each TMS measure were averaged across all trials. Significant SAI, LAI, SICI and ICF was determined by comparing the MEP amplitudes for the test stimulus preceded by conditioned stimulus with that of the test stimulus alone using the paired t-test. If normal distribution was not seen on Kolmogorov Smirov normality test ($p < 0.05$) non-parametric tests (SPSS 24) was used. One-way ANOVA test compared healthy controls and CD subjects. Clinical measures during DBS OFF and DBS ON were compared with Wilcoxon-signed rank test.

Results

TMS measures were noted. None of the subjects had a previous brain surgery or had underlying structural abnormalities on the preoperative MRI. One subject had a positive test for DYT1 gene in his records. The most frequent DBS settings consisted of double monopolar stimulation with 1.5 - 3.2 voltages, 90 - 160Hz frequencies and 60 - 150µs pulse widths. The mean total electrical energy delivered was estimated using the formula $voltage^2 \times$ pulse width × frequency/impedance was 54.8 ± 21.4µJ.[6] All 10 CD patients complained of dystonia symptoms upon turning off the DBS. Two subjects reported anxiety and had to be reassured that their dystonia would be controlled again once the DBS was turned back ON. With DBS OFF, CD subjects scored moderately on the clinical rating scale with four subjects complaining of significant pain and five

reporting frequent pulling of neck muscles. With DBS ON, all participants showed improvements on the TWSTRS scale (55-80% range).

Trials with significant background EMG area (about 500ms) before the TMS pulse were rejected (<15% of trials). RMT recorded during DBS OFF (51.6 ± 9.5% stimulator output) when compared to DBS ON (50.7 ± 8.8%) remained the same ($p = 0.35$) and correlated significantly with the duration of DBS ($r = 0.51$, $p = 0.04$). The paired t-test was significant ($p < 0.05$) in CD when the unconditioned test stimulus was compared to conditioned stimulus for all SAI and LAI measured except for LAI 200. In the between-subjects comparison, SAI during DBS OFF in CD was significantly different from healthy controls (SAI 20, $p = 0.03$; SAI 30 $p = 0.04$).With DBS ON, there were significant improvements in the TWSTRS severity scores **(**DBS OFF 20.2 ± 5.4; DBS ON 8.5 ± 4.2; $p = 0.008$), TWSTRS pain scores (DBS OFF 9.9 ± 6.1; DBS ON 2.9 ± 1.9; $p = 0.001$), VAS disability scores (DBS OFF 6.6 ± 1.9; DBS ON 3.5 ± 2.5; $p = 0.01$) and the VAS pain scores (DBS OFF 4.1 ± 2.8; DBS ON 1.5 ± 1.4; $p = 0.009$). LAI 200 OFF was also significantly reduced compared to healthy controls ($p = 0.03$). With regards to PAS measure, PAS_{mean} and $PAS_{maximal}$ recorded with DBS ON were not different from healthy controls (PAS_{mean} $p = 0.25$; $PAS_{maximal}$ $p = 0.41$). The paired t-test was significant ($p < 0.05$) for all participating subjects when the unconditioned test stimulus was compared to conditioned stimulus in the SICI and ICF paradigm.

Legends

Supplemental Figure 1: (A) Short latency afferent inhibition (SAI) in a cervical dystonia subject while DBS is turned OFF and turned ON. Each trace represents averaged motor evoked potentials (MEPs) of 10 trials, the top trace reveals results in a patient for the test stimulus (TS) alone, the second and third trace represent afferent inhibition after median nerve stimulation (MNS) at interstimulus inhibition (ISI) of 20ms. There was increased SAI when DBS was turned OFF. (B) Long latency afferent inhibition (SAI) in a cervical dystonia subject. Each trace represents averaged MEPs of 10 trials. The top trace reveals results in a patient for the test stimulus (TS) alone, the second and third trace represent afferent inhibition after median nerve stimulation (MNS) at interstimulus inhibition (ISI) of 200ms. LAI reduces when DBS is turned OFF with single nerve stimulation,

Supplemental Figure 2: (A) Correlation between change in TWSTRS severity score and change in SAI (average of SAI elicited at 20 and 30 interstimulus intervals). Of the subjects who reported improvements in severity on the TWSTRS scale, the scatter plot illustrates a significant correlation between change in severity scores and change in SAI. The grey squares represent the data and the dark line represents the trend line for TWSTRS severity data. There is also illustrated the correlation analysis for TWSTRS pain score and change in SAI. White triangles represent the data and the segmented line represents the trend line for TWSTRS pain score. (B) Correlation between change in VAS severity score and change in SAI. Of the subjects who reported improvements in severity on the VAS scale, the scatter plot illustrates a significant correlation between change in VAS dystonia score and change in SAI. The grey diamonds represent the data and the dark line represents the trend line for VAS severity score. There is also correlation analysis between change in VAS pain score and change in SAI. White triangles represent the data and the segmented line represents the trend line for VAS pain scores

Supplemental Figure 3: PAS amplitude in three groups at the three time points; immediately, 15 min and 30 min. Dark Grey bar represents DBS OFF, light grey represents DBS ON and white bar represents healthy control subjects. Error bars represent standard errors.

References

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