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Short latency activation of cortex by clinically effective thalamic brain stimulation for tremor

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Abstract

Deep brain stimulation relieves disabling symptoms of neurologic and psychiatric diseases when medical treatments fail, yet its therapeutic mechanism is unknown. We hypothesized that ventral intermediate nucleus stimulation for essential tremor activates cortex at short latencies and that this potential is related to suppression of tremor in the contralateral arm. We measured cortical activity with electroencephalography in 5 subjects (7 brain hemispheres) across a range of stimulator settings, and reversal of the anode and cathode electrode contacts minimized the stimulus artifact, allowing visualization of brain activity. Regression quantified the relationship between stimulation parameters and both the peak of the short latency potential and tremor suppression. Stimulation generated a polyphasic event related potential in ipsilateral sensorimotor cortex with peaks at discrete latencies beginning less than one millisecond after stimulus onset (mean latencies 0.9±0.2, 5.6±0.7, and 13.9±1.4 milliseconds, denoted R1, R2, and R3, respectively). R1 showed more fixed timing than the subsequent peaks in the response (p<0.0001, Levene's test), and R1 amplitude and frequency were both closely associated with tremor suppression (p<0.0001, respectively). These findings demonstrate that effective ventral intermediate nucleus thalamic stimulation for essential tremor activates cerebral cortex at approximately one millisecond after the stimulus pulse. The association between this short latency potential and tremor suppression suggests that deep brain stimulation may improve tremor by synchronizing the precise timing of discharges in nearby axons, and by extension the distributed motor network, to the stimulation frequency or one of its subharmonics.

Keywords

ventral intermediate nucleus; deep brain stimulation; essential tremor; thalamus; cerebral cortex; event related potential

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Introduction

Despite the remarkable effectiveness of deep brain stimulation (DBS) for medically refractory symptoms of neurologic and psychiatric diseases, its underlying therapeutic mechanism is unclear (1-5). Both stereotactic lesioning/ablation and DBS of the ventral intermediate (VIM) thalamus and subthalamic nucleus eliminate essential tremor and parkinsonian tremor, yet multiple functional imaging studies paradoxically show that effective DBS increases glucose utilization/blood flow at or near the stimulation target, opposite the predictions from lesioning procedures (6-8). Furthermore, electrophysiology and network simulations suggest that subcortical stimulation alters neuronal activity in various output structures throughout the motor network and particularly in cerebral cortex (9-16). Collectively, these unexpected findings raise questions about whether the symptomatic effects of DBS arise from neuronal activation, inhibition, or some combination of the two, and perhaps more importantly, about how DBS alters the timing of neuronal activity and oscillations throughout the distributed motor system (17).

Prior studies evaluating cortical event related potentials (ERPs) from DBS are limited because stimulation is associated with an electrical artifact that obscures underlying brain activity (18-22). Using techniques to eliminate this artifact, we recently found non-synaptic activation of neurons in cerebral cortex during clinically effective subthalamic stimulation in humans with Parkinson disease (23). In this context, we hypothesized that ventral intermediate nucleus thalamic DBS activates cerebral cortex at short latencies as well, and that the amplitude of the ERP is related to tremor suppression in the contralateral arm. Better knowledge of the mechanism of DBS has the potential to improve efficacy and decrease adverse stimulation effects, to guide innovation in novel indications for DBS, and to advance our understanding of the pathophysiology of neurologic and psychiatric diseases.

Subjects / Materials and Methods

This study received prior approval from the Institutional Review Board. Subjects were diagnosed with essential tremor and underwent DBS as part of routine care (24). Prior to recruitment, appropriate electrode placement was confirmed with routine postoperative magnetic resonance images, using previously published methods (25).

Adjustment to Bipolar Stimulation

The DBS electrode is a linear array of four contacts in the brain (numbered 0, 1, 2, and 3), each 1.5 millimeters in height, separated by 1.5 millimeters, and connected to a single channel pulse generator in the chest wall (lead model 3387, Medtronic Neuromodulation, Inc., Minneapolis MN, USA). Experimental DBS settings were based upon effective home settings. Monopolar stimulation (a contact in the brain as the cathode and the pulse generator in the chest wall the anode) results in an electrical artifact that obscures the underlying brain activity, therefore we transitioned subjects to bipolar stimulation with adjacent contacts as anode and cathode. Preliminary studies were performed in one subject, and 5 subjects (7 brain hemispheres) underwent the range of stimulator settings used in the group statistical analyses.

Electroencephalographic Recordings

A standard 16-channel electroencephalography system in a 10 by 20 montage without an electrode cap sampled at 10,000 Hertz with low pass filter of 3000 Hertz and the mastoid contralateral to the DBS as common reference. The stimulation voltage was increased in 1 Volt increments, beginning at 0.5 Volts until either a maximum of 7.5 Volts or else the highest voltage that was tolerated symptomatically at frequencies of 20 and ≥130 Hertz,

with the pulse width held constant at 60 microseconds. Between each stimulation condition, there was a pause of approximately 10 seconds followed by activation of the DBS at the next stimulation condition for at least 20 seconds prior to data acquisition, and an identical pair of recordings was obtained at each setting, except that the anode/cathode contacts were reversed in random order (i.e., from 2+1− to 2−1+). After identifying the stimulation voltage that improved tremor during high frequency stimulation, we delivered DBS across a range frequencies (5, 20, 40, 70, 100, 130, 160, and 185 Hertz) at that threshold voltage. Subjects were blinded to stimulator settings at all times.

Calculation of ERPs / Peak Latency and Amplitude Measures

ERPs were calculated by averaging epochs aligned to stimulus onset. The pair of ERPs associated with anode/cathode reversal was summed to generate a composite ERP for each DBS condition. The assumption is that this summation will suppress stimulus artifact and amplify the underlying brain response (red traces, Figure 1). Stimuli were randomly and independently sampled without replacement to generate multiple ERPs from an electrode of interest in each subject. During 20 Hertz stimulation, the amplitudes and latencies of the initial downgoing (negative) and upgoing (positive) peaks in the ERP were measured (R1, R2, R3, and S1, S2, respectively). For the group analyses, the peak amplitudes were divided by 2 to represent an average of the summation of the two anode/cathode pairings. Additionally, two-dimensional topographic plots and contour plots were generated in Matlab (Matlab®, Natick, MA, United States). Finally, to estimate the dose of R1 over time, we multiplied the peak amplitude of R1 by the stimulation frequency.

Tremor Measurement

Subjects deactivated their stimulator on the evening prior and were instructed to hold a bottle in a drinking position, similar to previously described methods (12). An acclimation period of at least 20 seconds to each DBS setting was allowed prior to the task, and a triaxial accelerometer measured acceleration sampling at 10,000 Hertz. To estimate physical displacement in the arm from tremor, we multiplied the instantaneous acceleration by the frequency of the tremor. Two-way analysis of variance (ANOVA) with stimulation voltage and anode/cathode pair as factors and tremor displacement as subject showed no significant effect for anode/cathode pair (p=0.45), therefore the tremor data were pooled for the group analyses regardless of the anode/cathode pair. One subject was excluded from tremor analyses *a priori*, because he had no recurrence of tremor when his stimulator was deactivated, presumably because of a persistent “microlesion” effect (26).

Statistical Analyses

Mixed effects within-subjects repeated measures linear models quantified the effects of stimulation voltage and frequency on R1 peak amplitude and tremor suppression, as well as tremor suppression adjusted for R1 amplitude. For additional details on experimental and statistical methods, see the online Supplementary Materials.

Results

All subjects received the full range of stimulation voltages except one who had tremor suppression but experienced persistent numbness in the contralateral arm and face at stimulation intensities of greater than 4.5 Volts (Table 1). The electrode locations in midcommissural space are presented in Table 2.

Event Related Potential to Ventral Intermediate Nucleus Thalamic Stimulation

The analysis methods minimized the electrical stimulus artifact, demonstrating a polyphasic ERP with initial downgoing (positive) peaks at latencies of 0.9±0.2 milliseconds in 5 of 5 subjects, 5.6±0.7 in 5 of 5 subjects, and 13.9±1.4 in 4 of 5 subjects (6 of 7 brain hemispheres), denoted R1, R2, and R3, respectively (mean standard deviation, Figure 1). Corresponding negative (upgoing) peaks were present at 2.60.5 and 8.60.8 milliseconds (S1 and S2, respectively). R1 displayed fixed, invariant timing, in contrast to the progressively more variable latencies of R2 and R3 (Levene's test, $p<0.001$, respectively). Although source localization was not the primary goal of this study, two-dimensional topographic plots of scalp field potentials for the large, initial peak of the stimulus artifact show the expected polarity inversion associated with anode/cathode reversal and are consistent with a deep, near-midline source corresponding to the DBS electrode contacts in the thalamus. In contrast, R1 and R2 occur later and demonstrate field potentials over ipsilateral sensorimotor cortex.

The following observations indicate that R1 is not an electrical stimulus artifact: (1) within single EEG electrodes, its polarity is independent from the preceding stimulus artifact upon reversal of the DBS anode and cathode electrodes; (2) across different EEG electrodes, the stimulus artifact and R1 are spatially independent and therefore cannot arise from the same source; and (3) R1 and the later peaks in the ERP are not observed in a bowl of saline containing an externalized DBS system.

The morphology of the ERP and tremor suppression are both related to the intensity and timing of the thalamic stimulus

Contour plots demonstrate the reproducible, instantaneous nature of R1 and its non-linear dependence on stimulation voltage, with the frequency and pulse width held constant at 160 Hertz and 60 microseconds (Figure 2). Means plots demonstrate a dose-response relationship between R1 amplitude and tremor suppression with increasing stimulation voltages, both within and across subjects. Mixed effects repeated measures models show that R1 amplitude and tremor suppression were both predicted by stimulation voltage ($p<0.0001$), which was treated as a categorical variable to better isolate potential thresholds. Additional analyses demonstrate the effects of DBS voltage on the ERP during symptomatically ineffective 20 Hertz stimulation, allowing evaluation of changes in the peak amplitudes of the later peaks (R2 and R3). Finally, contour plots demonstrate the effects of stimulation frequency on ERP morphology (Figure 3). R1 is visible at a constant latency across all stimulation frequencies ($p=0.31$, peak latency versus frequency). Stimulation frequency significantly altered R1 amplitude ($p<0.0001$), although the magnitude of this effect was smaller than that from changes in stimulation voltage. As expected, stimulation frequencies of ≥100 Hertz were associated with tremor cessation ($p<0.0001$). Although R1 amplitude alone was not associated with tremor suppression across the different stimulation frequencies, there was a close association between tremor and the ERP when R1 dose was estimated by multiplying R1 amplitude by the stimulation rate.

Discussion

Cerebral cortex is activated at less than one millisecond after the stimulus pulse during clinically effective VIM DBS for essential tremor. The association between the amplitude of this short latency response (R1) and tremor suppression during high frequency stimulation suggests that it might represent a biomarker for dose, regardless of its underlying mechanism(s) or whether it is causally related to symptomatic improvement. In particular, the non-linear dependence of both R1 amplitude and tremor suppression on DBS voltage suggests that increasing stimulation voltages activate progressively larger volumes of

surrounding tissue. The geometry of this volume is likely complex and dependent upon on anisotropies in tissue impedance, electrode location, stimulation parameters, accumulated charge density, and other variables (27). Furthermore, both R1 amplitude and tremor suppression show ceiling effects at higher stimulation voltages (Figure 2B), suggesting that the activation of proximal axons is saturated and that insufficient charge density is generated at greater distances to recruit additional axons. Interestingly, R1 continues to rise as the DBS voltage and frequency are increased beyond the threshold required for acute tremor suppression (Figures 2B and 3C), suggesting that a range of dosages is associated with symptomatic improvement.

R1 most likely represents non-synaptic, retrograde (antidromic) activation of sensorimotor cortex, based upon the following: (1) its latency is too short to represent synaptic activity; (2) it shows more precise timing than later peaks in the response (R2 and R3), presumably because they are associated with the variability of synaptic release; and (3) it is present at a fixed latency across a wide range of stimulation frequencies. A caveat to this interpretation, however, is that we cannot demonstrate collision, because these were non-invasive scalp potentials in human subjects with essential tremor. Despite this, reciprocal connectivity between thalamus and cortex is well-established (28-30), including single unit recordings in awake, behaving cats showing antidromic activation, collision, and conduction velocities of 60 meters/second in descending corticothalamic axons (31). Since cortex and thalamus are separated by approximately 5 centimeters in humans, this rapid conduction velocity agrees with the R1 peak latency we measured and is consistent with retrograde activation of the large diameter, myelinated descending axons of cortical pyramidal cells.

Another potential contributor to early components of the ERP is orthodromic depolarization of ascending thalamocortical axons, prior to their release of neurotransmitter onto cortical dendrites. Although we cannot exclude this entirely, several observations suggest that this mechanism does not contribute significantly to the earliest peak (R1). First, it is unclear how reliably these presynaptic axonal depolarizations can be detected at the scalp because of their short duration (<2 μs) and limited current density relative to the depolarization of entire pyramidal cells (32-34). Second, small amplitude, early peaks in somatosensory evoked responses have recently been attributed to presynaptic thalamocortical activity in awake, behaving humans, estimating conduction velocities of approximately 33 meters/second (35, 36). This slower conduction is consistent with transmission through the smaller diameter, less densely myelinated axons of thalamic relay neurons, implying that depolarization of their presynaptic terminals at cortex would be detected by scalp electrodes no earlier than 1.5 milliseconds after stimulus onset, considerably later than the observed peak latency of R1 at 0.9 milliseconds. Finally, anatomical studies demonstrate that the corticothalamic projections vastly outnumber their reciprocal thalamocortical axons, by many estimates on the order of 100 to 1 (27-30, 38). Regardless of these mechanistic/technical considerations, our analyses distinguish the components of the ERP from the stimulation artifact and demonstrate its association with behavioral improvement from DBS.

The more variable timing of the later peaks (R2 and R3) versus R1 during low frequency stimulation suggests that they are associated with synaptic activity. The intermediate peaks (S1/R2) are compatible with monosynaptic, orthodromic activation of the thalamocortical pathway, while the later responses (S2/R3) more likely reflect polysynaptic activation of cortex. However, we cannot exclude potential contributions from phase resetting of cortical activity by antidromic activation followed by synchronized, spontaneous bursting; antidromic activation at longer latencies through slower conducting fibers; local network activation via cortico-cortical synapses or interneurons; and activation of other anatomical pathways as components of these later peaks. Regardless, synchronization or regularization of neuronal discharges, oscillations, resonance, and beat phenomena have been proposed as

potential contributors to the therapeutic action of DBS (39, 40). Indeed, the small variations we observed in R1 amplitude across the stimulation frequencies might represent resonance effects with the later peaks in the ERP (R2 and R3) from prior stimuli.

In parallel with the detection of R1 at the scalp, stimulation presumably also activates corticothalamic axons bidirectionally, such that the magnitude and precise timing of orthodromic discharges onto thalamic neurons is altered as well (41). Therefore, in the context of the paradoxical functional imaging findings, this interpretation would suggest that effective DBS both increases the discharge rate and alters the precise timing of neuronal activity at or near the site of the stimulus, most specifically in subcortical neurons receiving axonal projections from cerebral cortex. Regardless of whether subcortical lesions and high frequency electrical stimulation share the same functional mechanism, these findings imply that they may differ with respect to the discharge rate in the targeted subcortical nucleus. Furthermore, to the extent that cortical ERPs associated with thalamic stimulation for essential tremor and subthalamic stimulation for Parkinson's disease are similar, they represent a shared cortical physiology associated with suppression of tremor by DBS across these subcortical targets and disease states (23, 42-44).

Pathological tremor is thought to arise from oscillations throughout a distributed central motor network (45). Although studies have implicated the cerebellothalamic pathway in essential tremor, considerable work has also described a role for cerebral cortex and its reciprocal thalamic connections (46-51). Our findings suggest that modulation of activity in this latter pathway is an important component of the therapeutic mechanism of DBS in humans with tremor. Consistent with this, both direct motor cortex stimulation and transcranial magnetic stimulation improve/reset tremor, optical stimulation of cortical axonal projections to the subthalamic region improves movement in a mouse model of PD (52-55), and a recent tractography study suggests that effective thalamic DBS locations showed connectivity to areas of pre-motor and supplementary motor cortex (56). Furthermore, we have demonstrated similar short latency activation of cortex during clinically effective subthalamic stimulation in humans with Parkinson's disease. Despite these converging findings, we still cannot exclude potential contributions of other anatomical pathways, including cerebellothalamic projections, in the underlying mechanism of DBS and the pathophysiology of tremor. Regardless of whether tremor originates from a discrete anatomical source or is an emergent property of the distributed motor system, our data argue that reciprocal activation of axons in the thalamocortical system is associated with tremor suppression in humans with essential tremor.

This study has potential limitations, many of which were imposed by efforts to balance the duration and tolerability of the experiments. First, short stimulation epochs might improve tremor temporarily or cause carry-over effects, however tremor typically responds within seconds to DBS activation/inactivation (57). Additionally, improvement still might not be sustained days after the acute stimulator adjustments, as has been described previously (58). Second, ineffective stimulation locations were not tested, however ineffective DBS was delivered from appropriately located contacts (i.e., all of the lower stimulation voltages and frequencies). Despite this, the relationship between the cortical response and tremor suppression may not be specific, particularly if the DBS electrode is not positioned optimally within the thalamus. Third, an assumption of our paradigm is that stimulation with the two anode/cathode pairs, if not exactly identical, is nevertheless very similar. This is supported by the similar peak amplitudes and latencies of the ERPs in the two opposite stimulation polarities across subjects (Figure 1), that two-way analysis of variance showed no effect of anode/cathode pairing on tremor suppression in the contralateral arm, and the *a priori* decision to utilize adjacent DBS contacts, exploiting the narrowest possible spacing between the electrode contacts (3 millimeters). Finally, although relatively few subjects

were enrolled, our findings were consistent within and across subjects, and repeated, independent assessment of both the ERPs and tremor improved statistical power.

In summary, we found that symptomatically effective ventral intermediate nucleus thalamic DBS in humans with essential tremor synchronizes cortical activity to the stimulation frequency or one of its sub-harmonics. By extension, this suggests that DBS alters the precise timing and magnitude of cortical discharges to the cerebellar thalamus, as well. Since current DBS systems can deliver more settings that can be evaluated practically, a therapeutic implication is that non-invasive scalp ERPs might eventually be incorporated into dose titration during DBS programming. Speculatively, these techniques or their extensions might be expanded to confer greater or more sustained efficacy, fewer adverse effects, less frequent follow-up appointments for stimulator readjustments, fewer surgeries for battery depletion, and lower cost. Furthermore, while tremor typically responds to effective DBS within seconds, patients undergoing DBS for dystonia and emerging neuropsychiatric indications may not experience maximal symptomatic effects until days or weeks after stimulator activation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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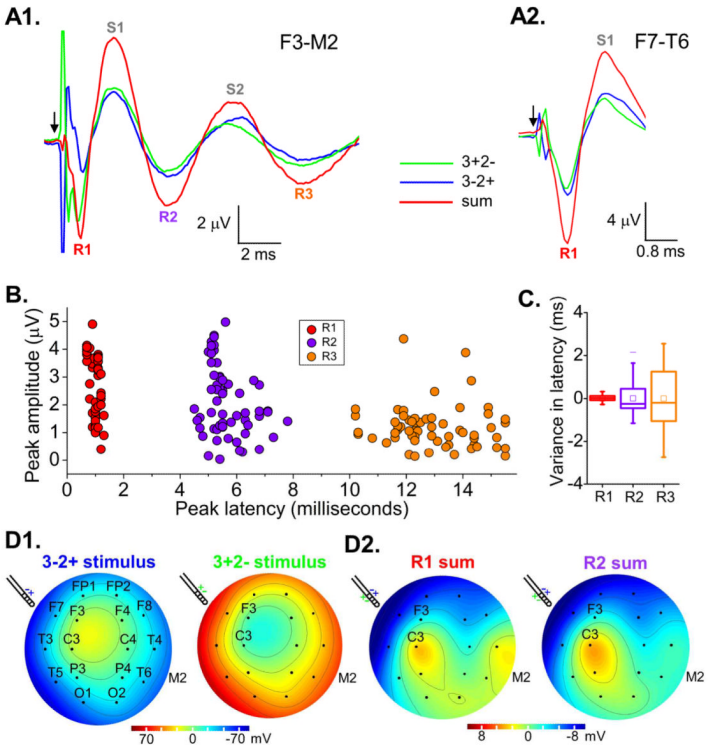

Figure 1. Short latency cortical activation by thalamic DBS for essential tremor

(**A1**) Reversal of the anode and cathode contacts (3+2− and 3−2+, blue and green traces, respectively) inverts polarity of the stimulus artifact, yet the later brain responses retain the same polarity. Summation of the pair of bipolar stimulus responses yields composite ERPs (red traces), which minimize the electrical stimulus artifact and demonstrate the underlying brain activity. Thalamic DBS at 20 Hertz from a representative subject yields a polyphasic ERP at F3-M2 with initial downgoing (positive) peaks at latencies of approximately 0.9, 6, and 22 milliseconds after stimulus onset (denoted R1, R2, and R3, respectively). (**A2**) A different channel pairing (F7-T6) in the same subject shows a smaller stimulation artifact followed by the brain response at 0.9 milliseconds latency (R1). The polarity of the brain response is independent from the polarity of the stimulus artifact that precedes it. (**B, C**) Scatter and box plots across all subjects demonstrate precise timing of R1 versus the more temporally dispersed latencies of the subsequent peaks ($p<0.0001$ for R1 versus R2 and R3, respectively, 5 independent ERPs per subject). (**D1**) Topographic plots of scalp field potentials for the stimulus artifact peaks show the expected polarity inversion upon reversing the DBS anode and cathode contacts. These field potentials are consistent with a deep near-midline source corresponding to the electrode contacts in the left thalamus. (**D2**) In contrast, the brain responses (R1 and R2) show localizations consistent with left sensorimotor cortex, ipsilateral to the DBS electrode.

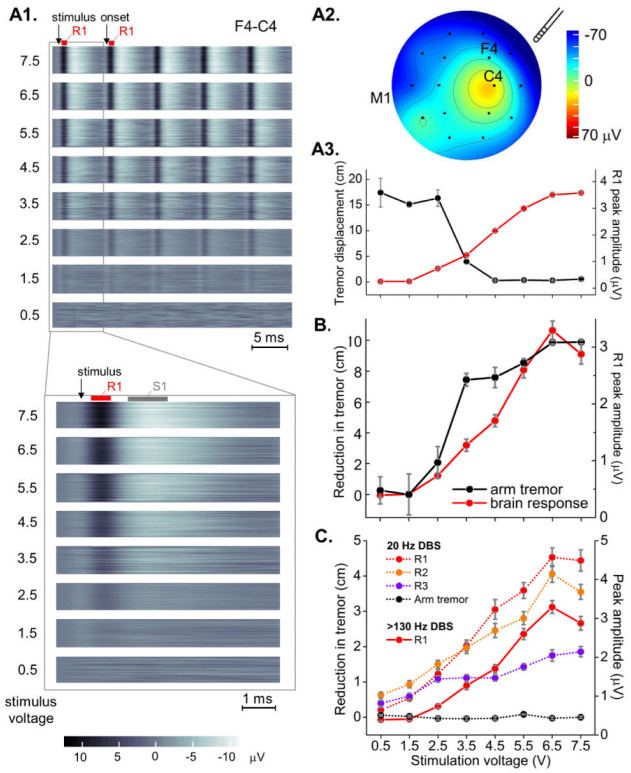

Figure 2. The peak amplitude of the short latency cortical response (R1) increases non-linearly with stimulation voltage

(A1) In this representative subject, the stimulus artifact is essentially eliminated by the summation procedure, and contour plots demonstrate the short latency peak at 0.9 milliseconds after stimulus onset across a range of stimulation voltages during 160 Hertz right ventral intermediate thalamic DBS. The inset shows the same response over a shorter time interval. (**A2**) Topographic scalp field potential shows localization consistent with right sensorimotor cortex, ipsilateral to the DBS electrode. (**A3**) Means plots for R1 amplitude and tremor displacement in the contralateral arm for this subject (**B**) Across subjects, R1 peak amplitude and tremor suppression both change non-linearly with increasing DBS voltages and show ceiling effects at the highest stimulation intensities. Note that R1 amplitude continues to increase beyond the threshold voltage for tremor suppression in the contralateral arm, suggesting that a dynamic range of R1 amplitudes is associated with tremor suppression in individual subjects. (**C**) R1, R2, and R3 peak amplitudes during ineffective 20 Hertz stimulation across stimulation voltages. R1 peak amplitude during high frequency stimulation (≥130 Hertz) is displayed from **2B** above, allowing comparison of the effects of stimulation frequency on R1 across DBS voltages. R2 and R3 are obscured by ongoing stimulus pulses during high frequency DBS. Tremor displacement is not changed significantly by 20 Hertz DBS across stimulation voltages ($p = 0.12$).

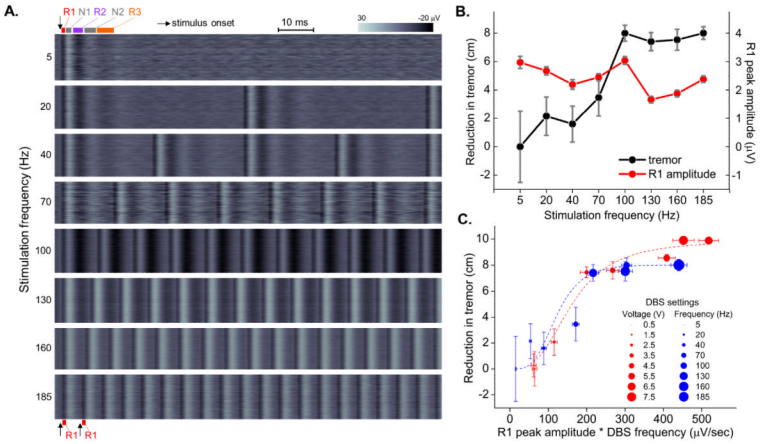

Figure 3. The morphology of the ERP to VIM DBS and tremor suppression are both related to stimulation frequency

(**A**) Contour plots demonstrate the effects of stimulation frequency on the morphology and timing the ERP in a representative subject. Arrows and bars denote stimulus onset and the various components of the ERP. Interestingly, R2 amplitude increases significantly in this subject during 100 Hertz stimulation (the frequency threshold for tremor cessation), possibly because R2 overlaps or resonates with R3 from the previous stimulus pulse. The later peaks in the ERP (R2 and R3) are obscured by ongoing stimulation as the DBS frequency is increased above 100 Hertz. (**B**) Across all subjects, means plots demonstrate that R1 amplitude is altered by stimulation frequency ($p<0.0001$), and that tremor cessation occurs with increasing stimulation frequencies, most significantly at ≥100 Hertz ($p<0.0001$). (**C**) Grand averages of R1 peak amplitude across stimulation voltages (red) and frequencies (blue). DBS frequency was varied at the voltage required to suppress tremor during high frequency stimulation. R1 peak amplitude is multiplied by the number of pulses delivered per second, such that R1 is adjusted by stimulation rate prior to correlation with tremor suppression.

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Table 1

					Home DBS settings					Experimental DBS settings					
Subject	**Age (y)**	**Disease duration (y)**	**DBS duration (y)**	**Side**	**Anode/ Cathode**		**Voltage (Volts)**	**Pulse width (μsec)**	**Frequency (Hertz)**	**Anode / Cathode pair**		**Voltage threshold (Volts)**		**Pulse width (μsec)**	**Frequency (Hertz)**
										dorsal	**ventral**	**dorsal**	**ventral**		
1	67	20	9.8	R	2−,1−	3+	3.6	120	185	2−	1+	5.5	5.5	60	160
2	58	39	0.2	L	1−	Case+	4.0	60	160	1−	2+	6.5	6.5	60	160
3	55	38	1.8	L	3−	1+	4.1	90	185	0−	1+	3.5	3.5	60	160
4	51	4	1.4	L	0−	Case+	3.0	60	185	0−	1+	5.5	5.5	60	130
5	51	4	0.3	R	1−	3+	3.7	60	160	1−	2+	3.5	3.5	60	160
6	63	11	0.1	R	0−	3+	3.8	90	160	0−	1+	4.5	4.5	60	160
7	63	11	2.2	L	1−	Case+	2.8	90	160	2−	1+	2.5	2.5	60	160
Mean (SD)	58.3 (6.3)	18 (14.9)	2.3 (3.5)				3.6 (0.2)	81.4 (8.5)	171 (5.1)			4.5 (0.5)	4.5 (0.5)	60 (0)	155.7 (4.3)

Table 2

Subject number	Electrode contact pair used in protocol	Coordinates of electrode contacts relative to anterior commissure - posterior commisure midpoint (millimeters)		
		X	Y	Z
1	2	n/a	n/a	n/a
	1	n/a	n/a	n/a
2	2	−13.0	−4.4	5.1
	1	−12.6	−5.0	2.2
3	1	−14.6	−1.2	2.6
	0	−13.8	−2.3	−0.1
4	1	−14.1	−5.6	3.7
	0	−13.4	−6.2	0.9
5	2	14.4	−3.1	6.6
	1	13.6	−3.7	3.8
6	1	13.1	−3.5	1.3
	0	12.3	−4.4	−1.4
7	2	−14.0	−2.8	4.3
	1	−13.3	−3.6	1.5
	Mean (SEM)	**13.51*** (0.2)	**−3.8** (1.4)	**2.5** (2.3)