Acute low frequency dorsal subthalamic nucleus stimulation improves verbal fluency in Parkinson's disease

Darrin J. Lee a, b, c, d, *, Neil M. Drummond a, Utpal Saha a, d, Philippe De Vlooa, a, b, c, Robert F. Dallapiazza a, b, Robert Gramera, b, Tameem M. Al-Ozzi a, b, Jordan Lam c, d, Aaron Loh a, Gavin J.B. Elias a, Alexandre Bouteta, f, Jurgen Germanna, Mojgan Hodaie a, b, Alfonso Fasano a, g, h, Renato P. Munhoza a, g, h, William Hutchison a, b, Melanie Cohn a, i, Robert Chen a, g, h, Suneil K. Kalia a, b, Andres M. Lozano a, b

a Krembil Research Institute, University Health Network, 60 Leonard Avenue, Toronto, ON, M5T 2S8, Canada
b Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, 399 Bathurst Street, Toronto, ON, M5T 2S8, Canada
c Department of Neurological Surgery, University of Southern California, 1200 North State Street, Suite 3300, Los Angeles, CA, 90033, USA
d USC Neurorestoration Center, Keck School of Medicine of USC, 1333 San Pablo Street, McKibben Hall B51, Los Angeles, CA, 90033, USA
e Department of Neurosurgery, University Hospitals Leuven — KU Leuven, Herestraat 49, 3000, Leuven, Vlaams-Brabant, Belgium
f Joint Department of Medical Imaging, University of Toronto, Toronto, ON, Canada
g Division of Neurology, Department of Medicine, University of Toronto, Toronto, Canada
h Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, Ontario, Canada
i Department of Psychology, University of Toronto, Toronto, Canada

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ABSTRACT

Background: Parkinson's disease (PD) is a common neurodegenerative disorder that results in movement-related dysfunction and has variable cognitive impairment. Deep brain stimulation (DBS) of the dorsal subthalamic nucleus (STN) has been shown to be effective in improving motor symptoms; however, cognitive impairment is often unchanged, and in some cases, worsened particularly on tasks of verbal fluency. Traditional DBS strategies use high frequency gamma stimulation for motor symptoms (~130 Hz), but there is evidence that low frequency theta oscillations (5–12 Hz) are important in cognition.

Methods: We tested the effects of stimulation frequency and location on verbal fluency among patients who underwent STN DBS implantation with externalized leads. During baseline cognitive testing, STN field potentials were recorded and the individual patients’ peak theta frequency power was identified during each cognitive task. Patients repeated cognitive testing at five different stimulation settings: no stimulation, dorsal contact gamma (130 Hz), ventral contact gamma, dorsal theta (peak baseline theta) and ventral theta (peak baseline theta) frequency stimulation.

Results: Acute left dorsal peak theta frequency STN stimulation improves overall verbal fluency compared to no stimulation and to either dorsal or ventral gamma stimulation. Stratifying by type of verbal fluency probes, verbal fluency in episodic categories was improved with dorsal theta stimulation compared to all other conditions, while there were no differences between stimulation conditions in non-episodic probe conditions.

Conclusion: Here, we provide evidence that dorsal STN theta stimulation may improve verbal fluency, suggesting a potential possibility of integrating theta stimulation into current DBS paradigms to improve cognitive outcomes.

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Introduction

Idiopathic Parkinson’s disease (PD) is the second most common progressive neurodegenerative disorder after Alzheimer’s disease [1]. The predominant clinical motor features of PD are akinesia, bradykinesia, resting tremor, and muscular rigidity; however, posture, gait, sleep, speech, swallowing, micturition and other changes can be variably affected in PD. Deep brain stimulation (DBS) is effective at treating the cardinal motor features of PD, but is less effective at treating non-motor symptoms [2].

The primary anatomical DBS targets are the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPI). While both STN and GPI DBS are likely to be equally efficacious at treating motor symptoms [3,4], STN DBS provides the additional benefit of reducing PD medications. Although cognitive decline is seen in advanced PD, there is evidence that DBS can worsen specific executive function processes, specifically verbal fluency [5]. STN DBS is also associated with a greater cognitive burden compared to GPI DBS, particularly with declines in verbal fluency and visual motor processing speed [4,6]. With cognitive scores, including verbal fluency, directly correlated with patient quality of life and caregiver burden, efforts to improve cognitive outcomes following DBS are of considerable importance [7].

Current DBS parameters utilize high frequency gamma stimulation (100–180 Hz) to treat the cardinal motor symptoms of PD; however, there is increasing evidence that low frequency STN theta oscillations (5–12 Hz) within the STN and its cortical associations are important in cognition, including verbal fluency, color-word interference, and spatial and episodic memory [8–12]. Increased STN-specific theta oscillations have also been correlated with improved verbal fluency, conflict resolution, working memory, response inhibition and sensorimotor function [9–11,13–15].

While DBS targets the STN for its role in motor symptoms, the STN has at least three functional components: motor (dorsolateral STN), associative (ventral) and limbic (ventromedial) [16]. Although DBS stimulation targets the motor (dorsolateral) STN, there is increasing evidence that STN DBS may also affect the ventral region which is strongly involved in cognition [17]. Here, we evaluated the effects of acute dorsal and ventral STN theta and gamma stimulation on verbal fluency measures in PD patients.

Materials & methods

This prospective study was designed to evaluate the effects of acute low and high frequency DBS of the dorsal and ventral STN on verbal fluency. The study was approved by the University Health Network Research Ethics Board (REB: 05–0668) and performed at the Toronto Western Hospital, University Health Network. Nine patients underwent preoperative neurology, neurosurgery and neuropsychology evaluations. Patients were prospectively enrolled and underwent STN DBS implantation for PD after informed consent was obtained. All patients were implanted with bilateral STN electrodes (Medtronic model 3387, Medtronic, Minneapolis, MN, USA) under local anesthesia and utilized intraoperative electrophysiology and fluoroscopy to confirm electrode placement [18]. After surgery, patients were allowed to recover in the hospital and resume their normal medications. Cognitive and electrophysiological testing were performed during one session for each patient 2–4 days postoperatively. During a baseline verbal fluency task, left STN field potentials were recorded across contact 0 and contact 3 of the electrodes with the stimulation turned off, and the individual patient’s peak theta power frequency was measured at rest and during each cognitive task between contact 0 and contact 3 of the electrodes. Left STN stimulation alone was performed as there is evidence that there are differing lateralizing roles of the frontal cortex in verbal fluency [19].

Stimulation parameters

Five distinct stimulation paradigms were evaluated: (1) no stimulation, (2) left dorsal (contact #3) gamma (130 Hz) frequency, (3) left ventral (contact #0) gamma (130 Hz) frequency, (4) left dorsal theta and (5) left ventral theta frequency stimulation. Frequency for both dorsal and ventral theta stimulation were set as the peak theta frequency recorded during baseline testing. Notably, the first three patients in the study did not undergo dorsal stimulation (theta or gamma). The voltage was set to 2.5 V and the pulse-width was set to 100 μs based on preclinical data utilizing DBS for memory [20,21]. Randomization of verbal fluency tasks with stimulation frequency was counterbalanced across eight possible order combinations to control for stimulation order. Cognitive testing began 5 min after each frequency change to allow for acclimatization and stimulation washout [22]. Stimulation was turned off at the end of the session.

Cognitive testing

Verbal fluency was evaluated by instructing patients to name as many words as they could in 1 min following specific probes. Probe types were divided into those with high autobiographical or spatial context (episodic category cues, e.g. ‘names of your friends’, ‘kitchen utensils’) and those with low autobiographical or spatial context (non-episodic category cues, e.g. ‘modes of transportation’ or a phonemic cue e.g. “words beginning with T”) as previously described [23–26]. Patients completed all of the same tests in the same order, but the stimulation frequency and location order was counterbalanced to control for probe difficulty. Total number of unique words generated in each 1-min category were counted.

Volume of tissue activation

Volume of tissue activated (VTA) modelling for each patient was retrospectively performed using the program Lead-DBS V2 (lead-dbs.org) as previously described [27]. Electrodes were semi-automatically localized, with manual refinement of position, on post-operative MRI. We then rigidly co-registered the patient’s post-operative MRI with their pre-operative MRI using SPM (filion.ucl.ac.uk/spm). To refine co-registration, correction of brain shift (e.g., secondary to pneumocephalus) was performed. The co-registered image was then transformed (non-linearly normalized), using the ‘low variance’ preset, into Montreal Neurological Institute (MNI) standard space (ICBM 152 2009b Nonlinear Asymmetric) using ANTs (nitrcc.org/projects/ants) [28]. These normalization settings were used because they have been shown to optimally normalize sub-cortical structures relevant to DBS [29,30]. This transform was then applied to patients’ localized electrodes in order to convert them into standard space. Following electrode normalization, left-sided VTAs corresponding to each patient’s parameters when stimulating at the i) most dorsal and ii) most ventral contacts, were generated using finite element modelling. Finally, sum maps of these dorsal and ventral VTAs were generated. Given that the current VTA modelling does not take into account differences in frequency, which limits its accuracy, this analysis was limited to visually demonstrating a group-level spatial difference between the stimulation of the most ventral and dorsal contacts.
Statistical analysis

Data were analyzed and graphics were generated in SPSS 26 (IBM). Normality of data was assessed with the Shapiro-Wilk test. Linear mixed modelling was used to assess the within-subject effects of verbal fluency probe type and stimulation setting (off, dorsal gamma, dorsal theta, ventral gamma, and ventral theta), with a random effect of subject. Analysis was stratified by verbal fluency category (episodic, non-episodic) to investigate the differential effects of stimulation settings on different types of verbal fluency. Post-hoc analysis was performed through pairwise comparisons between the five stimulation settings using the Bonferroni correction to control for multiple comparisons. Significance was assigned to \( p < 0.05 \).

Results

Nine patients were enrolled in the study (mean age: 60.9, range 56–70 years; 6 males). Patient demographics are detailed in Table 1. During baseline cognitive testing, the peak left STN theta frequency was 5.7 ± 1.6 Hz (SD).

The Shapiro-Wilk test was nonsignificant for the verbal fluency measures across all stimulation settings (\( p > 0.05 \)) and with normality assumed. The overall main mixed-effect model showed a significant effect of stimulation setting (\( F (4.69) = 4.44, p = 0.003; \) Fig. 1A, D). There was no significant effect of type of verbal fluency subtype (\( F (1.69) = 0.48, p = 0.49 \)) and no significant interaction between frequency/location and verbal fluency subtype type (\( F (1.69) = 1.19, p = 0.33 \)). Post-hoc testing revealed increased performance during dorsal theta stimulation compared to off (\( p = 0.02 \)), dorsal gamma (\( p = 0.009 \)), and to ventral gamma (\( p = 0.005 \)) but not compared to ventral theta stimulation (\( p = 0.19 \)). There were no significant differences in verbal fluency between off, dorsal gamma, ventral gamma, and ventral theta (\( p > 0.05 \)). Notably, the three patients with mild cognitive impairment (MCI) had increased verbal fluency scores with dorsal theta stimulation relative to all other conditions.

Mixed-effect model of the episodic verbal fluency subtype revealed a significant effect of stimulation setting (\( F (4.30) = 5.34, p = 0.002; \) Fig. 1B,E). Post-hoc analysis revealed increased performance during dorsal theta versus off (\( p = 0.02 \)), dorsal gamma (\( p = 0.005 \)), and ventral gamma (\( p = 0.003 \)), and ventral theta (\( p = 0.02 \)). There were no significant differences between off, dorsal gamma, ventral gamma, and ventral theta (\( p > 0.05 \)).

As for non-episodic verbal fluency probes, the main mixed-effect model showed no significant effect of stimulation setting (\( F (4.30) = 1.90, p = 0.14; \) Fig. 1C,F).

The mean MNI coordinates of active contacts were \( x = -11.6 (±0.8), y = -15.9 (±1.5), z = -7.7 (±1.1) \) when stimulating through most ventral contacts, and \( x = -13.9 (±0.8), y = -10.2 (±1.6), z = 0.4 (±1.2) \) when stimulating through most dorsal contacts (Figs. 2 and 3). The average location of stimulation when using the most ventral or most dorsal contacts were significantly different (\( p < 0.05 \) in the x, y, and z planes, Fig. 2). The VTA sum maps also confirm a spatial difference between the stimulation of the most ventral and dorsal contacts (Fig. 3).

Discussion

In this study, we evaluated the effects of acute theta and gamma frequency DBS to either the dorsal or ventral STN on verbal fluency. Here, we found that dorsal theta STN DBS resulted in increased verbal fluency compared to “off” stimulation, ventral theta stimulation and either dorsal gamma or ventral gamma stimulation. While episodic verbal fluency was significantly improved by theta stimulation, there were no significant differences in non-episodic verbal fluency.

STN and cognition

The STN is a subcortical structure that is widely interconnected with various cortical and subcortical brain regions [31]. This connectivity allows for the facilitation and integration of functionality across a range of different modalities (i.e. executive, limbic, motor) [32]. While the role of the STN in motor functions has been extensively studied, its importance in cognition is still being explored. The STN is one of the primary targets for deep brain stimulation treatment of the cardinal PD motor symptoms; however, there is concern that it can lead to a decline in verbal fluency [12]. This further implicates the STN in cognitive processing.

Since the STN is viewed as a multifunctional integration hub, some suggest that different oscillatory frequency bands mediate different functions [33]. Indeed, different non-motor functions carried out by basal ganglia nuclei engage different frequency bands, which in turn, selectively entrain distinct neuronal ensembles [34]. Neural oscillations serve as a global linkage between individual neurons and distant cortical/subcortical areas and reflect the flow of information between neuronal networks, and synchronization highlights information processing [35]. Low frequency oscillations, namely theta, are of specific interest due to its robust presence and modulation in cortical activity recorded by EEG during working memory and cognitive processes (e.g. decision-making with conflict and errors) [36]. Recent studies have also found a cortico-STN theta coherence during conflict resolution [36,37]. The causal role of STN low frequency oscillations in conflict processing

| Patient | Age (years) | Gender | Duration of PD Diagnosis (years) | Years of Education | Preop Cognitive Diagnosis | Cognitive Deficit Domains | Peak Theta Frequency (Hz) | Length of Right STN (mm) | Length of Left STN (mm) |
|---------|-------------|--------|--------------------------------|------------------|--------------------------|--------------------------|--------------------------|-------------------------|------------------------|
| 1       | 56          | Male   | 14                             | 15               | Intact                   |                          | 8 Hz                     | 5.5                     | 6                      |
| 2       | 58          | Male   | 13                             | 17               | Intact                   |                          | 4 Hz                     | 5.5                     | 4.5                    |
| 3       | 54          | Female | 6                              | 16               | Intact                   |                          | 5 Hz                     | 6                       | 6                      |
| 4       | 59          | Female | 12                             | 16               | Intact                   |                          | 8 Hz                     | 5.25                    | 4.5                    |
| 5       | 58          | Male   | 5                              | 14               | MCI                      | Attention, Executive     | 5 Hz                     | 6                       | 5.5                    |
| 6       | 66          | Male   | 16                             | 13               | MCI                      | Executive, Memory        | 4 Hz                     | 4.5                     | 3.5                    |
| 7       | 70          | Male   | 6                              | 18               | Intact                   |                          | 7 Hz                     | 5.75                    | 4                      |
| 8       | 60          | Male   | 14                             | 16               | Intact                   | Executive, Memory        | 5.2 Hz                   | 4.75                    | 6                      |
| 9       | 67          | Female | 19                             | 17               | MCI                      |                          | 5.3 Hz                   | 4.5                     | 5.5                    |

PD: Parkinson’s Disease; STN: subthalamic nucleus; MCI: mild cognitive impairment.
was demonstrated by an event-related DBS study which showed that high frequency STN DBS increased theta power, disrupted conflict processing, and increased errors [15]. These electrophysiological studies support the role of STN-theta activity in cognitive processes and highlight the functional importance of the cortico-subthalamic hyperdirect pathway [38]. Furthermore, low frequency stimulation of the STN has shown to improve verbal fluency possibly by enhancing synchronization within cortical areas related to working memory processing [10]. More recently, significant increases in alpha-theta (6–12 Hz) power were recorded from STN LFPs as well as frontotemporal-STN coherence during a verbal generation task, which was more localized to the ventromedial STN [13]. Interestingly, our data did not show improvements in verbal fluency with ventral theta stimulation, but did demonstrate increased verbal fluency with dorsal theta stimulation.

**Theta stimulation and verbal fluency**

Previous studies have demonstrated that lower frequency (60–80 Hz) STN stimulation results in better articulation, respiration, phonation, prosody and phonemic verbal fluency compared to high frequency (110–200 Hz) stimulation [39]; however, only one previous study investigated the effect of theta (5–12 Hz) STN stimulation on verbal fluency. Wojchecki et al. demonstrated a 14% improvement in overall verbal fluency during theta versus gamma stimulation, but did not separately investigate subdivisions of verbal fluency [10]. Lam et al. also demonstrated a 16% improvement in episodic verbal fluency with acute STN theta compared to gamma stimulation in chronically implanted patients [40]. Similarly, in our current study, there was a 19% increase in overall verbal fluency with dorsal theta stimulation compared to no stimulation and a 30% improvement in overall verbal fluency relative to dorsal gamma stimulation. These improvements were driven by improvements in episodic verbal fluency (30% increase compared to no stimulation; 55% increase compared to dorsal gamma stimulation). Interestingly, there were no significant differences in non-episodic category or letter verbal fluency. This corroborates findings of increased hippocampal activation and poorer performance of patients with medial temporal damage in episodic versus non-episodic verbal fluency [23–26], in keeping with a well-established role of theta oscillations in episodic retrieval. Anatomically, this may also confirm known connections between the STN and the hippocampus/temporal lobe, including coherence in the 7–12 Hz range [41]. Notably, fMRI and DTI studies have positively correlating medial temporal activation and STN-medial temporal connectivity [26]. These studies suggest that the differential improvement of episodic fluency observed in our study may be explained by an effect of theta stimulation on episodic memory processes.

**STN topography and projections**

While previous studies investigating theta STN stimulation did not account for STN electrode contact location, our study separately examined dorsal versus ventral STN stimulation. The STN is thought to have three functional zones: motor (dorsolateral), associative (ventrolateral) and limbic (ventromedial) [16,42]. DTI studies have demonstrated increased connections with limbic structures in the ventromedial STN while highest connectivity to motor areas are found in dorsolateral areas along a mediolateral gradient [42,43]. While there has been some evidence that ventral STN stimulation is better for non-motor outcomes of PD (mood, apathy, attention, and memory) [44,45], these other studies did not evaluate the effects of
lead stimulation on verbal fluency, nor did they evaluate theta frequency stimulation. The posterior STN has connectivity consistent with motor function, including the posterior insula, posterior putamen and GPe, mid-caudate nucleus and ventrolateral thalamic nuclei. The anterior limbic STN has connections with the basolateral nucleus of the amygdala, anterior hippocampi, posterior-medial Gpi, GPe and anterior thalamic nuclei, while the associative STN has been shown to connect to both motor and limbic regions along a functional connectivity gradient and may provide a link between the motor and limbic STN [42]. In accordance, ventral DBS electrode position and a larger volume of activation has been associated with poorer verbal fluency outcomes [6,46].

Unexpectedly, we found improved performance during dorsal versus ventral STN theta stimulation. While there is topographical correlations with functions, these delineations may be a gradient rather than distinct sub-regions with cytoarchitectural and functional boundaries [42]. Furthermore, electrical stimulation may spread through the distinct subregions of the STN and beyond. Of note, the ventral-most contact in our study was typically partially in the substantia nigra pars reticulata, potentially leading to less activation of the STN. These results prompt further investigation into subdivisions and connections of the STN, particularly to limbic and associative structures including the hippocampus.

**Limitations**

The current study had a limited sample size and the first three patients did not undergo dorsal stimulation, limiting the conclusions of this study to interpretation in their preliminary context, and requiring larger studies to confirm these results. The study was single-blinded, with only the patient blinded to stimulation paradigm. We did not make an extensive effort to determine stimulation thresholds for motor or sensory side effects prior to the study, and the middle contacts were not tested. Although the order of stimulation paradigms was counterbalanced to account for motor fluctuations, motor fluctuations and effect of medications were not controlled, which may have impacted our results. While the VTA demonstrate stimulation of the dorsal and ventral STN, the results may be confounded by stimulation outside of the STN itself, including the substantia nigra pars reticulata ventrally and zona incerta dorsally. Stimulation was only performed along the left STN lead. Future studies may include evaluating right STN theta stimulation and bilateral STN theta stimulation.

Only stimulation frequency was varied, and pulse width and amplitudes were kept constant. Consequently, total electrical energy delivered (TEED) was lower for theta compared to gamma frequencies, and may have reduced motor improvement [47]. While the motor symptoms were not tested concomitantly during this study, our study may have underestimated the improvement in verbal fluency of theta compared to gamma stimulation if the theta stimulation had less TEED and subsequent motor symptom benefits compared to gamma stimulation. While there is evidence for a 5 min washout period for motor benefits, the same washout period may not apply to cognitive tasks [22]. Other studies have previously

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**Fig. 2.** Schematic of a sagittal view of the subthalamic nucleus (STN) and a superimposed Medtronic 3387 electrode. Red squares indicate relative position of the dorsal stimulation regions relative to the ventral contact based upon the individual length of the STN. Ra.pl: prelemniscal radiations, RT: reticular thalamus, SNr: substantia nigra pars reticulata, STN: subthalamic nucleus, Vim: nucleus ventrointermediate, Voa: nucleus ventrooralis anterior, Vop: nucleus ventrooralis posterior, Zi: zona incerta. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

**Fig. 3.** Location of ventral versus dorsal VTAs. Sum maps representing the number of overlapping VTAs when stimulating at i) most ventral (blue), and ii) most dorsal electrode contacts are shown overlaid on sagittal (left panel), coronal (top right), and axial (bottom right) slices of a T1 standard brain template (MN152 brain). Abbreviations: L = left, MNI = Montreal Neurological Institute, No. = number, R = right, VTA = volume of tissue activated. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
utilized interstimulus washout time periods up to 30 min or 48 h [9,14,48]. Due to the lack of data on the use of theta frequencies in DBS, uncertainties exist regarding its application in the clinical setting. This includes the chronic effect of theta stimulation; the effects on motor symptoms; and the effects of combining theta with gamma frequencies, all of which were not examined in this study.

**Future directions**

As advancements are made with electrode design, expanded stimulation parameters and closed-loop stimulation become available, it is possible that subdomains of the STN could be differentially stimulated to improve both motor symptoms of PD and potential cognitive and executive functions. This study provides preliminary evidence that dorsal STN theta stimulation may improve episodic verbal fluency. As stimulation at frequencies below 50 Hz do not improve motor signs and may potentially worsen movement [48], this data could potentially be utilized either in an interleaved stimulation paradigm or in an adaptive neuromodulation system to expand the breadth of symptoms that can be addressed with DBS.

**Conclusions**

We demonstrate improved acute episodic category verbal fluency during dorsal STN theta stimulation compared to gamma, ventral and no stimulation. Our results corroborate and add to previous studies demonstrating a benefit of theta STN stimulation and raise the possibility of integrating theta stimulation into current DBS paradigms to improve cognitive outcomes. However, further research is required to substantiate a benefit of long-term theta stimulation and explore the effect of electrode location within the STN specific to theta stimulation.

**CRediT authorship contribution statement**

**Darrin J. Lee:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Neil M. Drummond:** Data curation, Writing – review & editing. **Utpal Saha:** Data curation, Writing – review & editing. **Philippe De Vloog:** Data curation, Writing – review & editing. **Robert F. Dallapiazza:** Data curation, Writing – review & editing. **Robert Gramer:** Data curation, Writing – review & editing. **Tameem M. Al-Ozzi:** Data curation, Writing – review & editing. **Jordan Lam:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Aaron Loh:** Methodology, Formal analysis, Writing – review & editing. **Gavin J.B. Elias:** Methodology, Formal analysis, Writing – review & editing. **Alexandre Boutet:** Methodology, Formal analysis, Writing – review & editing. **Jurgen Germann:** Methodology, Formal analysis, Writing – review & editing. **Mohjan Hodaie:** Investigation, Writing – review & editing. **Alfonso Fasano:** Writing – review & editing. **Renato P. Munhoz:** Writing – review & editing. **William Hutchison:** Investigation, Methodology. **Melanie Cohn:** Conceptualization, Methodology, Validation, Formal analysis. **Robert Chen:** Conceptualization, Methodology, Validation, Investigation. **Sueneil K. Kalia:** Conceptualization, Methodology, Validation, Investigation. **Andres M. Lozano:** Conceptualization, Methodology, Formal analysis, Validation, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration.

**Declaration of competing interest**

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