Surgical Target Fact Brief: Purpose Statement

Medtronic DBS Surgical Target Fact Brief:

Subthalamic Nucleus (STN)

Globus Pallidus internus (GPi)

Ventralis intermedius (Vim) Nucleus of the Thalamus

Anterior Nucleus of the Thalamus (ANT)

The purpose of this document is to provide summary technical information related to DBS lead placement within targeted brain nuclei for approved indications/intended uses of Medtronic DBS Therapy. Implanting physicians should have expertise with functional stereotactic neurosurgical treatment of movement disorders and/or epilepsy. Such expertise should include knowledge of the anatomical and neurophysiological characteristics of the targeted nucleus, surgical and/or implantation techniques for the Medtronic DBS System, operational and functional characteristics of the Medtronic DBS System, and experience in the continued management of patients by stimulation parameter adjustment. Physicians should use their medical judgment and product labeling to optimize therapy for individual patients.

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1. STN Anatomy

a. Biconvex nucleus situated within the midbrain, ventral to the thalamus, and contains both motor and non-motor functional sub-regions:

Dorsolateral Region:	*Sensorimotor Neurons - the target region for Medtronic deep brain stimulation*
Ventromedial Region:	*Limbic Neurons*
Central Region:	*Associative and Oculomotor Neurons*

b. The size and position of STN across a population are found to be highly variable.

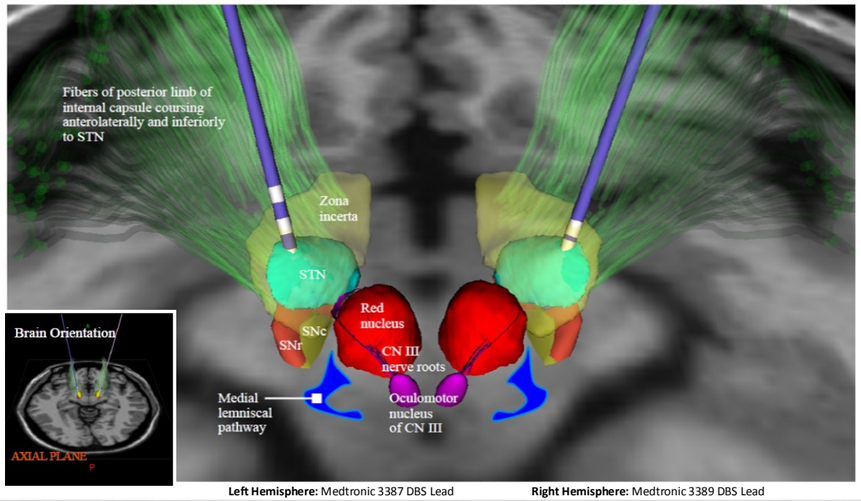
Average dimensions *of STN :*

***Dorsoventral Axis:**	8.5 mm
***Anteroposterior Axis:**	7.7 mm
***Mediolateral Axis:**	6.0 mm
Average Volume:	~ 106 mm^3

** As determined from MRI in 26 patients (16 males, 23-70 years old & 10 females, 38-71 years old) with Parkinson's disease. Mean values shown. Note that the STN is subject to age-related shrinkage, particularly in the anteroposterior and mediolateral axes.*

c. Dorsolateral STN Somatotopy: Leg-related neurons located more dorsally, anteriorly and medially. Arm-related neurons are more ventral and lateral.

2. Anatomical Neighborhood



Left Hemisphere: Medtronic 3387 DBS Lead **Right Hemisphere:** Medtronic 3389 DBS Lead

2.1 ANATOMY SURROUNDING STN:

Posterior Limb of Internal Capsule
Lateral, anterior and ventral to dorsolateral STN

Zona incerta
Dorsal to dorsolateral STN

Substantia Nigra
Ventral to dorsolateral STN

Medial Lemniscus
Posterior to dorsolateral STN

Red Nucleus
Posteromedial to dorsolateral STN

Nerve Roots of CN III
Ventromedial to dorsolateral STN

2.2 The desired target for a Medtronic DBS implant for Parkinson's Disease or Dystonia[§] within the STN is thought to be:

a. Along a trajectory where at least 5+ mm of neurons characteristic of motor STN are observed via MER
b. Where stereotypical side-effects are generated at stimulation parameters greater than the therapeutic window as determined by the programming physician
c. Where improvement of motor symptoms is observed in response to test stimulation
d. Where dyskinesias may have been elicited during intra-operative test stimulation

3. AC-PC Targeting Coordinates and Anatomical Approach Angles for STN

3.1 AC-PC COORDINATES*

X:	11.0 — 12.0 mm	Lateral from AC-PC Line
Y:	3.0 — 4.0 mm	Posterior to MCP
Z:	4.0 — 5.0 mm	Inferior to AC-PC Line

3.2 TRAJECTORY ANGLES*

ANTERIOR:	*50°—70°* Posterior from an axial plane parallel to AC-PC plane
	OR, EQUIVALENTLY STATED AS:
	20°—40° Anterior from a coronal plane perpendicular to AC-PC plane
LATERAL:	*10°—20°* Lateral from a sagittal plane perpendicular to AC-PC plane

**Target coordinates and trajectory angles are patient-specific and ultimately determined by underlying cortex, ventricles, vessels, anatomical variability and surgeon preference*

Abbreviations Used Throughout:

AC: *Anterior Commissure* PC: *Posterior Commissure* MCP: *Mid-Commissural Point* CN: *Cranial Nerve* MER: *Microelectrode Recording*
ALO: *Apraxia of Lid Opening* SNr: *Substantia Nigra pars reticulata* SNc: *Substantia Nigra pars compacta* STN: *Subthalamic Nucleus*

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4. Characteristics of a STN MER Trajectory

Although anatomical variability is a factor, a trajectory with target positioned at the base of the lateral STN using approach angles of ~ 15 degrees lateral and ~ 60 degrees posterior off of the AC-PC plane will often encounter the following structures:

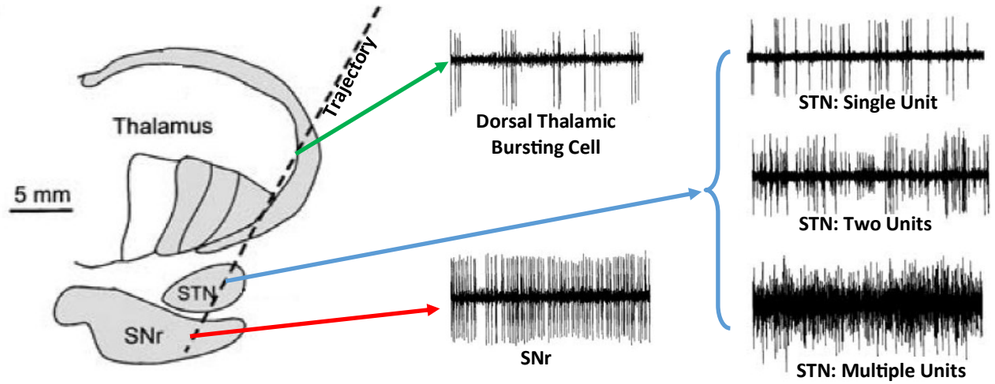
Descending along the trajectory...

Dorsal or Reticular Thalamus	- Low density of spontaneously firing neurons, not movement-responsive
Ventral Oralis anterior* (VOa) Nucleus of the Thalamus OR ***Ventral Oralis posterior* (VOp) Nucleus of the Thalamus***	- Low density of sporadically firing neurons, not movement-responsive
	- Moderate density and discharge frequency, voluntary movement-responsive cells - Presence of cells with bursting activity
Base of Thalamus	- Marked decrease or cessation of neuronal activity
Zona Incerta	- Low frequency units, low cellular density
STN	- Significant increase in background activity and neuronal density - Very active with possible tremor cells - Movement-responsive neurons in dorsal 2/3 of STN - Dramatically elevated background
White Matter (Quiet zone)	- Quiet zone of variable thickness between STN and SNr
SNr	- High-frequency activity with regular discharge rates, lower background

* *dependent on trajectory and angle. A more anterior approach may traverse VOa while a more posteriorly-positioned approach may encounter VOp*

5. Representative MER Signatures Along a STN Trajectory

If MER is performed, the following are representative traces in various nuclei along a trajectory (dotted line) to the STN. The drawing represents a sagittal section adapted from the Schaltenbrand Wahren atlas. Each trace is 1 second long.



6. Is the Electrode in the Correct Place?

Location*	MER Observations	Stimulation Effects (& *Anatomical Correlate*)
Posterior	- Thalamic cells were active and typical of Vop - STN encountered lower than expected - STN cross section < 5 mm	- Paresthesias (*Medial lemniscus*)
Anterior	- STN encountered higher than expected - SNr not detected (or large gap between STN and SNr) - STN cross section < 5 mm - Less thalamus encountered than expected	- Muscle Contractions, Dysarthria (*Internal Capsule*)
Lateral	- STN encountered higher than expected - SNr not detected (or large gap prior to) - Little to no thalamus encountered - STN cross section < 5mm	- Muscle Contractions, Dysarthria, Contralateral Gaze Deviation (*Internal Capsule*)
Medial	- STN encountered lower than expected - Larger cross section of thalamus than expected - SNr not encountered - STN cross section < 5 mm - "STN-like" activity > 8 mm (suspect Red Nucleus, posteromedial)	- Diplopia, deviation of ipsilateral eye, dizziness, ALO (*CN III*) - Personality/impulsivity changes, depression (*Limbic STN*) - Sweating, nausea, extreme discomfort, paresthesias, warm sensations (*Red nucleus*, *posteromedial*)
Superior†	- Thalamic cells observed or low cellular activity (Zona incerta)	- Possible impact on dyskinesias and/or tremor (*Zona incerta*)
Inferior†	- SNr cells encountered or no cellular activity	- Possible mood changes, akinesias (*SNr*)

* *relative to dorsolateral STN* † *along the trajectory path*

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1. GPi Anatomy

a. One of the primary output nuclei of the basal ganglia, the GPi contains both motor and non-motor functional sub-regions.

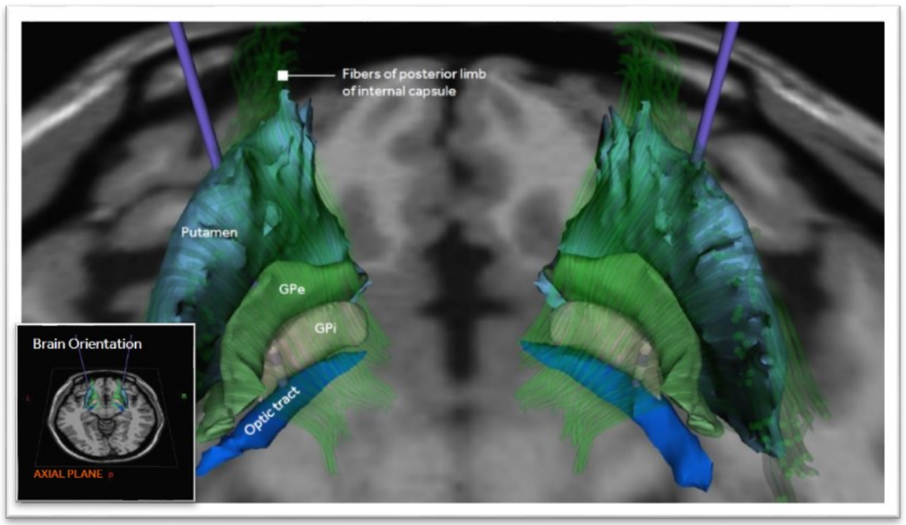
Posteroventral Lateral Region:	*Sensorimotor Neurons - the target region for Medtronic deep brain stimulation*
Anteromedial Region:	*Associative Neurons*
Anteroventral Region:	*Limbic Neurons*

b. Average dimensions of GPi along different axes:

Dorsoventral Axis:	~ 10 mm
Anteroposterior Axis:	~ 15 mm
Mediolateral Axis:	~ 8 mm
Average Volume:	~ 500 mm^3

c. Somatotopy: Arm representation is ventral, lateral and posterior. Leg representation is further anterior, dorsal and medial.

2. Anatomical Neighborhood



2.1 ANATOMY SURROUNDING GPi:

Posterior Limb of Internal Capsule
Medial and posterior to GPi

Globus Pallidus externus (GPe)
Lateral to GPi

Optic Tract
Ventral to GPi

2.2 The desired target for a Medtronic DBS implant for Parkinson's Disease or Dystonia[§] within the GPi is thought to be:

a. Along a trajectory where neurons characteristic of motor GPi are observed via MER (if performed)

b. Where stereotypical side-effects are generated at stimulation parameters greater than the therapeutic window as determined by the programming physician

c. Where improvement of motor symptoms (Parkinson's Disease only) was observed in response to test stimulation

3. AC-PC Targeting Coordinates and Anatomical Approach Angles for GPi

3.1 STANDARD* AC-PC COORDINATES

X:	18 - 21 mm	Lateral from AC-PC Line
Y:	2 - 3 mm	Anterior to MCP
Z:	3 - 6 mm	Inferior to AC-PC Line

Target is often close to the dorsolateral border of the optic tract

3.2 STANDARD* TRAJECTORY ANGLES

ANTERIOR: *~60°* Posterior from an axial plane parallel to AC-PC plane

OR, EQUIVALENTLY STATED AS:

~30° Anterior from a coronal plane perpendicular to AC-PC plane

LATERAL: ~0 to 5° Lateral from a sagittal plane perpendicular to AC-PC plane
(consideration should be given to maintaining a parasagittal approach)

**Target coordinates and trajectory angles are patient-specific and ultimately determined by underlying cortex, ventricles, vessels and anatomical variability*

Abbreviations Used Throughout:

AC: *Anterior Commissure* PC: *Posterior Commissure* MCP: *Mid-Commissural Point* MER: *Microelectrode Recording*
GPi: *Globus Pallidus internus* GPe: *Globus Pallidus externus*

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Brief Statement: Medtronic DBS Therapy for Epilepsy

Medtronic DBS Therapy for Epilepsy: Product labeling must be reviewed prior to use for detailed disclosure of risks.

Indications: Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

Contraindications: Medtronic DBS Therapy is contraindicated for patients who are unable to properly operate the neurostimulator. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if the patient has an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

Warnings and Precautions: There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths. Extreme care should be used with lead implantation in patients with a heightened risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious injury, including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Tunneling the extension too superficially or too deeply may result in nerve or vascular injury, or tunneling through unintended anatomy. The lead-extension connector should not be placed in the soft tissues of the neck due to an increased incidence of lead fracture. Cessation, reduction, or initiation of stimulation may potentially lead to an increase in seizure frequency, severity, and new types of seizures. Symptoms may return with an intensity greater than was experienced prior to system implant, including the potential for status epilepticus. Loss of coordination in activities such as swimming may occur. Depression, suicidal ideations and suicide have been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause-and-effect relationship has been established. Preoperatively, assess patients for depression and carefully balance this risk with the potential clinical benefit. Postoperatively, monitor patients closely for new or changing symptoms of depression and manage these symptoms appropriately. Patients should be monitored for memory impairment. Memory impairment has been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause and effect relationship has been established. The consequences of failing to monitor patients are unknown. When stimulation is adjusted, monitor patients for new or increased seizures, tingling sensation, change in mood, or confusion.

Adverse Events: Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy and weight gain or loss.

The safety and effectiveness of this therapy has not been established for patients without partial-onset seizures, patients who are pregnant or nursing, patients under the age of 18 years, patients with coagulopathies, and patients older than 65 years.

Medtronic DBS systems are MR Conditional which means they are marked to indicate they are safe in the MR environment as long as certain conditions are met. Read and fully understand the *MRI Guidelines for Medtronic deep brain stimulation systems* before conducting the MRI examination. Go to www.medtronic.com/mri or contact Medtronic at 1-800-707-0933 for a copy. Also review current MRI manufacturer labeling before conducting the MRI.

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4. Characteristics of a GPi MER Trajectory

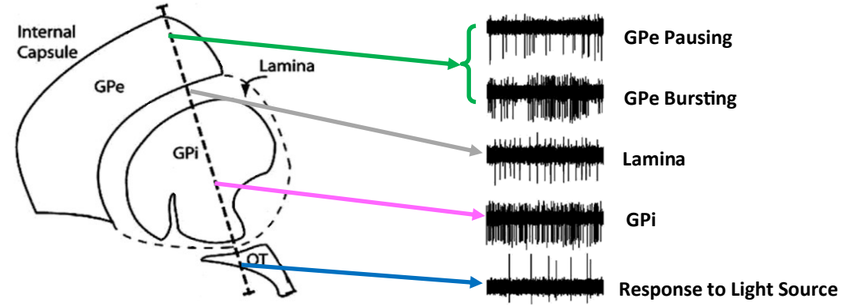
Although anatomical variability is a factor, a trajectory with target positioned at the base of the posterior GPi using approach angles of ~ 10 degrees lateral and ~ 60 degrees posterior off of the AC-PC plane will often encounter the following structures:

Descending along the trajectory...

Putamen OR Caudate*	- Low density of spontaneously firing neurons, not movement-responsive
Lamina	- Marked decrease or complete cessation of neuronal activity (thin layer of white matter)
GPe	- Two general types of neuronal discharge observed: - **Pausing Cells:** Exhibit sustained, high frequency discharges interrupted by brief pauses - **Bursting Cells:** Exhibit short, high-frequency bursts interrupted by long periods of inactivity - These cells types are more reliably detected in the GPe of PD patients than those of dystonic patients
Lamina	- Marked decrease or complete cessation of neuronal activity (thin layer of white matter)
GPi	- High density, high frequency cells encountered - Moderate to low background activity - Possible tremor cells and motor-responsive neurons - A thin internal lamina exists within the GPi which can be misinterpreted as the base of GPi - Unlike parkinsonian patients, GPi and GPe signatures of dystonia patients can have similar discharge frequencies making the distinction between the two difficult
Optic Tract	- Cessation of neuronal activity. Activity may be evoked during introduction of bright light to patient eyes - The absence of an optic tract light response, in the presence of a clear region of motor-GPi, should not weigh too heavily on the decision as to the optimal target location

** A more lateral trajectory angle is more likely to encounter putamen while a more medial trajectory angle is more likely to encounter caudate*

5. Representative MER Signatures Along a GPi Trajectory



Sagittal section through the pallidum showing trajectory. *Representative MER traces.*

6. Is the Electrode in the Correct Place?

Location*	MER Observations	Stimulation Effects (& *Anatomical Correlate*)
Posterior	- Entry into GPe and GPi lower than expected - Internal capsule encountered - Ratio of length of GPe to GPi: High	- Muscle contractions, dysarthria (*Internal capsule*)
Anterior	- Entry into GPe and GPi lower than expected - Internal capsule not encountered - Ratio of length of GPe to GPi: High	- No effect (*central GPi*)
Lateral	- Entry into GPe and GPi lower than expected - Internal capsule not encountered - Ratio of length of GPe to GPi: High	- No effect (*GPe*)
Medial	- Entry into GPe and GPi higher than expected - Internal capsule encountered - Ratio of length of GPe to GPi: Low	- Muscle contractions, dysarthria (*Internal capsule*)
Inferior†	- Lack of cellularity, presence of optic tract	- Phosphenes (*optic tract*)

** relative to posteroventral GPi † along the trajectory path*

1. Vim Anatomy

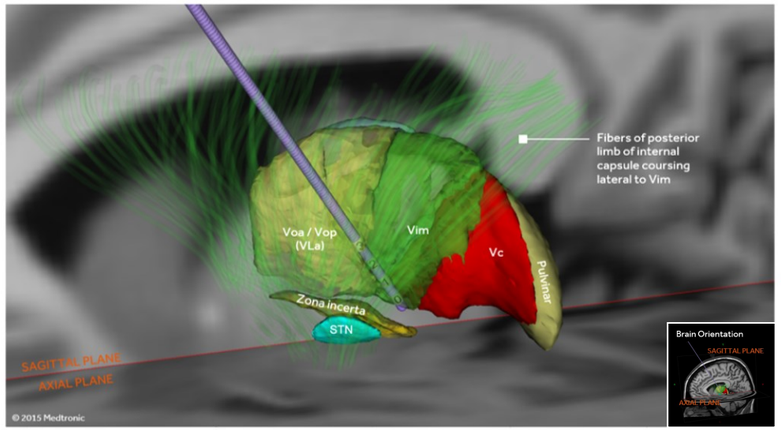
a. The Vim is a cerebellar-receiving nucleus that contains sensorimotor neurons and is part of the ventral tier thalamic nuclei.

b. Average dimensions of Vim:

Dorsoventral Axis:	~ 10 mm
Anteroposterior Axis:	~ 3-4 mm
Mediolateral Axis:	~ 10 mm

c. Vim Somatotopy: Leg-related neurons located laterally within the nucleus. Face-related neurons are located medially

2. Anatomical Neighborhood



2.1 ANATOMY SURROUNDING Vim:

Posterior Limb of Internal Capsule
Lateral to Vim

Ventralis caudalis (Vc) Nucleus of the Thalamus
Posterior to Vim

Ventralis oralis posterior (Vop) Nucleus of the Thalamus
Anterior to Vim

Zona incerta
Ventral to Vim

Centromedian/Parafascicular Complex of the Thalamus (CM/Pf) - Not shown
Medial to Vim

2.2 The desired target for a Medtronic DBS implant for Parkinson's Disease tremor or Essential Tremor within the Vim is thought to be:

a. Along a trajectory where motor neurons modulated by passive patient movements and characteristic of Vim are observed via MER (if performed)

b. Where stereotypical side-effects are generated at stimulation parameters greater than the therapeutic window as determined by the programming physician

c. Where improvement of patient tremor is observed in response to test stimulation, anterior to the region where stimulation evokes persistent sensations

d. In the posteroventral aspect of the Vim, 2-3 mm anterior to the border with the Vc nucleus

3. AC-PC Targeting Methods and Anatomical Approach Angles for Vim

3.1 STANDARD* AC-PC COORDINATES

Methods for Calculating X:

1) **X:** 10.0 - 11.5 mm lateral to wall of third ventricle at Y position

2) **X:** 11.5 mm + 1/2 width of third ventricle, lateral to AC-PC line at Y position

Methods for Calculating Y:

1) **Y:** 25 - 27% of AC-PC line length posterior to MCP

2) **Y:** 6 mm anterior to PC (with 4 mm anterior to PC correlating with Vc)

Calculating Z:

Z: Positioned at 0.0 mm (at the axial location of the AC-PC line)

3.2 STANDARD* TRAJECTORY ANGLES

ANTERIOR: *~60°* Posterior from an axial plane parallel to AC-PC plane

OR, EQUIVALENTLY STATED AS:

~30° Anterior from a coronal plane perpendicular to AC-PC plane

LATERAL: ~0 to 15° Lateral from a sagittal plane perpendicular to AC-PC plane

**Target coordinates and trajectory angles are patient-specific and ultimately determined by underlying cortex, ventricles, vessels and anatomical variability*

Abbreviations Used Throughout:

AC: *Anterior Commissure* PC: *Posterior Commissure* MCP: *Mid-Commissural Point* MER: *Microelectrode Recording* ZI: *Zona incerta*
Vim: *Ventralis intermedius* Voa: *Ventralis oralis anterior* Vop: *Ventralis oralis posterior* Vc: *Ventralis caudalis* STN: *Subthalamic Nucleus*

Brief Statement: Medtronic DBS Therapy for Parkinson's Disease, Tremor and Dystonia

Medtronic DBS Therapy for Parkinson's Disease, Tremor and Dystonia: Product labeling must be reviewed prior to use for detailed disclosure of risks.

Indications:

Medtronic DBS Therapy for Parkinson's Disease: Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson's Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

Medtronic DBS Therapy for Tremor: Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) using Medtronic DBS Therapy for Tremor is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Medtronic DBS Therapy for Dystonia: Unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Dystonia is indicated as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above.

Contraindications: Medtronic DBS Therapy is contraindicated for patients who are unable to properly operate the neurostimulator and, for Parkinson's disease and Essential Tremor, patients for whom test stimulation is unsuccessful. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if they have an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

Warnings and Precautions: There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths and, for Parkinson's disease and essential tremor, a potential risk to drive tremor using low frequency settings. Extreme care should be used with lead implantation in patients with an increased risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious injury, including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Tunneling the extension too superficially or too deeply may result in nerve or vascular injury, or tunneling through unintended anatomy. The lead-extension connector should not be placed in the soft tissues of the neck due to an increased incidence of lead fracture. Abrupt cessation of stimulation should be avoided as it may cause a return of disease symptoms, in some cases with intensity greater than was experienced prior to system implant ("rebound" effect). Onset of status dystonicus, which may be life-threatening, may occur in dystonia patients during ongoing or loss of DBS therapy. Patients using a rechargeable neurostimulator for Parkinson's disease or Essential Tremor should check for skin irritation or redness near the neurostimulator during or after recharging, and contact their physician if symptoms persist. Loss of coordination in activities such as swimming may occur. Depression, suicidal ideations and suicide have been reported in patients receiving Medtronic DBS Therapy for Movement Disorders, although no direct cause-and-effect relationship has been established.

Adverse Events: Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy, and weight gain or loss.

Safety and effectiveness has not been established for patients with previous surgical ablation procedures, dementia, coagulopathies, or moderate to severe depression, or patients who are pregnant. Parkinson's disease and essential tremor: safety and effectiveness has not been established for patients under 18 years or patients with neurological disease other than idiopathic Parkinson's disease or Essential Tremor. Essential tremor: safety and effectiveness has not been established for bilateral stimulation or for patients over 80 years of age. Dystonia: age of implant is suggested to be that at which brain growth is approximately 90% complete or above.

Humanitarian Device (Dystonia): Authorized by Federal Law as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated.

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[§]Humanitarian Device (Dystonia): The effectiveness of this device for this use has not been demonstrated.

4. Characteristics of a Vim MER Trajectory

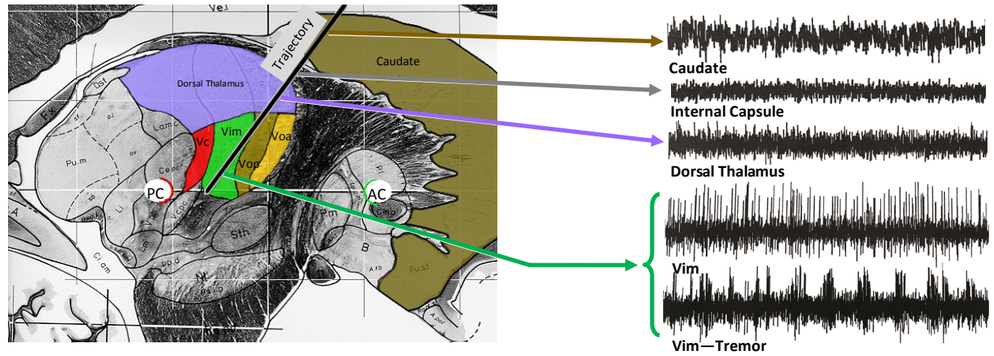
Although anatomical variability is a factor, a trajectory with target positioned at the base of the posterior Vim using approach angles of ~ 15 degrees lateral and ~ 60 degrees posterior from the AC-PC plane will often encounter the following structures:

Descending along the trajectory...

Caudate Nucleus	- Very slow rate of spontaneously discharging cells
Internal Capsule	- Quiet, no cellular activity
Dorsal Thalamus	- Relatively quiet in the awake patient but shows occasional slow bursting activity
Vop	- Presence of Kinesthetic cells which fire in synchrony with voluntary movements - Possible detection of tremor synchronous cells - Presence of non-tremor synchronous bursting cells
Vim	- Kinesthetic cells which fire in synchrony with passive patient movements - Kinesthetic cells are somatotopically organized: Face medial, foot lateral - Possible detection of tremor synchronous cells
Vc *(if slightly posterior)*	- Tactile cells responding to specific deep and, if slightly more posteriorly, superficial tactile stimuli - Tactile cells are somatotopically organized: Mouth medial, foot lateral
Zona incerta	- Generally low background and sporadic cellular activity

5. Representative MER Signatures Along a Vim Trajectory

Representative trajectory (LEFT) targeting the posteroventral aspect of Vim and corresponding recordings (RIGHT)



6. Is the Electrode in the Correct Place?

Location*	MER Observations (*& Anatomical Correlate*)	Stimulation Effects (*& Anatomical Correlate*)
Posterior	- Cells responsive to deep pressure (anterior Vc, or "Proprioceptive Shell") - Cells responsive to tactile stimulation of the patient - Exit thalamus lower than expected	- Paresthesias that increase in severity with increasing stimulation (*Vc nucleus*)
Anterior	- Entry point into thalamus lower than expected - Cells responsive to voluntary patient movements (*Vop*) - Non-tremor synchronous bursting cells present (*Vop*) - Tremor cells (*Vop and Vim*) - Exit thalamus higher than expected	- No effect (*Voa*) - Some improvement in tremor at higher stimulation thresholds (*Vop*)
Lateral	- Quiet stretch preceding late or no entry into Vim - Kinesthetic activity correlating with lower limb movements (*Vim*) - Sensory responsive cells correlating with lower limb tactile stimuli (*Vc*)	- Dysarthria, muscle contractions (contracting muscles correspond to the region of the capsular homunculus) (*Internal capsule*)
Medial	- Kinesthetic activity correlating with jaw movements (*Vim*) - If within Vc, sensory responsive cells correlating with oral/facial tactile stimuli	- Possible dysarthria in addition to tremor control (*medial Vim*) - No effect (*CM/Pf, medial to Vim nucleus*)
Superior†	- Low amplitude, sporadically firing cells (*Dorsal Thalamus*)	- No effect (*Dorsal thalamus*) - Possible impact on tremor (*Dorsal Vim/Vop*) - Lateral & Dorsal: Dysarthria, muscle contractions (*Internal capsule*)
Inferior†	- Low amplitude, sporadically firing cells (*Zona incerta, Prelemniscal radiation*)	- Possible impact on dyskinesias and/or tremor (*ZI, Prelemniscal radiation*) - Ventral & Medial: Ataxia (*Brachium conjunctivum*) - Ventral & Posterior: Paresthesias (*Medial lemniscus*) - Ventral & Lateral: Dysarthria, muscle contractions (*Internal capsule*)

** relative to posteroventral Vim* † *along the trajectory path*

1. ANT Anatomy

a. The anterior nucleus of the thalamus is located:
- at the anterior-superior-medial aspect of the thalamus and constitutes its anterodorsal border
- at the floor of the lateral ventricle

The ANT is partially enveloped by a myelin-rich sheath belonging to the mammillothalamic tract (MTT) and the internal medullary lamina.
It is surrounded by the choroid plexus, the thalamostriate vein, and the internal cerebral vein

b. Connectivity:
The ANT receives input from the mesial temporal structures via the fornix, mammillary body and MTT and sends projections to the ipsilateral cingulate cortex, medial frontal lobe, and temporal lobe. It is a central node in the Circuit of Papez

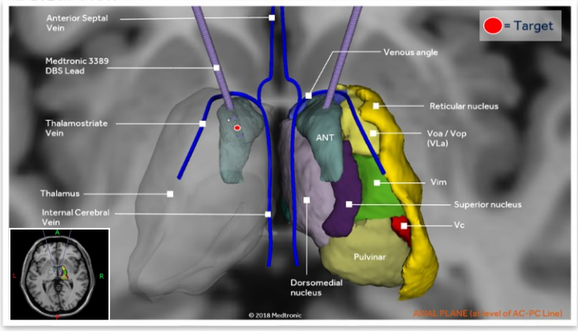
c. Average Dimensions of the ANT:
Due to the relatively large variations in individual anatomy of the anterior thalamic area in both histological and radiological studies, it is difficult to approximate sizes. However, one study* suggests, on average, the ANT is approximately:

Dorsoventral Axis:	~ 4.0 mm
Anteroposterior Axis:	~ 10.0 mm
Mediolateral Axis:	~ 5.5 mm

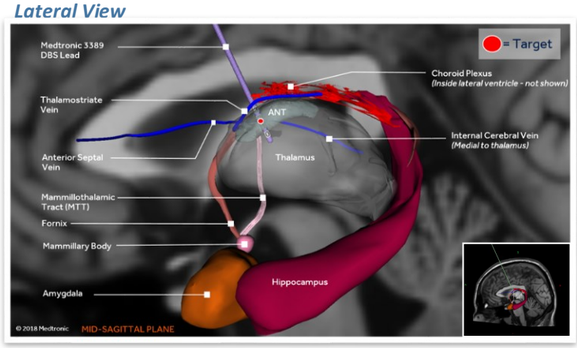
** As determined from a sample of 8 patients with medically refractory epilepsy using 3T STIR MR images. Mean values shown.*

2. Anatomical Neighborhood

Dorsal View



Lateral View



2.1 ANATOMY SURROUNDING ANT:

Thalamostriate Vein - *Anterior and lateral*	**Ventral Anterior nucleus** - *Lateral*	**Mammillothalamic Tract** - *Inferior*
Internal Cerebral Vein - *Medial*	**Dorsomedial nucleus** - *Inferomedial*	**Internal Medullary Lamina** - *Inferior, medial & lateral*

2.2 The desired target for a Medtronic DBS implant for epilepsy is:

a. Within the anteroventral subdivision of the ANT, superior and slightly posterior to the entry of the MTT into the ANT (see images above)
b. Identified along a trajectory utilizing a transventricular approach that avoids the major veins in the target region and the choroid plexus

3. AC-PC Targeting Coordinates and Anatomical Approach Angles for ANT

A high degree of anatomical variation has been reported in the location of ANT in stereotactic space in patients treated with DBS for epilepsy. Direct anatomical-based targeting on stereotactic MRI is preferable whenever possible.

3.1 AC-PC COORDINATES*

X:	5.0 — 6.0 mm	Lateral from AC-PC Line
Y:	0.0 — 2.0 mm	Anterior to MCP
Z:	10.0 —12.0 mm	Superior to AC-PC Line

3.2 TRAJECTORY OBJECTIVES* FOR TRANSVENTRICULAR APPROACH

ANTERIOR: *~60°* Posterior from an axial plane parallel to AC-PC plane
OR, EQUIVALENTLY STATED AS:
~30° Anterior from a coronal plane perpendicular to AC-PC plane

LATERAL: Transventricular angle, such that the trajectory runs through the vascular window between the superior choroidal and the thalamostriate veins while avoiding intraventricular vasculature.

Trajectory angle should be adapted to align with the individual shape of the ANT

**Target coordinates and trajectory angles are patient-specific and ultimately determined by underlying cortex, ventricles, vessels and anatomical variability*

Abbreviations Used Throughout:
AC: *Anterior Commissure* PC: *Posterior Commissure* MCP: *Mid-Commissural Point* ANT: *Anterior Nucleus of the Thalamus* MER: *Microelectrode Recording*
MTT: *Mammillothalamic Tract* IML: *Internal Medullary Lamina* DM: *Dorsomedial Nucleus of the Thalamus* VA: *Ventral Anterior Nucleus of the Thalamus*

Surgical Target Fact Brief: The Anterior Nucleus of the Thalamus (ANT)

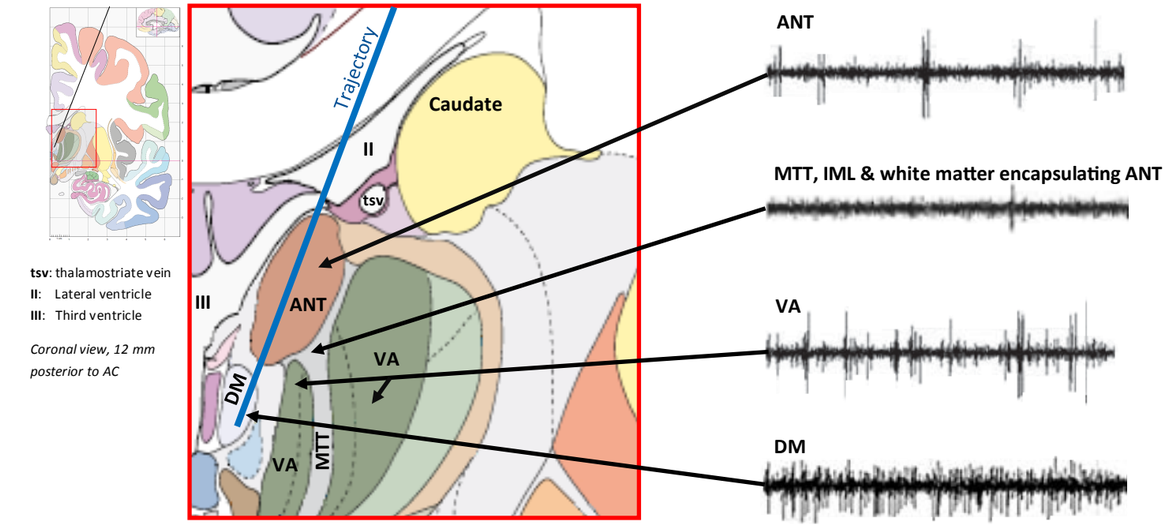
4. Characteristics of a Transventricular ANT MER* Trajectory

**** The value of MER for ANT DBS has not been established***

Descending along the trajectory...

Lateral Ventricle	Quiet
ANT	Low frequency spikes with low background activity and bursting cells present
Internal Medullary Lamina	Spiking activity attenuates at the inferior aspect of the ANT when electrode passes into the IML (white matter)
Dorsomedial (DM) Nucleus of the Thalamus	A slightly more **medial** trajectory may encounter the DM nucleus The DM exhibits more regular firing patterns than the ANT and with a lower spike amplitude
OR	
Ventral Anterior (VA) Nucleus of the Thalamus	A slightly more **lateral** trajectory may encounter the VA nucleus The VA exhibits higher frequency spiking activity than that observed in the ANT

5. Representative MER Signatures Along a Transventricular ANT Trajectory



tsv: thalamostriate vein
II: Lateral ventricle
III: Third ventricle

Coronal view, 12 mm posterior to AC

6. Is the Electrode in the Correct Place?

Location*	MER Observations	Stimulation Effects (*& Anatomical Correlate*)
Posterior	- Thinner MER cross-section if posterior to target region of ANT - Posterior to ANT = No neuronal activity (*IML*)	Published data not available
Anterior	- Anterior to ANT = No neuronal activity (*lateral ventricle*) - Cells representative of ANT if within the nucleus but anterior to target region	
Lateral	- No neuronal activity (*IML*) - Spiking activity with higher frequency than ANT (*VA nucleus*)	
Medial	- No neuronal activity (*IML*) - Spiking activity with lower spike amplitude and more regular firing patterns than ANT (*DM nucleus*)	
Inferior†	- No neuronal activity (IML) - Spiking activity with lower spike amplitude and more regular firing patterns than ANT (*DM nucleus - inferomedial*) - Spiking activity with higher frequency than ANT (*VA nucleus - inferolateral*)	

** relative to target region of ANT* *† along the trajectory path*

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