



BMJ Open Connectomic profiling and Vagus nerve stimulation Outcomes Study (CONNECTIVOS): a prospective observational protocol to identify biomarkers of seizure response in children and youth

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ABSTRACT

Introduction Vagus nerve stimulation (VNS) is a neuromodulation therapy that can reduce the seizure burden of children with medically intractable epilepsy. Despite the widespread use of VNS to treat epilepsy, there are currently no means to preoperatively identify patients who will benefit from treatment. The objective of the present study is to determine clinical and neural network-based correlates of treatment outcome to better identify candidates for VNS therapy.

Methods and analysis In this multi-institutional North American study, children undergoing VNS and their caregivers will be prospectively recruited. All patients will have documentation of clinical history, physical and neurological examination and video electroencephalography as part of the standard clinical workup for VNS. Neuroimaging data including resting-state functional MRI, diffusion-tensor imaging and magnetoencephalography will be collected before surgery. MR-based measures will also be repeated 12 months after implantation. Outcomes of VNS, including seizure control and health-related quality of life of both patient and primary caregiver, will be prospectively measured up to 2 years postoperatively. All data will be collected electronically using Research Electronic Data Capture.

Ethics and dissemination This study was approved by the Hospital for Sick Children Research Ethics Board (REB number 1000061744). All participants, or substitute decision-makers, will provide informed consent prior to be enrolled in the study. Institutional Research Ethics Board approval will be obtained from each additional participating site prior to inclusion. This study is funded through a Canadian Institutes of Health Research grant (PJT-159561) and an investigator-initiated funding grant from LivaNova USA (Houston, TX; FF01803B IIR).

Strengths and limitations of this study

- This study will enrol up to 500 patients to assess the long-term outcomes of vagus nerve stimulation (VNS) therapy on seizure frequency, seizure severity and quality of life in children with epilepsy with data collection up to 2 years postoperatively.
- This study will build a working collaboration among leading paediatric epilepsy treatment centres across North America performing VNS in children with epilepsy.
- This study will develop a machine learning predictive model to identify patients who may benefit most from VNS based on clinical phenotypes and differences in structural and functional brain connectivity.
- A potential limitation of this study is loss to follow-up due to the lengthy 2-year follow-up period resulting in missing or incomplete data.

INTRODUCTION

Epilepsy is the most common serious neurological condition of childhood.¹ Approximately one-third of children continue to have debilitating seizures and are diagnosed with drug-resistant epilepsy after failure of optimised two or more antiepileptic drugs over 2 years.² This cohort of patients with medically intractable epilepsy is disproportionately affected by the medical and psychosocial burden of the illness³ and consumes 80% of epilepsy-related healthcare expenses.^{4 5} Furthermore, uncontrolled seizures are known to interfere with typical childhood development,⁶ culminating in disability and challenges with schooling.

To mitigate the burden of epilepsy, surgical interventions are increasingly emphasised, with resective surgery demonstrating the best long-term outcomes.^{3,7,8} In those children who are not candidates for resective surgery, or those who continue to have debilitating seizures postoperatively, neuromodulation strategies may be considered.

Vagus nerve stimulation (VNS) is a form of neuromodulation whereby an electrical stimulus is delivered to the vagus nerve at the level of the neck through an implanted pulse generator resulting in the modulation of cortical excitability.⁹ VNS has been shown to reduce seizure frequency in children with intractable epilepsy leading to improvements in quality of life, arrest of cognitive decline and improved mood and behaviour.^{10–12}

The individual patient response to VNS is highly variable and unpredictable. A meta-analysis of randomised controlled trials of VNS encompassing 439 adults and children demonstrated considerable heterogeneity in outcomes, with fewer than half of implanted patients achieving significant seizure reduction.¹³ Furthermore, in paediatric populations, seizure response rates following VNS may be as low as 25%,¹² suggesting that a significant number of patients accept surgical risk with a low likelihood of seizure-freedom. The lack of objective markers to preoperatively identify good VNS candidates subjects some children to an unnecessary invasive surgical procedure and, in resource-limited health systems, deprives others who would be more likely to benefit. As a result, there is an unmet need to identify preoperative predictive markers that can identify and stratify patients who will benefit from VNS.

A recent review identified biomarkers of VNS responsiveness in patients with drug-resistant epilepsy.¹⁴ Notably, differences in intrinsic brain network connectivity were found to be a highly promising biomarker in identifying patients likely to benefit from VNS. The therapeutic effect of VNS is thought to be mediated by afferent projections of the vagus nerve via brainstem pathways to the thalamus and cortex, which serves to modulate cortical excitability, rendering the brain less susceptible to seizures.^{15,16} Collectively, this system is termed the vagus afferent network (VagAN).¹⁷ Measures of structural and functional brain network connectivity within the VagAN have been previously studied to investigate the variability in patient responsiveness to VNS therapy.^{18–20} Such connectomic studies leverage advanced imaging and neurophysiological tools to study neural architecture by statistically mapping fibres and shared patterns of neuronal activity linking different brain regions.²¹

The proposed study will build on previous findings through a multi-institutional, prospective observational design. VNS outcomes will be measured in terms of seizure control and health-related quality of life (HRQoL) of both the child and their primary caregiver up to 2 years post implantation. Resting-state functional MRI (rs-fMRI), diffusion tensor imaging (DTI) and magnetoencephalography (MEG) will be used to investigate how structural and functional brain connectivity within the VagAN

differs among patients who demonstrate good and poor response to VNS, relative to a historical normative age-matched and sex-matched cohort. Somatosensory evoked fields (SEFs) during MEG will be used to study associations between afferent brainstem pathways and seizure response to VNS. Last, we will leverage recent advances in the imaging of brain connectomics in combination with machine learning to characterise and predict VNS responsiveness in intractable epilepsy. It is anticipated that this work may aid in identifying paediatric patients with intractable epilepsy who are most likely to benefit from VNS.

STUDY OBJECTIVES AND DESIGN

The primary goal of this study is to collect longitudinal, multicentre data to identify the ideal surgical candidate for VNS. This study will build a collaboration between leading epilepsy centres across North America with technology, expertise and experience in VNS therapy. Each centre will contribute clinical, parent-reported and patient-reported outcomes and multimodal imaging data to the study over a period of 4 years.

The specific objectives of the study are:

To assess the long-term outcomes of VNS in children with intractable epilepsy

Seizure control will be compared between baseline and prespecified postoperative time points (6 months, 12 months and 24 months) using standardised measures. Changes in HRQoL of both the child and primary caregiver will be measured using a series of parent-reported and child-reported measures. Effects of VNS therapy on health-resource utilisation (HRU) will also be explored.

To identify clinical and imaging predictors of seizure outcome for VNS

We will study the association between the preimplantation structural and functional connectome in patients and their seizure response to VNS strategies. Individual indices of VNS outcome will be compared against neuroimaging data.

To develop a predictive model to identify patients who may benefit from VNS

By combining structural and functional imaging connectomics of the VagAN into a machine learning algorithm, a predictive model to identify response to VNS will be developed and made freely accessible. The predictive model may enable better prediction of which patients are likely to benefit from VNS and assist with clinical decision-making.

METHODS AND ANALYSIS

Study environment

The study will be led by the Hospital for Sick Children (SickKids), Toronto, Ontario, Canada. Thirteen additional institutions across North America will participate,

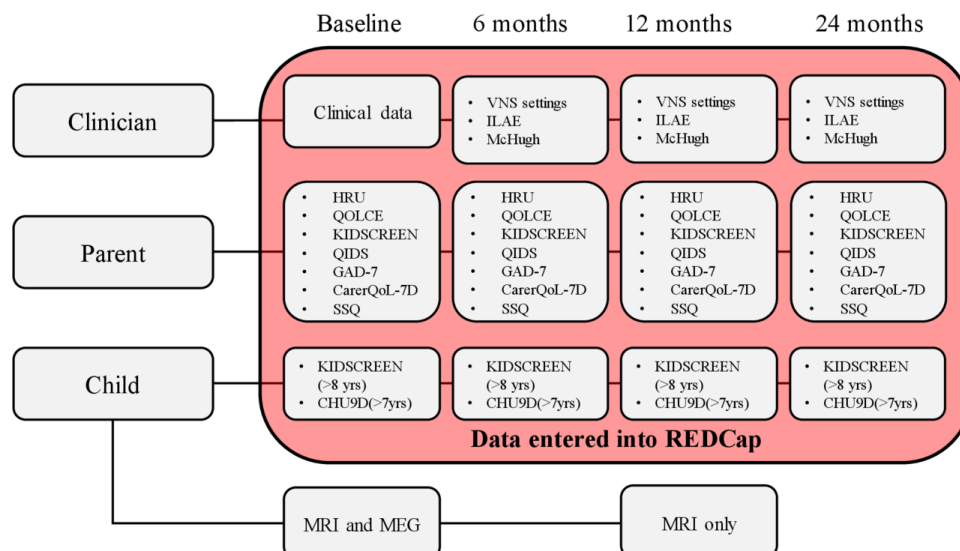


Figure 1 Organisational structure of the study. Participating clinicians enter data directly into the Research Electronic Data Capture (REDCap) online database at baseline, 6 months, 12 months and 24 months. Parent-reported and child-reported measures are completed through secure REDCap links at the same time points. Neuroimaging is completed at baseline and 12 months postoperatively. CarerQoL, The Care-related Quality of Life Instrument; CHU9D, Child Health Utility; GAD-7, Generalised Anxiety Disorder Scale; HRU, health resource utilisation; ILAE, The International League Against Epilepsy seizure classification; KIDSCREEN, KIDSREEN generic health-related quality of life measure; McHugh, The McHugh classification of seizure freedom; MEG, magnetoencephalography; QOLCE, The Quality of Life in Childhood Epilepsy Questionnaire; QIDS, The Quick Inventory of Depressive Symptomatology; SSQ, The Seizure Severity Questionnaire; VNS, vagus nerve stimulation.

including CHU Sainte-Justine in Montreal, Arkansas Children's Hospital, University of Pittsburgh Medical Center, University of Utah, University of Indiana, Washington University, University of Alabama, Seattle Children's Hospital, Children's Hospital of Wisconsin, Nicklaus Children's Hospital in Miami, University of British Columbia, Baylor College of Medicine in Texas and University of California, Los Angeles. Independently, each of the collaborating centres are leaders in the comprehensive evaluation and surgical treatment of epilepsy. All institutions have access to a 3T MRI scanner with experience in imaging children with epilepsy. In addition, a subset of these sites have expertise in and access to MEG research.

Organisational structure and governance

All data will be collected and managed using Research Electronic Data Capture (REDCap; V.9.5.3) tools, hosted on secure servers at SickKids.^{22 23} REDCap is a web-based software platform designed to support data capture for research studies. Clinical data will be directly entered into the online REDCap database by the investigating physicians at baseline, 6 months, 12 months and 24 months post implantation. Child-reported and parent-reported information will also be directly entered into the database through secure, unique email links at the same time points. The organisation structure of the study is shown in figure 1.

All study data will be deidentified using unique study codes for each site. Each site will be responsible for maintaining their own participants' personal health information on a master list. Only the lead site (SickKids) will have access to the deidentified data from all sites. The study

team at SickKids will oversee access and data security, appropriate follow-up and communications with external sites. The scientific advisory committee responsible for making decisions for sharing data and providing input regarding data analysis, data interpretation and research publications will comprise of the SickKids study team as well as the PIs at the external sites. The SickKids principle investigator (PI) is responsible for all data collected for the study and the deidentified clinical imaging data collected from all sites as part of the study.

Eligibility criteria

Children aged 0–18 years who will be undergoing VNS for the treatment of medically intractable epilepsy will be included in the study for clinical data collection and parent-reported and child-reported scales where able. Children 6 years and older will additionally be invited to complete preoperative and postoperative neuroimaging. The decision to pursue VNS therapy will be made locally at each site, in part influenced by the surgeon and/or patient/family preference; this study does not play any role in the decision-making of treating patients with VNS. Children who have had previous resective epilepsy surgery and subsequent VNS will also be included.

Ability to read and understand English and/or French is not mandatory for all participants. Completion of the questionnaires is optional and dependent on the participant and parent's ability to understand English or use language interpretation services provided by the hospital.

We estimate that each year approximately 50 children will undergo VNS at SickKids, and we will recruit 200 patient–parent pairs globally (approximately 20 patients



from each site). This sample size is sufficient to adjust for clinical heterogeneity of subjects and to test a predictive model in an independent cohort. A sample size calculation with a conservative effect size of 0.4, desired power of 0.8 and significance of 0.05 would require only 52 patients for a paired analysis of seizure frequency before and after VNS. However, given the number of institutions involved, expectation of a complicated hierarchical mixed-effects model, and the high likelihood of missing data across multiple institutions, we believe that 200 patient–parent pairs is a parsimonious target to produce accurate and reliable analyses.

Recruitment

Patients scheduled to undergo VNS will be identified by the clinical team at their respective institution, who will inform the patients and families about the study. Further information about the study will be provided to the patients and families inviting their participation. The study research coordinator will contact the families within a few days to answer any questions. For those who wish to participate, the research coordinator will obtain informed consent from both the child and their parent/legal guardian. For children who do not have capacity to consent for themselves, consent will be sought by their substitute decision-maker and assent will be sought from the child.

All patients will undergo a history, physical and neurological examination, video electroencephalography, and occasionally, neuropsychological testing as part of the clinical workup for VNS and epilepsy surgery, which is the standard practice at all participating sites. Relevant clinical data will be collected from patient charts for all participants (table 1).

Outcomes

The primary outcome of interest is change in clinical seizure control after VNS implantation. Secondary outcomes include differences in intrinsic structural and functional connectivity within the VagAN, changes in brain connectivity over time, HRQoL of both the child and

primary caregiver and HRU. All clinical seizure control and VNS stimulation settings will be measured at baseline, 6 months, 12 months and 24 months post implantation. This study will not enforce a no-drug-change window to mimic realistic clinic practice and understand the effect of VNS for patients with medically refractory epilepsy. If available, neuropsychologic test data are collected prior to surgery and a year after VNS implantation, depending on individual site resources and clinical indications. Specific measures used are described below.

Clinical seizure control

Seizure control will be assessed using the following scales:

- i. *International League Against Epilepsy (ILAE) classification.*²⁴
- ii. *The McHugh classification.*²⁵
- iii. *The Seizure Severity Questionnaire (SSQ),*²⁶ a caregiver-reported review of aspects of seizures before, during and after seizures, with responses related to the individual's most common type of seizure.

VNS stimulation settings

Stimulation settings of the patient's current parameters will be recorded prior to adjustment or changes.

- i. Percentage of time and autostimulation function.
- ii. Current (mA) normal mode, current (mA) autostimulation and current (mA) of the magnet.
- iii. Heart rate sensitivity and heart rate threshold.
- iv. System resistance.

Health-related quality of life

We will measure changes in HRQoL of the child and caregiver using the following instruments:

The Quality of Life in Childhood Epilepsy Questionnaire (QOLCE)

- ▶ *The Quality of Life in Childhood Epilepsy Questionnaire,*^{27–29} a parent-rated epilepsy-specific instrument that covers five domains: physical, social, emotional well-being, cognition and behaviour. Items are rated on a 5-point Likert scale, with the time referent being the previous 4 weeks.

Table 1 Clinical data collected in Research Electronic Data Capture

Form	Data fields
Clinical background	Age at VNS procedure, sex, age at seizure onset, handedness, IQ before VNS insertion, genetic mutations, comorbid conditions, family history of seizures, presence of infantile spasm, number and type of antiepileptic drugs (AEDs), seizure classification, frequency and aetiology, video EEG localisation, normal versus abnormal neuroimaging results, location of lesion, previous surgeries, date of VNS procedure, VNS model
Follow-up (6 months, 12 months, 24 months after VNS implantation)	Seizure frequency and severity, seizure classification, number and type of AEDs, HRQoL, HRU, adverse events, VNS settings: Percentage of time and autostimulation function, current (mA) normal mode, current (mA) autostimulation, current (mA) magnet, heart rate sensitivity, heart rate threshold and system resistance

EEG, electroencephalography; HRQoL, health-related quality of life; HRU, health resource utilisation; IQ, intelligence quotient; VNS, vagus nerve stimulation.

- ▶ *The KIDSCREEN-27*, a dual child-rated and parent-rated generic instrument^{30,31} that measures five dimensions: physical well-being, psychological well-being, autonomy and parents, social support and peers and school environment. This scale has been validated for the ages of 8–18 years in children with a variety of chronic illness and developmental disorders.^{32–37}
- ▶ *The Child Health Utility (CHU9D)*, a child-rated generic instrument that measures nine dimensions: worry, sadness, pain, tiredness, annoyance, school, sleep, daily routine and activities. The CHU9D has been validated in children aged 7–17 years.^{38–42}

We will ask parents to complete questionnaires on their own depressive and anxiety symptoms and quality of life using the following measures:

- ▶ *The Quick Inventory of Depressive Symptomatology*.⁴³
- ▶ *The Generalised Anxiety Disorder Scale*.⁴⁴
- ▶ *The Care-related Quality of Life Instrument*,⁴⁵ a measure of the impact of providing informal care on caregivers in terms of subjective burden and happiness.

Health resource utilisation

HRU is a parent-reported measure which includes: (1) physician visits (family physician, paediatrician, neurologist, psychiatrist and other specialists); (2) emergency department visits; and (3) number of hospitalisations and number of days hospitalised. We will also measure caregivers' productivity days lost related to their child's health.

Neuroimaging

Timing

Neuroimaging measures will be collected at baseline and 12 months postoperatively (MR-based measures only). Patients who are ineligible for neuroimaging without sedation may still be enrolled for collection of clinical and neuropsychological data without the imaging component.

MRI

At SickKids, MR imaging will be acquired on our research scanner, a Siemens Prisma 3T using the 20-ch head and neck matrix coil. Imaging at participating sites will be performed on MRI scanners with similar capabilities and imaging protocols will be matched as closely as possible. Preimplantation, the following images will be acquired:

1. *Five minutes eyes-open resting state BOLD fMRI*, during which participants will be instructed to passively view a centrally presented fixation cross (repetition time (TR): 1500 ms, echo time (TE): 30 ms, fractional anisotropy (FA): 70°, field of view (FOV): 222×222×150 mm, 3.0 mm isotropic voxels).
2. *Sagittal T1-weighted 3D Magnetization Prepared - Rapid Gradient Echo (MPRAGE) images* (TR: 1870 ms, TE: 3.14 ms, FA: 9°, FOV: 240×256×192 mm, 0.8 mm isotropic voxels).
3. *Sagittal T2-weighted images* (TR: 3200 ms, TE: 408 ms, FOV: 263×350×350 mm, 0.8 mm isotropic voxels).

4. *Multishell DTI* (TR: 3800 ms, TE: 73 ms, FOV: 244×244×140 mm, 2.0 mm isotropic voxels) at gradient strengths of $b=1000\text{ s}\cdot\text{mm}^{-2}$ with 36 directions; $b=1600\text{ s}\cdot\text{mm}^{-2}$ with 46 directions; $b=2600\text{ s}\cdot\text{mm}^{-2}$ with 67 directions.

For images acquired at the 12-month follow-up, we have adapted the above sequences for compatibility with the MR-conditional VNS stimulator. Additionally, these images will be acquired at 3T with a head transmit/receive coil, which is available at all participating institutions acquiring these images.

1. *Axial T1-weighted 3D images* (TR: 1640 ms, TE: 2.3 ms, FA: 8°, FOV: 263×350×350 mm, 0.5 mm isotropic voxels, 2D distortion corrected, iPAT off).
2. *Single-shell diffusion weighted imaging* (TR: 13700 ms, TE: 92 ms, FOV: 220×220×144 mm, 3.4×3.4×3.0 mm voxels, 30 direction, $b=1000\text{ s}\cdot\text{mm}^{-2}$).
3. *Seven minutes eyes-open resting state BOLD fMRI* (TR: 2530 ms, TE: 30 ms, FA: 90°, FOV: 220×220×144 mm, 2.7×2.7×4.0 mm voxels).

During anatomical and DTI scans, participants are invited to view their choice of movie through the available MRI video systems at each institution, typically MRI-compatible goggles.

The MR session will take approximately 1 hour. In our experience, this amount of time is sufficient for the children to become acclimatised and settled, run all the sequences and allow for repetition due to movement if necessary. Structural scans will be pushed to the clinical Picture Archiving and Communication System (PACS) and read by a neuroradiologist. Incidental findings will be shared with the family. Given our extensive experience in paediatric imaging, we do not anticipate any technical challenges in data collection.

Magnetoencephalography

MEG data will be recorded at 2400 Hz with an online 600 Hz antialiasing low-pass filter using a 151-channel CTF system (CTF MEG International Service, Coquitlam, British Columbia, Canada) within a magnetically shielded room and processed off-line. MEG recording will take half an hour, with breaks as needed. MEG data will be acquired with continuous head localisation allowing us to reject data with excessive head motion.^{46,47} Resting state MEG will be acquired while participants are positioned supine for 5 min with eyes open focusing on a fixation cross and for 10 min viewing the Inscapes video; a non-social, non-verbal movie paradigm consisting of slowly moving abstract shapes with a gentle piano score^{48,49} produced with the goal of increasing compliance in children while maintaining the resting state as much as possible.

Somatosensory evoked fields (SEFs)

SEFs will be acquired during a median nerve stimulation paradigm (electrical stimulation, constant current square wave, 0.2 ms duration, 4 Hz, 400 trials, supramotor threshold, median nerve at the wrist, left arm).⁵ We have previously successfully applied this method to detect



somatosensory responses in children with epilepsy.⁵⁰ The afferent pathways that produce the SEF are closely related to the ascending brainstem circuits of the VagAN,^{51 52} which also project to the primary somatosensory cortex.⁵¹ SEF is therefore ideal to study associations between afferent brainstem pathways and seizure response to VNS.

Data analysis

Treatment outcomes

To assess the outcomes of VNS, we will evaluate the baseline characteristics and outcomes at each follow-up on all parent-reported and child-reported measures. For each participant, there will be frequency measurements of the main (most disabling) and the total (all types) of seizures. This will inform the relationship between VNS and the quality of life of children and their caregivers. We will use absolute change in seizure outcome (McHugh Scale) at 2 years post implantation as the dependent variable in a repeated measures analysis of variance. The independent variables will include age, age at seizure onset, number of antiseizure drugs, ILAE classification, normal versus abnormal MRI, type and location of lesion (if applicable). Bi-variable regression will be used to identify variables for inclusion into multivariable linear regression analysis, and those with $p < 0.2$ will be included in the multivariable regression. A subgroup analysis will be performed for children with resective surgery.

Structural and functional imaging analysis

Imaging correlates of outcome will be evaluated using a hierarchical linear mixed effects model including age and seizure outcomes as explanatory variables to be regressed against neuroimaging data. Analysis of the neuroimaging data will consist of (1) measures of microstructure (fractional anisotropy), (2) inter-regional structural connectivity (on the basis of streamline fibre-tracking), (3) measures of functional connectivity (bold correlations in fMRI, envelope amplitude correlations in MEG, bandlimited phase synchrony in MEG) and (4) evoked fields in MEG. The proposed work will additionally profile the connectome of VNS responders and non-responders patients to develop a predictive model and identify the relevant circuitry mediating the therapeutic effect of treatment. Responders to VNS will be defined as those who experience 50% or greater reduction in seizure frequency after VNS, as is consistent with the literature.¹⁸ Greater granularity will result from collection of outcomes such as the SSQ and HRQoL, which can be directly compared with seizure response and neuroimaging data.

Our previous neuroimaging studies in this population have revealed the following correlates to VNS responsiveness: (1) VNS responders exhibit enhanced preoperative connectivity of the thalamus to the anterior cingulate cortex and left insula compared with non-responders on rs-fMRI¹⁸; (2) responders have higher fractional anisotropy values in left-sided thalamocortical, limbic and hemispheric association fibres compared with

non-responders on DTI¹⁹; (3) responders demonstrate significantly greater functional connectivity in a network encompassing left thalamic, insular and temporal nodes on preoperative MEG¹⁹; and (4) responders show significantly greater functional connectivity in limbic and sensorimotor brain networks in response to median nerve stimulation on SEFs recorded during MEG.²⁰ These findings were supported using a support vector machine (SVM) learning algorithm trained to classify response to VNS based on this connectivity, with responders correctly classified with 86% and 89.5% accuracy.^{18 19}

Predictive machine learning model development

Using multidimensional data, we will develop, publish and share with the research community a prediction model for presurgical identification of children undergoing VNS. An appropriate machine learning model will be selected and trained using inputs (structural and functional connectivity and SEF properties and connectivity) and known responses (McHugh class) to find the best classification scheme to categorise patients as responders or non-responders. We will use supervised machine learning algorithms, during which a labelled training dataset is used first to train the underlying algorithm, then applied to an unlabeled test dataset to categorise them into similar groups. Accepted outcome measures applicable to a range of machine learning models will be used to measure how well the model can distinguish between the two cohorts (responders vs non-responders). Different supervised machine learning models will be tested to identify the method to provide the best predictive power; a non-comprehensive list of model options include logistic, random forest, decision tree, SVM, XGBooster, neural network. Not only will this tool stand to benefit patients who may undergo VNS for medically refractory epilepsy, it will also provide a robust framework for characterising neural connectivity and applying this knowledge to primary neurological conditions, amenable to surgery.

Patient and public involvement

Patients and their families were not involved in the design of the original protocol. The dissemination of the study results will involve patients, families and the public as data are planned to be presented at epilepsy awareness events.

ETHICS AND DISSEMINATION

This study was approved by the Hospital for Sick Children Research Ethics Board (REB number 1000061744). This study has also been approved by the Saint Justine University Hospital Center REB, Nicklaus Children's Research Institute Office for Human Research Protection Program, Mattel Children's Hospital and David Geffen School of Medicine at the University of California Los Angeles Institutional Review Board (IRB), University of Alabama IRB for Human Use, Arkansas Children's Hospital IRB, IRB Nicklaus Children's Research Institute

Office for Human Research Protection Program, University of Pittsburgh IRB, Seattle Children's Hospital IRB, the University of British Columbia/Children's and Women's Health Centre of British Columbia REB, University of Utah IRB, the Washington University in St. Louis IRB, the Children's Hospital of Wisconsin IRB and the Baylor College of Medicine IRB. Participants, or substitute decision-makers, will provide informed consent prior to be enrolled in the study. Any incidental findings will be shared with a physician within the patient's circle of care for disclosure and appropriate follow-up. This study will allow us to assess the effectiveness of VNS in children with intractable epilepsy in a detailed and methodical manner. By identifying the factors that will predict good seizure outcome, we will be able to better predict patients who will benefit most from VNS and assist with appropriate patient selection on the basis of clinical and radiographic predictors. VNS is associated with significant capital and consumable costs related to the procedure. In addition to avoiding unnecessary surgeries in patients who are unlikely to benefit from therapy, improved patient selection will result in better allocation of healthcare resources and provide more access to VNS therapies for patients who may not be currently considered candidates. This work will also serve as a framework for applying connectomics to other neurological diseases as a novel approach for optimising patient care.

It is imperative to identify potential challenges to research productivity and methods to mitigate such potential obstacles. We anticipate challenges related to the multicentre nature of the study; imaging in the paediatric population; and confounding effects of clinical heterogeneity, including antiepileptic drugs. In relation to the multicentre nature of the study, we have standardised data collection across the centres. Quality assessment and control is performed on all neuroimaging datasets collected from the multisite collaboration. We will also apply multilevel random-effects statistics, which theoretically accounts for differences among centres. We have had success validating and integrating neuroimaging data from multiple centres using this approach.⁶ It should be emphasised that some degree of variability is welcome, as we wish to test the predictive model using data from the different centres in order to generalise its utility. Second, imaging in the paediatric population is associated with important challenges. All participating centres have exceptional and unique experience in the imaging of children. Our techniques of preimaging counselling and rehearsal have been successful in collecting imaging data on hundreds of school age children in special populations, including children with intractable epilepsy. Third, there will be unavoidable heterogeneity in clinical factors within each child studied, for instance the medications that are administered. We will collect an extensive database of clinical, electrophysiological and imaging variables to test whether any confounding factor is contributing to heterogeneity in VNS responsiveness or differences in connectomics. Importantly, our hypotheses

are grounded in the underlying neurobiology of the VNS circuitry; the common VagAN is thought to mediate treatment effect.⁵³ Because of these a priori considerations, we have previously performed connectomics studies in comparable patient cohorts successfully.⁵

We anticipate that integrated knowledge translation will include a final predictive model derived from this research, which will be freely available for download on a supported online platform for clinicians and scientists worldwide to improve patient selection for VNS in children with medically intractable epilepsy.

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