Supplementary Information

Supplementary Materials and Methods

Subjects

The age range of the subjects in the study was 9.0–17.8 years, corresponding approximately to 27–53.4 human years, assuming a 3:1 conversion factor (Yu, 1998).

Two of the subjects participating in the BL and RUL ECT and MST conditions had previously had intracerebral recording electrodes implanted through three 2–3 mm diameter burr holes in the occipital area of the skull. The electrodes had been explanted more than 3 years before the initiation of this study. When the electrodes were explanted, the skull holes were filled with bone wax, so significant current flow through these skull holes during transcranial stimulation is not expected.

Design

For one subject, only two BL TES motor threshold sessions were completed. For two BL ECT subjects and for one MST subject a complete set of ST titrations could not be obtained and their data were excluded from the seizure analysis.

Anesthesia and monitoring

The skin was shaved over the sites for TES/ECT, EEG, and ECG electrodes and on the distal legs for i.v. access. Physiological monitoring included ECG, EEG, saturation of peripheral oxygenation, end-tidal carbon dioxide, and blood pressure. Two channels of bilateral fronto-mastoid EEG and one channel ECG were recorded using a MECTA Spectrum 5000Q ECT device (MECTA Corp., Tualatin, OR) at a sampling rate of 140 Hz. EEG and ECG recording began at least 30 seconds before the administration of the procedure medications to collect baseline data. A MicroStim nerve stimulator (Neuro Technology Inc., Kerrville, TX) was used to monitor the effects of the muscle relaxant, but was turned off during the stimulus administration and resultant seizure to avoid afferent interference with the ongoing brain activity. A rubber tourniquet was placed on the left arm to isolate it from the effects of the muscle relaxant so that the presence and duration of motor seizures could be observed.

Electric stimulation

The electrode sites were prepared by cleaning with alcohol to remove scalp oils and then rubbing with an abrasive gel (NuPrep, Weaver & Co., Aurora, CO) to reduce impedance. The ECT electrodes (2.5–3.5 cm) were smaller in diameter than standard human electrodes (5 cm) to account for the smaller head size of the NHPs while maintaining safe current density levels. The electrodes for the RUL, BF, and FM configurations were smaller than those for BL ECT in order to prevent substantial current shunting that could result from the close spacing of the electrode edges in RUL, BF, and FM ECT. For the BL condition, the electrodes were positioned symmetrically with the electrode lower edge tangential to the mid-point of the line connecting the external canthus and tragus. For the RUL condition, one electrode was placed in the right BL position and the other electrode was placed with its left edge touching the vertex. In BF ECT, the electrodes were positioned symmetrically bilaterally above the eye-brow and centered above the outer canthus of the eye along a vertical line perpendicular to a line connecting the pupils. In FM ECT, the electrodes were placed along the midline with one electrode above the nasion and eye-brow ridge and the front edge of the other electrode touching the vertex.

The Digitimer DS7AH TES device was used to deliver the stimuli since standard ECT devices do not provide current amplitudes below 500 mA. The pulse width (0.2 ms) was the longest available on this stimulation device and is close the ultrabrief pulse range in conventional ECT (0.25–0.3 ms).

Magnetic stimulation

The MST coil was pre-cooled in ice to 8 °C to prevent overheating during the stimulus delivery. Maximum pulse amplitude corresponds to 1,800 V peak coil voltage.

Motor threshold titration

EMG was measured with platinum needle electrodes (model F-E2, Grass Technologies, West Warwick, RI) in belly-tendon montage, and recorded with an isolated bioelectric amplifier (BIOAMP-4, SA Instrumentation Co., San Diego, CA) connected to a digital oscilloscope (TPS2014, Tektronix, Beaverton, OR) triggered from the stimulator device. The interstimulus interval was maintained between 7 s and 10 s to avoid interaction between subsequent stimuli that could occur with shorter interstimulus intervals (Chen *et al*, 1997; Julkunen *et al*, 2011; Julkunen *et al*, 2012; Pascual-Leone *et al*, 1994). As well, the MT definition of 50 μV peak-to-peak MEP was matched to standard human MT procedures (Rossini *et al*, 1994) since the EMG signal-to-noise ratio allowed reliable resolution of signals at this level. We have obtained reliable TMS MT estimates using this approach in NHPs under the same kind of anesthesia in prior studies (Lisanby *et al*, 2001; Peterchev *et al*, 2008).

The MTs for the left and the right hand were titrated simultaneously. For BL, RUL, and BF ECT, the MT was titrated first with the anode (positive electrode) assigned to the right electrode. In FM ECT, the MT was titrated first with the cathode (negative electrode) assigned to the posterior electrode first. The order of stimulus polarity was maintained fixed to reduce variability within MT conditions and since the three samples per condition were too few to allow randomization of the polarity condition.

Seizure threshold titration

The pulse train parameters for ST titration were selected based on piloting and the following considerations: First, a relatively large number of pulses is required for reaching low amplitude-titrated STs (Liberson, 1948, 1953). Second, the frequency of 50 pulse per second (25

Hz with respect to pulse pairs) is similar to frequencies conventionally used in ECT ST titration and appears to be more efficient for seizure induction than the higher frequencies typically used in ECT and MST treatments (Devanand *et al*, 1998; Peterchev *et al*, 2010a; Peterchev *et al*, 2010b). Third, we limited the total train duration to 10 s so it is commensurate with the maximum stimulus durations used in ECT (8 s) and MST (10 s); the effects of longer convulsive stimulus trains have been explored only to a limited extent (Alexander, 1953).

For the BF and FM conditions, the pulse trains were bidirectional as in conventional clinical ECT. For the BL and RUL conditions the pulse trains were unidirectional with the cathode on the right, due to unavailability of the bidirectional stimulator option at the time of these studies.

If no seizure occurred at a given titration step, the subsequent stimulus was delivered after at least 20 s. If a seizure was induced at the first titration step, the procedure was repeated on another day. One MST session with seizure on the first step was counted in the analyses since the subject was not available for an additional session and since this titration step was equal to or lower than the two other MST STs for that subject. In 4 sessions (3 MST and 1 RUL ECT), there was robust tonic contraction during stimulation without notable movement or EEG ictal activity after the end of stimulation. The application of subsequent, stronger stimulus steps resulted in no contraction or substantially reduced contraction during stimulation, thereby suggesting that a seizure may have occurred during stimulus administration in the prior step that produced post-ictal inhibition. In these cases, the last titration step before the inhibition effect occurred was taken as best available estimate of ST.

Seizure duration

In 21 out of a total of 90 sessions, the duration of the EEG seizure could not be reliably determined, due to lack of visually identifiable seizure expression, including 5 RUL ECT, 4 BF ECT, 3 FM ECT, and 9 MST sessions. In the analysis, the EEG seizure duration for these sessions was assumed to be equal to the motor seizure duration.

The combination of relatively short seizure duration after the end of the stimulus trains and the presence of movement artifacts during this period precluded analysis of the power and spectral content of the seizure EEG recordings.

Statistical analysis

The mixed effects and multiple regression models were implemented in JMP (SAS Institute Inc., Cary, NC). The ICC calculation was carried out in SAS (SAS Institute Inc). The summary statistics and plots were generated in MATLAB (The MathWorks, Inc., Natick, MA).

Supplementary Figures

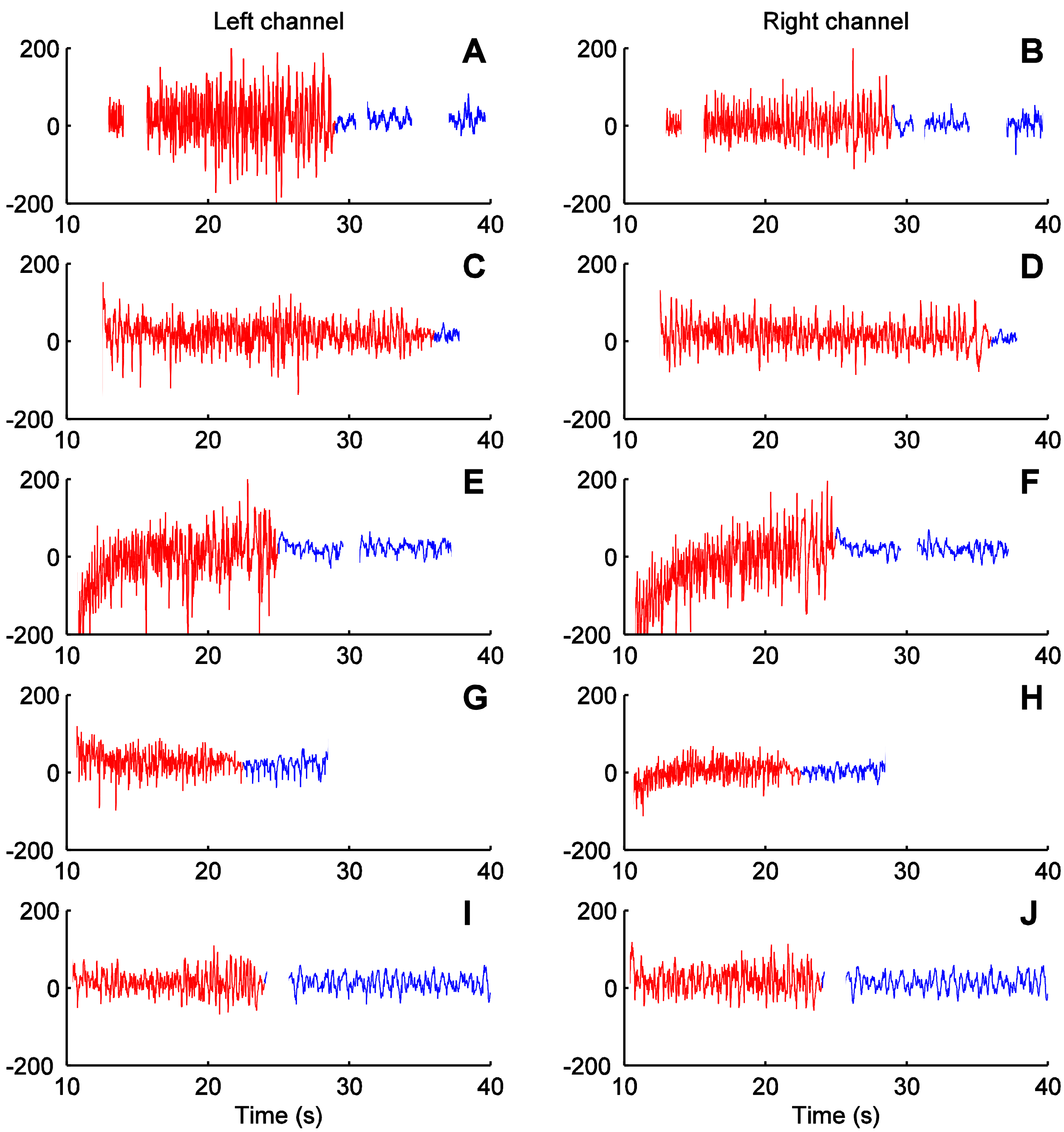

Figure S1. Representative two-channel ictal and post-ictal EEG waveforms (in units of μV) from one subject for (A–B) BL, (C–D) RUL, (E–F) BF, and (G–H) FM ECT as well as (I–J) MST. The waveforms are displayed for 30 s from the end of the stimulus train which is 10 s long. The red portion of the waveform denotes the estimated EEG seizure duration. Segments of the traces with substantial movement artifact are blanked out.

Supplementary Tables

Table S1. Motor threshold (MT) for the two hands. For the ECT modalities, MT is averaged across the two current polarities (cathodal and anodal stimulation). There were no statistically significant differences between the two hands.

		Left hand		Right hand	
		mean	SD	mean	SD
ECT (mA)	BL	61.8	15.5	65.2	23.0
	RUL	79.2	24.4	—	—
	BF	58.1	19.3	59.3	22.9
	FM	65.2	16.9	61.2	13.5
MST (% MA)		20.5	3.3	20.8	3.8

Table S2. Effect tests and parameter estimates from multiple regression analysis of normalized ST (z-score) across all ECT electrode configurations and MST. Significant parameters ($p < .05$) are marked in bold. Intercept was not modeled since ST is normalized.

Variable		df	*F*	*p*	*β*
MT (z-score)		1	**186**	**.0001**	**.863**
Session		1	0.538	.466	-.043
Age (years)		1	2.25	.138	-.108
Weight (kg)		1	3.29	.074	.110
Session×Modality	BF	4	0.269	.897	-.064
	BL				.014
	FM				.035
	RUL				.052
Age×Modality	BF	4	2.32	.065	.176
	BL				**-.289**
	FM				-.056
	RUL				.025
Weight×Modality	BF	4	1.77	.144	.119
	BL				.222
	FM				-.120
	RUL				-.212

Table S3. Motor and EEG seizure duration in seconds. There were no statistically significant differences among the stimulation modalities (see Table S4).

		Motor		EEG	
		mean	SD	mean	SD
ECT	BL	23.7	9.8	22.3	8.5
	RUL	18.0	3.6	17.3	4.5
	BF	20.3	6.0	19.4	5.7
	FM	21.0	5.9	19.5	5.3
MST		17.4	3.5	16.5	3.2

Table S4. Effect tests and parameter estimates from multiple regression analysis of log-transformed motor and EEG seizure duration across all ECT electrode configurations and MST. Significant parameters ($p < .05$) are marked in bold.

Variable		df	Motor			EEG		
			F	*p*	*β*	*F*	*p*	*β*
Modality	BF	4	1.61	.183	.257	2.19	.080	.299
	BL				.170			.190
	FM				.012			.037
	RUL				-.164			-.237
ST (z-score)		1	1.23	.271	-.122	**4.42**	**.039**	**-.225**
Session		1	1.25	.267	-.111	1.15	.287	-.104
Age (years)		1	**15.9**	**.0002**	**-.556**	**17.3**	**<.0001**	**-.566**
Weight (kg)		1	0.0132	.909	.025	0.226	.636	.099
ST×Modality	BF	4	0.335	.854	.139	0.239	.915	.135
	BL				.039			-.038
	FM				-.148			-.094
	RUL				-.058			-.038
Session×Modality	BF	4	2.31	.068	-.169	**2.90**	**.029**	-.149
	BL				.172			.167
	FM				**-.291**			**-.358**
	RUL				.075			.129
Age×Modality	BF	4	0.678	.610	-.158	0.283	.888	-.172
	BL				-.183			-.005
	FM				.029			.048
	RUL				.271			.087
Weight×Modality	BF	4	0.316	.867	.124	0.289	.884	.185
	BL				.135			.067
	FM				-.322			-.293
	RUL				.039			.082

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