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Distinct perceptive pathways selected with tonic and bursting patterns of thalamic stimulation

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ABSTRACT

Background: Novel patterns of electrical stimulation of the brain and spinal cord hold tremendous promise to improve neuromodulation therapies for diverse disorders, including tremor and pain. To date, there are limited numbers of experimental studies in human subjects to help explain how stimulation patterns impact the clinical response, especially with deep brain stimulation.
We propose using novel stimulation patterns during electrical stimulation of somatosensory thalamus in awake deep brain stimulation surgeries and hypothesize that stimulation patterns will influence the sensory percept without moving the electrode.
Methods: In this study of 15 fully awake patients, the threshold of perception as well as perceptual characteristics were compared for tonic (trains of regularly-repeated pulses) and bursting stimulation patterns.
Results: In a majority of subjects, tonic and burst percepts were located in separate, non-overlapping body regions (i.e., face vs. hand) without moving the stimulating electrode ($p < 0.001$; binomial test). The qualitative features of burst percepts also differed from those of tonic-evoked percepts as burst patterns were less likely to evoke percepts described as tingling ($p = 0.013$; Fisher's exact test).
Conclusions: Because somatosensory thalamus is somatotopically organized, percept location can be related to anatomic thalamocortical pathways. Thus, stimulation pattern may provide a mechanism to select for different thalamocortical pathways. This added control could lead to improvements in neuromodulation - such as improved efficacy and side effect attenuation - and may also improve localization for sensory prostheses.

Introduction

Novel bursting patterns of electrical stimulation have demonstrated more effective pain relief in spinal cord stimulation and greater motor improvement during deep brain stimulation (DBS) for movement disorders than traditional tonic stimulation patterns (trains with regularly repeated pulses) [1–6]. DBS for movement disorders applies a tonic pattern with a frequency of 130–180 Hz, which has been found to best reduce symptoms for the average patient. Initial studies exploring temporally irregular (non-tonic) patterns failed to outperform tonic designs [7–11]. However, recent

Abbreviations: DBS, deep brain stimulation; Vc, Ventral caudal nucleus; VIM, ventral intermediate nucleus of the thalamus; MRI, magnetic resonance imaging; AC-PC, anterior commissure–posterior commissure; S.E.M., standard error of the mean.

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work has shown that temporally irregular patterns reduce tremor, bradykinesia, and power consumption as well as avoid thalamic adaptation [2–6]. Methods to generate these patterns include use of models to generate patterns with the optimal trade-off between beneficial features (e.g. low power) and unwanted symptoms (e.g. tremor) [4,5,12]. Additionally, others have shown that motor movement can be improved if bursts of pulses are coordinated across spatial macro-contacts (coordinated reset) or bursts are optimally timed to occur at specific time points of a patient's tremor [2–5]. Finally, cycled patterns have been shown to better resist thalamic adaptation than traditional tonic patterns [3]. Since previous modeling work suggests that pauses in DBS stimulation may permit brief pathological activity [10,11], additional experimental insights are greatly needed to help explain how bursting stimulation improves symptoms.

In this work, we explore tonic and bursting stimulation patterns in human somatosensory thalamus (ventral caudal nucleus; Vc), which is highly amenable to intraoperative study [13–15]. As opposed to the terminal effects of other DBS targets that can be challenging to quantify and measure in an intraoperative setting, the terminal effects of Vc stimulation are sensations, called percepts, that can be easily reported. All tactile information from the face and body converge in this compact structure before being relayed to the cortex, and Vc is somatotopically organized with face and upper-body relay neurons located medially and lower-body relay neurons located laterally, although individual variability can exist [14,16,17]. Thus, percept locations can be related to anatomic pathways via this somatotopy, and neurosurgeons routinely rely on this relationship for intraoperative localization [18,19]. While the percept quality from Vc stimulation has been well-studied [13,20,21], we aim to compare percept locations during electrical stimulation with bursting and tonic patterns to provide insight into the underlying anatomic pathways and networks involved.

Materials and Methods

Study design

Our study included 15 consecutive subjects undergoing awake DBS placement in the ventral intermediate nucleus of the thalamus (VIM) for essential tremor during a 17-month period who were able to complete awake intraoperative testing. Three subjects had previously undergone VIM DBS on the contralateral side. Two patients were excluded from analysis due to suboptimal initial lead placement with inability to complete intraoperative experiments. The remaining 15 subjects included 13 males and 2 females, with ages ranging 37–82 years and a mean age of 67 years. The predominance of men is consistent with the known prevalence of males with essential tremor [22]. The study was approved by the Institutional Review Board of the University of Michigan. All participants signed written informed consent.

Twenty-seven anatomical sites, i.e. locations in the brain where macrostimulation was performed, were included if the location was estimated to be in sensory thalamus and subjects were able to feel sensations from thalamic stimulation. No sites were discarded (although one site could not be included because of audio recording failure) and research testing was stopped when intraoperative constraints dictated that we resume the clinical procedure. The subjects were blinded to the stimulation patterns.

Stimulation apparatus

Stimulation was performed using an intraoperative neural targeting system, as previously described [23], schematically illustrated in Fig. 1a. LabVIEW software (National Instruments, Austin, TX) was programmed on a Dell T5500 computer (Dell Inc., Round Rock, TX) and interfaced with a commercial intraoperative electrophysiology system (Neuro Omega™, Alpha Omega, Nazareth, Israel). The Neuro Omega™ applies current-controlled stimulation with an output sampling rate of 44 kHz. Stimulation pattern, stimulation amplitude, and stimulation electrodes were selected with the custom LabVIEW software, which was interfaced with the Neuro Omega™ via the Alpha Omega Software Development Kit. Stimulation was applied through the macro-contact of the Neuroprobe microelectrodes (STR-009080-10, Alpha Omega), with a macro-contact length of 1 mm, diameter of 0.56 mm, and 250–1250 kΩ impedance at 1 kHz [24].

Stimulation parameters

Stimulation patterns were created offline in MATLAB (MathWorks, Natick, MA) and loaded into the LabVIEW software. The pulse shape for all stimulation patterns were identical (Fig. 1b) and consisted of a one period, 400-μs sine wave with a 200-μs positive phase immediately followed by a 200-μs negative phase to maintain charge balance [25–27]. The individual sinusoidal pulses were separated by the appropriate interpulse interval to achieve the desired pulse frequency (e.g. 12.5 ms for 80 Hz). Pulse width and stimulation amplitude were selected to remain within 30 $\mu C/cm^2$ per phase charge density safety limits [25], while recruiting a maximal volume of thalamocortical neurons. In offline experiments, the output from the Neuro Omega™ was visually inspected on an oscilloscope to verify that the pulse morphology was sinusoidal as expected. The pulse rate for tonic stimulation was 80 Hz that is similar to the 60-Hz stimulation frequency used in many earlier studies to map Vc [28] but increased slightly to avoid 60-Hz noise.

Parameters for bursting stimulation include intraburst pulse rate, burst duration, and burst repetition interval. For consistency, we used an intraburst pulse rate of 80 Hz, equal to that of tonic stimulation. Burst duration and burst repetition intervals were empirically determined in Subject 1. Burst durations of around 62.5 ms and rest duration of 125 ms were perceived by Patient 1 as qualitatively different from the other combinations of burst/rest durations. For the remaining 14 patients we continued to use this pattern with a burst of 5 pulses repeated every 187.5 ms (Fig. 1b, bottom) given that the percepts were consistently distinct from tonic patterns. We refer to this pattern as a "bursting" because it is similar to the activity of thalamic relay cells that can burst with intra-burst frequencies around 50–70 Hz [29]. However, this "bursting" nomenclature is different than the bursting patterns in the spinal cord literature, where intra-burst frequencies are typically on the order of 500 Hz [1].

In a subset of 5 patients, low-frequency tonic patterns were created with the same stimulation amplitude and average number of pulses as the bursting patterns above. These patterns were similar to the tonic pattern in Fig. 1b except with a frequency of 27 Hz. In the final patient, a 30-Hz tonic pattern was compared with an 80 Hz-bursting pattern of 60 ms duration and repetition interval of 100 ms.

The 80-Hz tonic and bursting patterns were compared at the threshold of perception—the minimum amplitude needed to perceive electrical stimulation. Amplitudes greater than this are less likely to be perceived as naturalistic [21]. The amplitude used for the low-frequency tonic pattern was equal to the threshold of perception of the bursting pattern so that a charge-matched comparison could be made.

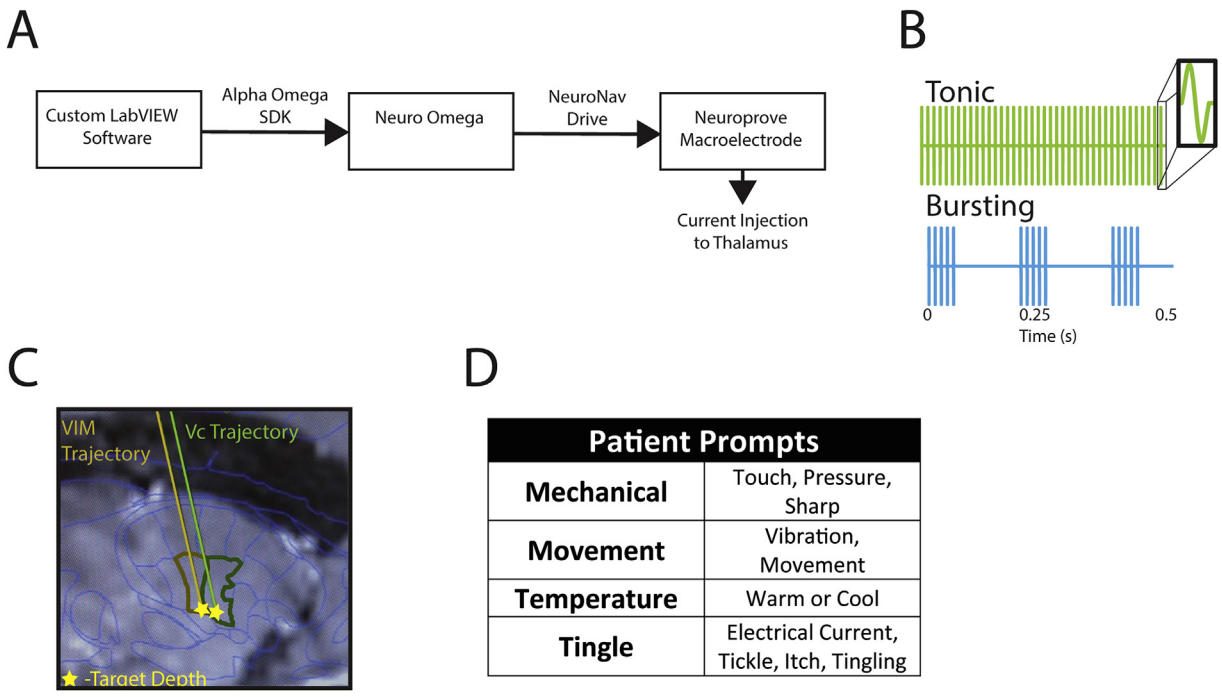


Fig. 1. System and experimental setup. (**a**) Customized LabVIEW software inputs into Neuro Omega that drives macroelectrode to provide electrical stimulation to brain tissue. (**b**) Depiction of 0.5-s segment of tonic (green) and bursting (blue) patterns. All pulses are identical and pictured to scale in the cutout window. (**c**) Preoperative MRI as shown on StealthStation during preoperative planning. The yellow line is the planned ventral intermediate nucleus of the thalamus (VIM) trajectory that ends in the star. The star is the estimated final position of the to-be-implanted permanent deep brain stimulation lead. The green trajectory represents a parallel trajectory 2 mm posterior to the VIM trajectory that passes through the somatosensory nucleus of the thalamus (Vc). The star at the tip of this trajectory signifies the same depth on this trajectory as the star on the VIM trajectory. (**d**) Table shown to subjects prior to the experiment to provide a list of potential responses. Patients were verbally counselled that they could choose words not on this list. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Thalamic localization

Preoperative 3T cranial magnetic resonance imaging (MRI) of all patients was obtained before DBS lead placement and co-registered to MR imaging obtained on the day of surgery after Leksell stereotactic frame (Elekta AB, Stockholm, Sweden) placement. Computed tomography (CT) imaging was substituted for 3 patients with existing DBS systems, which are incompatible with 3T MRI. Images were co-registered using commercial software (Analyze, AnalyzeDirect, Inc., Overland Park, KS) and uploaded into commercial frame-based targeting software (Framelink, Medtronic, Minneapolis, MN).

Atlas-based VIM targeting was performed. The initial ventrocaudal VIM target was assigned as 11.5 mm lateral to the wall of the third ventricle and 5 mm anterior to the posterior commissure in the intercommissural plane. A cranial entry point was selected at the coronal suture, approximately 2.5 cm lateral to midline. The entry point to VIM target defined the "VIM trajectory" (Fig. 1c).

To verify hand localization within VIM, a second "Vc trajectory" was assigned parallel and 2 mm posterior to the VIM trajectory. The point of transition from the VIM to the Vc nucleus along the Vc trajectory was estimated using the Schaltenbrand-Wahren atlas built into the Framelink software [30]. Typically, the last 3 mm of the posterior trajectory localized to Vc (Fig. 1c). For notational purposes, all depths are reported relative to target depth: a depth of 3 mm is 3 mm above target and a depth of −3 mm is 3 mm below target depth (Fig. 1c).

Testing protocol

During the operative procedure, the stimulating microelectrodes were advanced through VIM and Vc. Patient responses to stimulation and stimulation parameters were recorded simultaneously using a high-definition video camera and a wireless microphone. Tonic stimulation through the macro-contact on the microelectrode was utilized to verify VIM localization and somatotopy, according to standard operative practices. Sites were excluded from the analysis if no percept was elicited by either tonic or burst stimulation or if the reported tonic percept was non-physiological (e.g., bilateral headache, ipsilateral percepts). One site could not be included in the analysis because of audio recording failure. In total, twenty-seven sites within Vc were analyzed. The number of test sites for each subject was limited by the available time for testing. The subjects were blinded to the stimulation patterns.

The first objective in testing a stimulation pattern was to determine the threshold amplitude of perception. To prevent thalamic adaptation, the initial amplitude was set to either 0.1 or 0.2 mA and incrementally increased until a percept was reported. Also to minimize thalamic adaptation [31], stimulation was limited to either 4 s or the minimum time needed for a subject to report a percept. If the initial stimulation amplitude was perceived, stimulation was immediately halted and the amplitude was lowered to the threshold of stimulation.

We determined and recorded the stimulation amplitude at the threshold for stable percepts for tonic and bursting patterns (i.e., the threshold of perception). As the patterns were charge balanced, we assigned the charge per pulse as the area under a half sine wave period multiplied by the threshold of perception. The total charge per second was reported as the charge per pulse multiplied by the average number of pulses per second. The threshold for perception for the burst pattern in Subject 13 was not explicitly determined, and this site was excluded from the amplitude and charge analysis at the threshold of perception (in Fig. 4).

At each site in the first 6 subjects, subjects were asked if the stimulation was perceived ("Do you feel anything now?"). Patients usually proceeded to describe where the percept was located and the sensory quality. If the subject did not report location and quality, the experimenter would ask for location ("Where do you feel it?") and quality ("What does it feel like?"). During the first few trials, subjects were shown the table in Fig. 1d as a list of potential responses, which is a slight modification of the table used to assess sensory quality by Ohara et al. [32].

When time allowed, and simulation pattern differences produced percepts at different locations or with different qualities, stimulation patterns were either alternated or randomly varied. Stimulation lineups, when varied at a given site, are reported in the Results section.

Statistical analysis

We used a one-way binomial test to exclude the null hypothesis that percept location changes by chance and does not depend on stimulation pattern. This test requires a probability, p, that the location will change by chance even though the stimulation pattern does not change. From experience, we know that this probability is low because bursting and high-frequency tonic patterns were stable in 31/32 trials (see Results). Thus, we conservatively overestimate p as 0.1 for the binomial test.

To evaluate whether bursting patterns were less likely to "tingle" than tonic counterparts, we used Fisher's exact test to compare the number of non-tingling sites between tonic and burst percepts. Statistical significance was assessed with a 2-sided, 2-sample t-test when comparing: the amplitude between tonic and bursting patterns at the perception threshold, the amplitude between sites with similar vs. disparate percepts, and the depth of stimulation sites with similar vs. disparate percepts. The relationship between burst/tonic percept locations and whether the final implanted lead required adjustments was evaluated with a Fisher's exact test. The number of low-frequency tonic and bursting trials with percepts located near high-frequency tonic percepts were compared with Fisher's exact test. A statistical significance level of 0.05 was used.

Results

Our analysis includes fully awake and unanesthetized patients who underwent stimulation of the somatosensory (Vc) thalamus during DBS surgery for essential tremor. For each patient, stimulation with tonic and bursting patterns were tested within Vc. Testing was performed at a total of 27 sites in 15 patients. The amplitude of stimulation was set to the threshold of perception, which is the lowest amplitude at which subjects reported a percept.

Stimulation pattern controls percept location

While 14/27 sites of stimulation had similar location percepts for both bursting and tonic waveforms, in 13/27 sites (in 8/15 subjects tested), 80 Hz tonic and bursting percepts (in Fig. 1b) were perceived in distinct, non-overlapping locations, specifically hand versus face. The difference in 13 sites was statistically significant ($p < 0.001$; binomial test). Fig. 2a graphically illustrates typical results for the first 6 subjects, and a table of results for all subjects is shown in Fig. 2b. Tonic percepts arose in the hand/arm in a majority of sites (19/27) as expected since the hand region of VIM is targeted for DBS. Tonic percepts localized to the face/head in 6 sites, and arose in both hand and face regions at 2 sites. Bursting percepts occurred in the head/face region in 17/27 sites, occurred in the hand/arm in 7 sites and arose in both areas at 3 sites. Even among stimulation sites where tonic and burst percepts were located in close proximity, small differences in location often existed, e.g., cheek versus lip in Subject 2 and 2nd/3rd fingers versus thumb in Subject 10.

Percept size and location were assessed through detailed, recorded subject descriptions. Spontaneous patient terminology was clearly non-overlapping. Patients 4, 6 and 10–14 all reported tonic percepts in the hand (e.g. "thumb" or "fingers"), whereas bursting percepts were in the face (e.g., "jaw," "neck," "lip," "side of [the] face," and "mouth [or] throat"). Tonic percepts were located in the face for Patients 1 and 3 (mouth, tongue, lips or cheek) with bursting percepts in the fingers and arm. Patient 1, with bursting percepts in the fingers, denied any facial component. Patients uniformly denied overlap between tonic and bursting percepts when asked explicitly. Patients 4, 6, 10, 11, and 14 denied bursting percepts located in the hand, where tonic percepts were located. Patients 10 and 14 also denied tonic percepts where bursting percepts arose. Finally, and similar to macrostimulation results from Heming et al. [20], percepts for each pattern were mostly of "medium" size since they typically covered parts of limbs or multiple fingers, although more focal percepts were also reported.

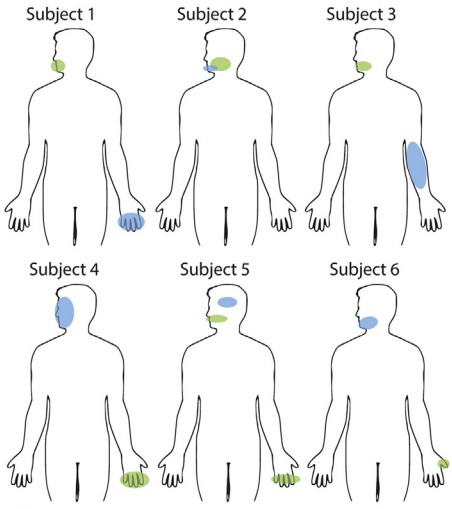
Percept location as a function of tonic versus bursting stimulation pattern remained stable even when stimulation patterns were repeated or alternated (Fig. 2c). Stimulation trials were repeated in all 8 subjects where bursting and tonic percept locations differed, and 31/32 stimulation trials remained stable with hand percepts remaining in the hand and face percepts remaining in the face. The only discrepancy was in the first site of Subject 14 where the burst percept was originally in the face but transitioned to the hand when the stimulation was repeated a few minutes later. Additionally, in 4 subjects (5 sites), tonic and burst patterns were alternated a total of 15 times, and the location remained stable.

Percept locations affected by the temporal distribution of pulses

Bursting and 80-Hz tonic patterns have three important differences: the temporal distribution of pulses, the average number of pulses in time, and the amplitude at the threshold of perception. To determine whether percept location differences were caused by the temporal distribution of pulses (and not one of the other differences between bursting and tonic patterns), we created low-frequency (27 or 30 Hz) controls with the same number of pulses and amplitude as the bursting patterns. *These patterns differed only in the temporal distribution of pulses.* These patterns were compared in 6 sites (in 5 subjects) where bursting produced percepts in the face and 80-Hz-tonic produced percepts in the hand. As illustrated in Fig. 3a and b, the burst percepts (blue data points) were located in the head at all 6 sites. However, low frequency tonic patterns (magenta data points) produced percepts in the hand – like 80-Hz tonic patterns – at 4/6 sites. However, at sites 3 and 6, the percept location was not stable and occasionally generated face percepts like the bursting patterns. This instability led to the proportion of head or face percepts being less than 1. For completeness, Fig. 3c depicts the number of stimulation trials conducted for each stimulation pattern at each site. Across all trials, low-frequency tonic percepts were statistically different ($p < 0.001$; Fisher's exact test) than bursting patterns and produced hand percepts in 12 trials (similar to 80-Hz tonic), head percepts in 10 trials (like bursting), and percepts in both head and hand in 1 trial (see Fig. 3a–c).

As an illustrative example in Subject 3, bursting and 27-Hz-tonic stimulation patterns were compared at a constant amplitude of 1.2 mA (Fig. 3d and e). The 27-Hz tonic waveform produced hand percepts (similar to the 0.5 mA, 80-Hz tonic percepts), while the bursting stimulation produced percepts in the jaw/neck region. Six trials randomly alternating between 27-Hz tonic and bursting

A



B

Pt.	Depth (mm)	Location		Res. - Imp. Lead (mm)
		Tonic	Bursting	
1	3.0	mouth, tongue, lips	fingers	(0,-2, 0)
2	3.0	cheek	bottom lip	(0,-2, 0)
3	2.5	lip and cheek	lip, cheek	(0,-2, 0)
	2.0	lip	arm	(0,-2, 0)
4	3.6	hand	face	(0,-2, 0)
	2.6	fingers	face	(0,-2, 0)
	1.6	hand	face	(0,-2, 0)
	0.6	fingers	hand	(0,-2, 0)
	-0.4	hand	face	(0,-2, 0)
5	3.0	teeth, hands	middle of head	**(-2,-2, 0)***
	1.5	teeth, hands	face	(0,-2, 0)
	0.0	fingertips	mouth and hand	(0,-2, 0)
6	1.0	thumb	jaw	(0,-2, 0)
	-0.1	thumb	face, head	(0,-2, 0)
7	0.0	mouth	mouth	**(-2, 0, 0)**
8	1.0	fingers to wrist	palm, wrist	**(-2,-2, 0)**
	0.0	fingers to wrist	hand	**(-2,-2, 0)**
9	1.0	side of head	jaw	**(+2,-2, 0)****
	0.0	side of face	face	**(+2,-2, 0)****
10	2.0	2nd, 3rd digits but not thumb	thumb	(0,-2, 0)
	0.0	hand	face	(0,-2, 0)
11	2.0	3rd, 4th fingers	face	**(-2,-2, 0)**
12	3.5	fingers	lip	**(+4,-2, 0)**
13	3.0	hand	jaw	**(-2,-2, 0)**
14	-0.2	fingers, wrist	mouth	**(+2,-3, 0)**
	3.0	fingers	hand, face	**(+2,-3, 0)**
15	0.0	arm	hand, arm	**(0,-4, 0)**

C

Trial #	Pattern	Percept Location
1	Tonic 80 Hz	thumb
2	Tonic 80 Hz	thumb
3	Burst	jaw
4	Burst	jaw
5	Tonic 80 Hz	thumb
6	Burst	jaw

Fig. 2. Stimulation pattern controls percept location. (**a**) A body map for the first six subjects that represents the disparate percepts between tonic (green) and bursting (blue) stimulation. All percepts for the hand and face were ipsilateral to each other, contralateral to the stimulation lead, and illustrated on the left side of the body map for illustration purposes. (**b**) Table shows percept location for tonic and burst stimuli at each site tested. Sites where percept locations are widely disparate are highlighted in yellow. Research minus implanted lead (Res. − Imp. Lead) denotes the (x, y, z) position of the research lead subtracted by the final implanted lead position. Without any adjustments to the final lead, the research lead would be 2 mm behind the implanted lead, i.e. (0, −2, 0) mm. Testing sites that differed from this planned relationship are denoted in bold font. A positive value for $\Delta x > 0$ indicates a research lead position lateral to the implanted lead position. The * denotes that the lead surgeon (P.G.P.) asked to move to a more lateral trajectory given the head percepts. The ** denotes that testing was performed on a trajectory 2 mm lateral to the intended trajectory because no percepts occurred at the original trajectory (**c**) Table displays an illustrative example site for subject 6 where stimulations were randomized at a single site, and a stable difference in the location of tonic and burst percepts was demonstrated. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

patterns in Fig. 3b demonstrated stable, non-overlapping percepts in all 6 attempts. Thus, the *irregular distribution of pulses,* independent of *amplitude* and *number of pulses*, led to differences in percept location.

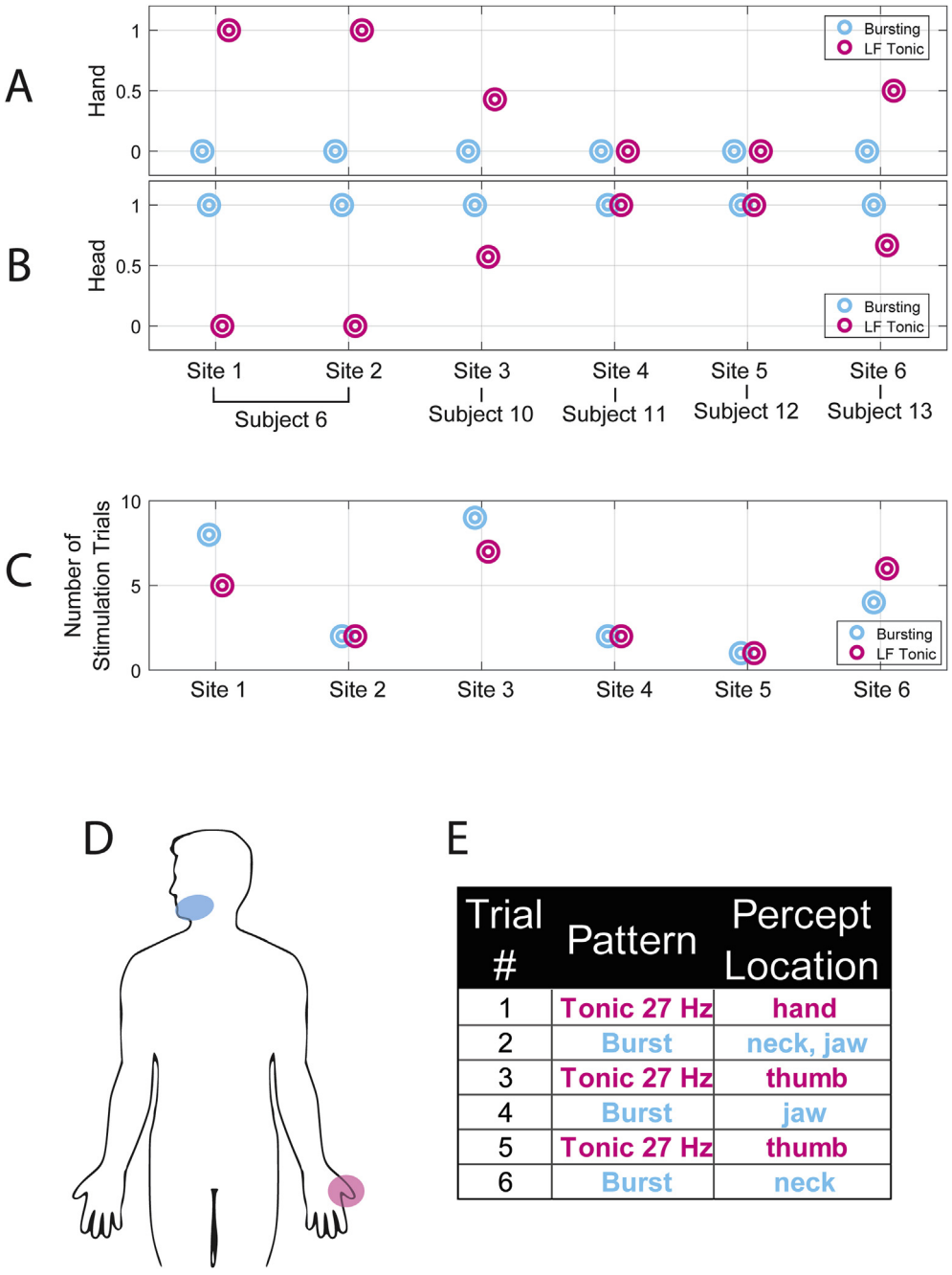
Differences in amplitude, charge, and site location

The perception threshold was lower for high-frequency tonic patterns compared to bursting patterns at all sites ($p < 0.001$; *t*-test). The perception threshold was 0.50 ± 0.09 mA (mean ± S.E.M.) for tonic patterns and 1.17 ± 0.11 mA for bursting patterns. In the subset of sites where tonic and burst percepts were nearby, the mean amplitude of tonic patterns, 0.64 ± 0.14 mA, was lower than the mean amplitude of burst patterns, 1.34 ± 0.13 mA ($p < 0.001$; *t*-test). In the subset of sites where tonic and burst percepts were located in disparate body areas, the mean amplitude of tonic patterns, 0.33 ± 0.07 mA, was lower than the mean amplitude of burst patterns, 0.97 ± 0.18 mA ($p < 0.001$; *t*-test) as shown in Fig. 4a, left pane.

To understand whether perception thresholds differed between sites with nearby versus disparate tonic and burst percepts, the perception thresholds were compared, see Fig. 4b, middle pane. Combining the amplitude at perception for both stimulation patterns revealed decreased amplitudes at sites with disparate tonic versus burst percepts relative to sites with similarly located percepts ($p = 0.039$; *t*-test).

The mean charge injected between tonic and bursting patterns, however, was not statistically different at all sites ($p = 0.26$; *t*-test), sites with similarly located percepts ($p = 0.19$; *t*-test), or sites with disparately located percepts ($p = 0.995$; *t*-test). The mean charge injected for the tonic pattern at threshold was 4.7 ± 0.8 μC/s for all sites, 6.0 ± 1.4 μC/s at sites with percepts near burst percepts, and 3.0 ± 0.7 μC/s at sites with percepts disparate from burst percepts. The mean charge injected for the bursting pattern at threshold was 3.7 ± 0.3 μC/s for all sites, 4.2 ± 0.4 μC/s at sites with percepts near tonic percepts, and 3.0 ± 0.6 μC/s at sites with percepts disparate from tonic percepts (Fig. 4c, right pane).

Similarly, there were no statistically significant differences in depth between sites with tonic and burst percepts located nearby and in disparate locations ($p = 0.55$; *t*-test). The mean depth when percepts were similarly located was 1.2 ± 0.3 mm. A positive value indicates the distance superficial to target (described in Materials



Trial #	Pattern	Percept Location
1	Tonic 27 Hz	hand
2	Burst	neck, jaw
3	Tonic 27 Hz	thumb
4	Burst	jaw
5	Tonic 27 Hz	thumb
6	Burst	neck

Fig. 3. Controlled experiment of percept location using tonic and burst stimuli in five subjects. Six sites showing the proportion of low-frequency tonic (magenta) and bursting (blue) patterns that generated percepts in the head (**a**) and in the hand (**b**). LF tonic denotes low frequency tonic patterns. (**c**) Number of stimulation trials at each site for low-frequency tonic (magenta) and bursting (blue) patterns. (**d**) A body map for Subject 6 illustrates focal percepts for low-frequency, 27-Hz tonic (magenta) stimuli compared to an anatomically distant bursting percept in the face (blue). (**e**) For the same site as (**d**), Table reports randomized stimulation trials showing the difference in low-frequency tonic and bursting patterns that are controlled for amplitude and number of spikes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and Methods). The mean depth when percepts were disparate was 1.7 ± 0.5 mm. There were also no statistically significant differences among the number of sites with similarly located versus disparately located percepts that required adjustment of the final lead position ($p = 0.44$; Fisher's exact test).

Less tingling from bursting stimulation

For completeness, in the first 6 subjects, we asked subjects to describe the quality of percepts. This was not continued in the remaining 9 subjects due to intraoperative time constraints. Bursting percepts were less frequently described by subjects as "tingling" than tonic percepts ($p = 0.013$; Fisher's exact test). At 8 of 14 sites where percept quality differed, tonic percepts were

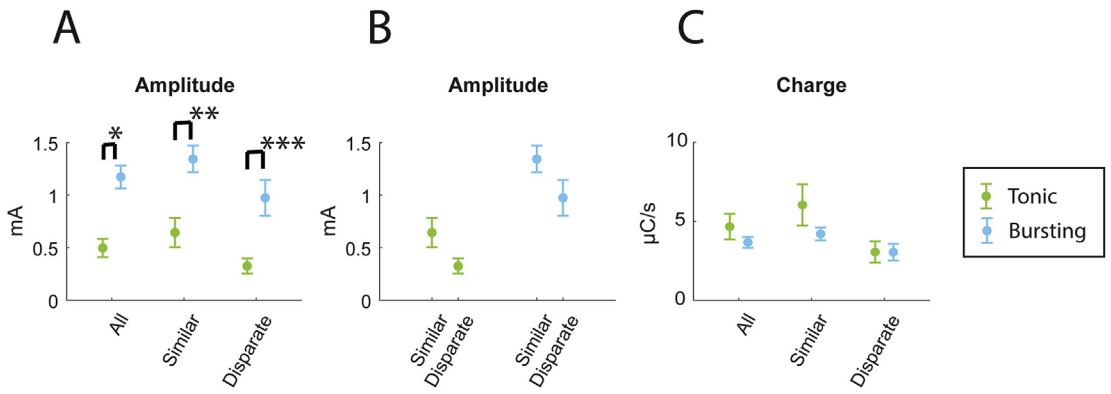


Fig. 4. Differences in amplitude and charge at the perception threshold. Amplitude differences in (**a**) demonstrate differences in tonic (green) and bursting (blue) amplitudes (in mA) at all sites (n = 26), at sites where percept locations are similar ("Similar; " n = 14), and at sites where percept locations are in disparate body regions ("Disparate; " n = 12). The asterisks represent statistical significance. Regrouping the tonic and bursting amplitudes together in (**b**) highlights the differences in similar and disparate sites. In (**c**), the different charge injected at the threshold of perception is depicted at all sites, those with similarly located percepts, and those with disparate percepts. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tingling in all cases, whereas bursting percepts were sometimes non-tingling. In particular, bursting patterns produced non-tingling percepts in 9/14 sites and in 5/6 subjects tested. On the other hand, tonic percepts were tingling in all but one site (see Fig. 5a). Bursting stimulation elicited a variety of non-tingling qualities, including pressure, sharpness, vertigo, and vibration, as depicted in Fig. 5b. Of note, in Subject 5, bursting percepts were similar to pressure, but on repeated stimulation the subject reported either pressure or tingling. Fig. 5c illustrates an example where bursting and tonic patterns were randomly alternated to give non-tingling bursting percepts and tingling tonic percepts.

Discussion

In this work, we found that bursting and tonic stimulation often activate distinct, non-overlapping perceptive pathways. Even though burst percepts required higher stimulation amplitudes to be perceived, the percept was not located near tonic percepts, and instead generated a percept in a unique, non-overlapping location. *Importantly, bursting patterns evoked percepts in different locations than tonic patterns with the same average pulse rate and same amplitude.* Hence, in many sites tested, the temporally irregular distribution of pulses provided control of percept location that was independent of stimulation amplitude or average pulse rate. In addition to the above findings, we also found that: (1) bursting percepts required increased amplitude but similar charge as percepts generated from tonic patterns, (2) the perception threshold was lower at sites with different tonic/burst percept locations than similar locations, and (3) tonic and bursting patterns elicited different perceptual qualities.

Activation of distinct thalamocortical networks through patterned stimulation

A similar phenomenon was reported by Kiss et al. in 2/19 sites near Vc using waveforms with different pulse-widths [33]. This difference was attributed to differential activation of local cells and axons of passage [33,34]. Kiss et al. state that, in a site presumed to be below Vc and in medial lemniscus, auditory sensations were produced using a 5-ms pulse width and the quality changed to tingling using a 500-μs pulse width. In the second site, hemibody pain at 5-ms pulse width transitioned to hand coolness at 3 ms and hand/leg tingling at 1 ms. Kiss et al. [33] proposed that local cells were activated through activation of the soma with high-pulse-width waveforms and not low-pulse-width waveforms. However, because extracellular stimulation of local cells initiates action potentials at the initial segment or at one of the nodes of Ranvier, this observation is likely due to relative differences in the electrode position with respect to the soma [34,35].

As opposed to varying the pulse width, we varied pulse density using either bursting or low-frequency stimulation patterns. When doing so, high-frequency tonic versus bursting percepts were produced in different and non-overlapping anatomical regions in roughly half of sites/subjects. Anatomically-distinct percepts could arise if distinct neural populations were activated with different stimulation patterns. Several groups have shown through computational models that stimulation patterns could potentially select different populations of neurons with neural elements that pass near the electrode [36–38]. McIntyre and Grill showed that high-frequency stimulation may more efficiently activate axons of passage (because the pulse arrives at a time of *increased* axonal excitability within a depolarizing afterpotential) and less efficiently activate local cells (because the pulse arrives at a time of *decreased* axonal excitability within a hyperpolarizing afterpotential) [36]. Yi and Grill also reported that local cells are less excitable with high-frequency stimulation compared to low frequency stimulation when the soma was closer to the electrode than the axon [37]. While further studies are needed to establish exact mechanisms, these studies provide insight into how distinct subpopulations of neurons (i.e. "hand" neurons versus "face" neurons) can be selectively activated to produce distinct percepts.

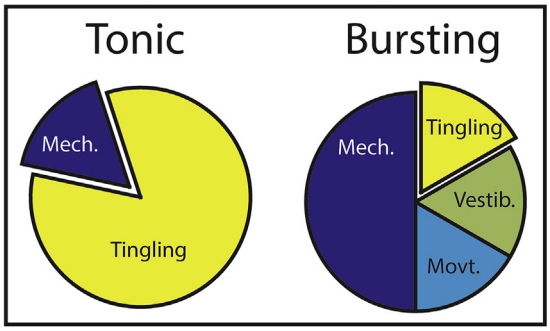
Given that various modalities of somatosensory stimuli evoke bursting in Vc [39], burst and tonic percept locations may be encoded differently in thalamocortical relay cells and interpreted differently by downstream cortical mechanisms [40–42]. Some have hypothesized that naturally occurring thalamic spiking modes, bursting and tonic, select for different thalamocortical pathways [41]. Iremoner et al. show that electrical stimulation of thalamic afferents of motor cortex neurons at high frequencies does not produce action potentials in motor cortex while low frequency stimulation reliably produces action potentials in cortical neurons [40]. Finally, cortical centers may process sensory information differently when action potentials are quantized in bursts (or packets) as opposed to those repeated at constant time intervals [42].

A

Pt.	Depth (mm)	Percept Quality	
		Tonic	Bursting
1	3.0	tingling	sharp
2	3.0	pressure	pulsed pressure
3	2.5	tingling	vibration
	2.0	tingling	shaking
4	3.6	tingling	vertigo
	2.6	tingling	vertigo
	1.6	tingling	vertigo
	0.6	tingling	tingling
	-0.4	tingling	vertigo
5	3.0	tingling	electric current
	1.5*	tingling	pressure
	0.0*	pins/needles	electric current
6	1.0	tingling	tingling
	-0.1	electric curent	tingling

*Lead moved 2 mm lateral

B



C

Patient 3

Trial #	Pattern	Percept Location
1	burst	vibration
2	tonic	tingling
3	burst	vibration
4	burst	vibration
5	tonic	tingling
6	tonic	tingling

Fig. 5. Tonic and burst stimuli affect percept quality. (**a**) The table lists percept quality evoked at all of the sites tested. The sites producing sensations of tingling, pins/needles, or electric current are highlighted in red. (**b**) Two pie charts representing the sensation quality for the least artificial percept quality in each subject. The purpose is to illustrate that percept differences existed in most patients. Specifically, 1/6 of the pie is assigned to each subject. If a non-tingling percept is produced by electrical stimulation, that subject's slice is assigned to that percept quality; otherwise, the slice is designated as tingling. Mech., Mechanical; Vestib., Vestibular; Movt., Movement. (**c**) Table is an example of percept stability in Subject 3 when switching between stimulation patterns. Artificial percept qualities are highlighted in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Anatomical location of stimulation sites

Not all stimulation sites produced pattern-dependent percepts. To gain insight into the location of sites, we did note a small but significant lower current threshold when anatomical areas were disparate. Sites of somatosensory thalamus with relatively lower amplitudes of perception have been found to occur in sites densely populated with neural elements [28,43]. Tasker et al. have shown especially low thresholds (0.1–0.5 mA; using 60-Hz, 3-ms pulses) at the medial-ventral base of Vc where medial lemniscus fibers enter [28]. Lenz et al. (with the same stimulation parameters) showed a lower threshold at sites in Vc where the receptive fields of numerous neurons overlapped suggesting a site densely populated with neural elements [43]. Given that face and hand somatotopic centers of Vc are in close proximity [44], a potentially unifying explanation for the data herein is that sites where patterned stimulation produces disparate hand and face percepts occur at the border of hand/face centers and are densely populated with neural elements, such as at the base of Vc. Specifically, burst patterns activate local face neurons, and tonic patterns activate either medial lemniscus fibers traveling to hand neurons or thalamocortical cell axons after leaving hand neurons.

Potential for clinical application

Herein bursting patterns are shown to select for distinct perceptive locations that may correspond to activating different subpopulations of thalamocortical-relay neurons. To this end, bursting patterns and multi-contact hardware designs may be combined so that a single DBS lead activates a high number of different neuron groups [21,45]. Additionally, since bursting patterns activate different neuronal populations than tonic stimulation, bursting patterns could be more effective than tonic patterns in stimulation of Vc for neuropathic pain [18,19], although further studies are needed. Finally, selective activation of the desired neuron group may lead to fewer side-effects if unwanted neurons are not activated.

Peripheral nerve stimulation with temporally irregular patterns (pulse-width modulation) was used for a sensory prosthesis by Tan et al. to restore naturalistic perception [46]. Patterned stimulation also demonstrated more tolerable paresthesias in spinal cord stimulation [47] and could also be attempted in spinal cord stimulation to restore somatosensation [48]. Previous reports using patterned thalamic stimulation to affect percept quality are mixed as Heming et al. found tonic patterns more naturalistic than temporally-irregular patterns and Swan et al. found patterns with up-ramping pulse rates were "slightly more" naturalistic than other tonic patterns [20,21]. In this work, bursting patterns achieved a higher number of non-tingling percepts (9/14) and increased percept variety compared to tonic stimulation that produced artificial paresthesias in all but one site. However, since these patterns may activate different groups of neurons, the difference in percept quality may be mediated in large part by the difference in the activated neuron groups and not necessarily because the patterns themselves are being interpreted differently by downstream cortical centers. These mechanisms await further study. Additionally, even though the bursting percepts from thalamic macrostimulation were not endorsed as naturalistic, more naturalistic percepts may be achieved with similar temporally-irregular designs.

Conclusions

Temporally patterned stimulation shows tremendous promise in advancing the field of neuromodulation, and tuning patterns of stimulation for specific patients and applications may lead to improvements in chronic pain therapies, intraoperative localization, avoidance of side-effects, and sensory prostheses. However, a paucity of studies exists exploring patterned stimulation in Vc where the terminal effect of stimulation pattern can be readily observed. Herein, we showed that patterned stimulation selects for distinct perceptive networks, and likely distinct thalamocortical networks. This specificity for distinct networks provides insight into the underlying mechanisms of temporally irregular patterns and may allow selective activation of optimal neuronal targets.

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Data and materials availability

All data associated with this study are available in the main text.

CRediT authorship contribution statement

Matthew S. Willsey: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Charles W Lu:** Methodology, Software, Investigation, Formal analysis, Writing - review & editing. **Sam R. Nason:** Investigation, Validation, Writing - review & editing. **Karlo A. Malaga:** Formal analysis, Validation, Writing - review & editing. **Scott F. Lempka:** Validation, Supervision, Writing - review & editing. **Cynthia A. Chestek:** Conceptualization, Supervision, Writing - review & editing. **Parag G. Patil:** Conceptualization, Investigation, Supervision, Writing - review & editing, Resources, Funding acquisition.

Declaration of competing interest

There are no competing interests.

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References

[1] Deer T, Slavin KV, Amirdelfan K, North RB, Burton AW, Yearwood TL, et al. Success using neuromodulation with BURST (SUNBURST) study: results from a prospective, randomized controlled trial using a novel burst waveform. Neuromodulation: Technol Neural Interface 2018;21(1):56–66.
[2] Adamchic I, Hauptmann C, Barnikol UB, Pawelczyk N, Popovych O, Barnikol TT, et al. Coordinated reset neuromodulation for Parkinson's disease: proof-of-concept study. Mov Disord 2014;29(13):1679–84.
[3] Heming EA, Choo R, Davies JN, Kiss ZH. Designing a thalamic somatosensory neural prosthesis: consistency and persistence of percepts evoked by electrical stimulation. IEEE Trans Neural Syst Rehabil Eng 2011;19(5):477–82.
[4] Brocker DT, Swan BD, Turner DA, Gross RE, Tatter SB, Koop MM, et al. Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease. Exp Neurol 2013;239:60–7.
[5] Brocker DT, Swan BD, So RQ, Turner DA, Gross RE, Grill WM. Optimized temporal pattern of brain stimulation designed by computational evolution. Sci Transl Med 2017;9(371):eaah3532.
[6] Cagnan H, Pedrosa D, Little S, Pogosyan A, Cheeran B, Aziz T, et al. Stimulating at the right time: phase-specific deep brain stimulation. Brain 2016;140(1):132–45.
[7] Dorval AD, Kuncel AM, Birdno MJ, Turner DA, Grill WM. Deep brain stimulation alleviates parkinsonian bradykinesia by regularizing pallidal activity. J Neurophysiol 2010;104(2):911–21.
[8] Montgomery Jr EB. Effect of subthalamic nucleus stimulation patterns on motor performance in Parkinson's disease. Park Relat Disord 2005;11(3):167–71.
[9] Montgomery JE, Baker KB. Mechanisms of deep brain stimulation and future technical developments. Neurol Res 2000;22(3):259–66.
[10] Swan BD, Brocker DT, Hilliard JD, Tatter SB, Gross RE, Turner DA, et al. Short pauses in thalamic deep brain stimulation promote tremor and neuronal bursting. Clin Neurophysiol 2016;127(2):1551–9.
[11] Birdno MJ, Kuncel AM, Dorval AD, Turner DA, Gross RE, Grill WM. Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation. J Neurophysiol 2011;107(1):364–83.
[12] Grill WM. Temporal pattern of electrical stimulation is a new dimension of therapeutic innovation. Curr Opin Biomed Eng 2018;8:1–6.
[13] Tasker RR, Organ LW, Hawrylyshyn PA. The thalamus and midbrain of man: a physiological atlas using electrical stimulation. Charles C. Thomas Publisher; 1982.
[14] Chien JH, Korzeniewska A, Colloca L, Campbell C, Dougherty P, Lenz F. Human thalamic somatosensory nucleus (ventral caudal, Vc) as a locus for stimulation by INPUTS from tactile, noxious and thermal sensors on an active prosthesis. Sensors 2017;17(6).
[15] Dostrovsky JO, Davis KD, Lee L, Sher GD, Tasker R. Electrical stimulation-induced effects in the human thalamus. Adv Neurol 1993;63:219–29.
[16] Mountcastle VB, Henneman E. The representation of tactile sensibility in the thalamus of the monkey. J Comp Neurol 1952;97(3):409–39.
[17] Schmid A-C, Chien J-H, Greenspan JD, Garonzik I, Weiss N, Ohara S, et al. Neuronal responses to tactile stimuli and tactile sensations evoked by microstimulation in the human thalamic principal somatic sensory nucleus (ventral caudal). J Neurophysiol 2016;115(5):2421–33.
[18] Gross RE, Boulis NM. Neurosurgical operative atlas: functional neurosurgery. Thieme; 2018.
[19] Starr PA, Barbaro NM, Larson PS. Neurosurgical operative atlas: functional neurosurgery. Thieme; 2009.
[20] Heming E, Sanden A, Kiss ZH. Designing a somatosensory neural prosthesis: percepts evoked by different patterns of thalamic stimulation. J Neural Eng 2010;7(6):064001.
[21] Swan BD, Gasperson LB, Krucoff MO, Grill WM, Turner DA. Sensory percepts induced by microwire array and DBS microstimulation in human sensory thalamus. Brain Stimul 2017.
[22] Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord 2010;25(5):534–41.
[23] Patil PG, Dodani S. Advanced intraoperative neural targeting system and method. Google Patents; 2018.
[24] Marmor O, Valsky D, Joshua M, Bick AS, Arkadir D, Tamir I, et al. Local vs. volume conductance activity of field potentials in the human subthalamic nucleus. J Neurophysiol 2017;117(6):2140–51.
[25] Kuncel AM, Grill WM. Selection of stimulus parameters for deep brain stimulation. Clin Neurophysiol 2004;115(11):2431–41.

[26] Merrill DR, Bikson M, Jefferys JG. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. J Neurosci Methods 2005;141(2):171–98.
[27] Cogan SF, Ludwig KA, Welle CG, Takmakov P. Tissue damage thresholds during therapeutic electrical stimulation. J Neural Eng 2016;13(2):021001.
[28] Tasker RR, Richardson P, Rewcastle B, Emmers R. Anatomical correlation of detailed sensory mapping of the human thalamus. Confin Neurol 1972;34(2):184–96.
[29] Crunelli V, Lőrincz ML, Connelly WM, David F, Hughes SW, Lambert RC, et al. Dual function of thalamic low-vigilance state oscillations: rhythm-regulation and plasticity. Nat Rev Neurosci 2018;19(2):107.
[30] Schaltenbrand G, Wahren W. Atlas for stereotaxy of the human brain. Thieme; 1977.
[31] McIntyre CC, Grill WM. Selective microstimulation of central nervous system neurons. Ann Biomed Eng 2000;28(3):219–33.
[32] Ohara S, Weiss N, Lenz FA. Microstimulation in the region of the human thalamic principal somatic sensory nucleus evokes sensations like those of mechanical stimulation and movement. J Neurophysiol 2004;91(2):736–45.
[33] Kiss ZH, Anderson T, Hansen T, Kirstein D, Suchowersky O, Hu B. Neural substrates of microstimulation-evoked tingling: a chronaxie study in human somatosensory thalamus. Eur J Neurosci 2003;18(3):728–32.
[34] Grill WM, Simmons AM, Cooper SE, Miocinovic S, Montgomery EB, Baker KB, et al. Temporal excitation properties of paresthesias evoked by thalamic microstimulation. Clin Neurophysiol : Off J Int Fed Clin Neurophysiol 2005;116(5):1227–34.
[35] Miocinovic S, Grill WM. Sensitivity of temporal excitation properties to the neuronal element activated by extracellular stimulation. J Neurosci Methods 2004;132(1):91–9.
[36] McIntyre CC, Grill WM. Extracellular stimulation of central neurons: influence of stimulus waveform and frequency on neuronal output. J Neurophysiol 2002;88(4):1592–604.
[37] Yi G, Grill WM. Frequency-dependent antidromic activation in thalamocortical relay neurons: effects of synaptic inputs. J Neural Eng 2018;15(5):056001.
[38] Anderson DN, Duffley G, Vorwerk J, Dorval AD, Butson CR. Anodic stimulation misunderstood: preferential activation of fiber orientations with anodic waveforms in deep brain stimulation. J Neural Eng 2019;16(1):016026.
[39] Lee J-I, Ohara S, Dougherty PM, Lenz FA. Pain and temperature encoding in the human thalamic somatic sensory nucleus (ventral caudal): inhibition-related bursting evoked by somatic stimuli. J Neurophysiol 2005;94(3):1676–87.
[40] Iremonger KJ, Anderson TR, Hu B, Kiss ZH. Cellular mechanisms preventing sustained activation of cortex during subcortical high-frequency stimulation. J Neurophysiol 2006;96(2):613–21.
[41] Halassa MM, Kastner S. Thalamic functions in distributed cognitive control. Nat Neurosci 2017;20(12):1669–79.
[42] Luczak A, McNaughton BL, Harris KD. Packet-based communication in the cortex. Nat Rev Neurosci 2015;16(12):745.
[43] Lenz FA, Kwan HC, Martin RL, Tasker RR, Dostrovsky JO, Lenz YE. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain 1994;117(3):531–43. Pt 3.
[44] Lenz FA, Dostrovsky JO, Tasker RR, Yamashiro K, Kwan HC, Murphy JT. Single-unit analysis of the human ventral thalamic nuclear group: somatosensory responses. J Neurophysiol 1988;59(2):299–316.
[45] Pollo C, Kaelin-Lang A, Oertel MF, Stieglitz L, Taub E, Fuhr P, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. Brain 2014;137(7):2015–26.
[46] Tan DW, Schiefer MA, Keith MW, Anderson JR, Tyler J, Tyler DJ. A neural interface provides long-term stable natural touch perception. Sci Transl Med 2014;6(257):257ra138.
[47] Tan D, Tyler D, Sweet J, Miller J. Intensity modulation: a novel approach to percept control in spinal cord stimulation. Neuromodulation: Technol Neural Interface 2016;19(3):254–9.
[48] Chandrasekaran S, Nanivadekar AC, McKernan GP, Helm ER, Boninger ML, Collinger JL, et al. Sensory restoration by epidural stimulation of dorsal spinal cord in upper-limb amputees. medRxiv 2019:19009811.