We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

6,300
Open access books available

170,000
International authors and editors

185M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Perspective Chapter: Functional Human Brain Connectome in Deep Brain Stimulation (DBS) for Parkinson's Disease (PD)

Germaine Hiu-Fai Chan

Abstract

Historically, the success of DBS depends on the accuracy of electrode localization in neuroanatomical structures. With time, diffusion-weighted magnetic resonance imaging (MRI) and functional MRI have been introduced to study the structural connectivity and functional connectivity in patients with neurodegenerative disorders such as PD. Unlike the traditional lesion-based stimulation theory, this new network stimulation theory suggested that stimulation of specific brain circuits can modulate the pathological network and restore it to its physiological state, hence causing normalization of human brain connectome in PD patients. In this review, we discuss the feasibility of network-based stimulation and the use of connectomic DBS in PD.

Keywords: connectome, deep brain stimulation, Parkinson's disease

1. Introduction

Parkinson's disease (PD) is the second commonest neurodegenerative disease affecting both motor and non-motor domains [1]. It affects 1 to 2% of persons over the age of 60 years [2]. At present, no treatment is available to stop or slow down disease progression. However, currently available therapies can offer symptomatic relief to the patients [1]. In general, with the use of oral dopaminergic treatment, their symptoms can be controlled for a few years after symptom onset before developing motor and non-motor complications [1, 3]. Device-aided therapies, especially deep brain stimulation (DBS), have been used in the management of advanced PD when oral pharmacological treatment is no longer sufficient to control the symptoms or when the patients cannot tolerate the drugs [4–9].

The success of DBS surgery depends on appropriate candidate selection, accuracy of localization of electrodes and optimal DBS programming and medication titration [10, 11]. Okun et al. reported that 46% of patients with referred DBS failure were found to have suboptimal lead placement. Among these patients with lead misplacement, 52% improved with lead replacement [10]. This highlights the importance of precise electrode localization in DBS surgery.

Historically, subthalamic nucleus (STN) and globus pallidus internus (GPi) are common surgical targets in PD patients undergoing DBS surgery [12–18]. Although neurostimulation at these surgical targets can improve motor function and may lead to a reduction in dopaminergic medication dosage, a few issues have been reported with the implantation of neurostimulators at STN and GPi. First, these surgical targets such as STN, though small, were found to be divided into functional subzones [19–21]. Therefore, even with precise electrode localization, patients undergoing DBS surgeries can develop neuropsychiatric complications. Lambert et al. showed that the STN was divided into 3 functional subzones (anterior: "limbic" subzone; middle: "associative" subzone; posterior: "motor" subzone) with the use of diffusion weighted imaging (DWI) [19]. Ewert et al. revealed that the GPi can divided into 7 subzones (motor, premotor, sensory, prefrontal, posterior parietal, temporal and occipital), of which motor, premotor and sensory subzones are grouped together as the sensorimotor functional zone and lie in the posterior third of the GPi [21]. Second, these surgical targets are small and close to other salient anatomical structures in the brain. Let us take the STN as an example. The STN is small ($12 \times 5 \times 3$ mm^3) and lies next to structures such as internal capsule, medial lemniscus, corticospinal tract, and red nucleus. With suboptimal electrode placement or overstimulation, electrical current can be spread to these adjacent structures, resulting in side effects (**Table 1**) [22]. Third, even though STN and GPi are known to be effective targets in relieving PD symptoms, different symptom may have small difference in the site for effective neurostimulation [23]. On the contrary, lesions from different brain locations can result in similar symptoms [24]. Therefore, PD DBS surgeries at these conventional surgical targets, even if the localization is accurate, can vary in treatment response. Furthermore, a PD patient may have more than one symptom, either motor or non-motor symptom, and so neurostimulation at one surgical target may not be sufficient to alleviate his symptoms.

Electrode location / Direction of current spread	Anatomical structures affected	Clinical effects
STN DBS		
Optimal location	STN	Dyskinesia
Too inferior / medial	Oculomotor fibers	Diplopia
Too posterior / medial	Medial lemniscus	Paraesthesia
Too anterior / lateral	Internal capsule Corticospinal fibers	Tonic muscle contraction
Too anterior / lateral	Internal capsule Corticobulbar fibers	Dysarthria
Too inferior	Cerebellothalamic tract	Ataxia
Too inferior	Substantia nigra	Mood changes
GPi DBS		
Too posterior / medial	Internal capsule	Tonic muscle contraction
Too posterior / medial	Internal capsule Corticobulbar fibers	Dysarthria
Too inferior	Optic tract	Visual phenomena

Table 1.
Side effects of STN / GPi DBS with respect to the anatomy of the surgical targets [22].

To better control symptoms with DBS surgery, researchers have explored the possibility of better localizing the sites responsible for patients' symptoms and linking these sites together to form a circuit or network. It has been postulated that if a circuit connecting these sites can be mapped out for each patient individually, stimulating the circuit, instead of the traditional way of stimulating the anatomical structure, may be a better therapeutic option.

In this review, we will discuss

• The concept of human connectome

• The concept of normative connectome

• The application of normative connectome in neuromodulation

• Connectomic DBS in PD

2. The concept of human connectome

According to the classical teaching, localization of lesions in the nervous system accounts for most of the neurological features. In reality, we found that this approach has some limitations. First, lesion-based localization approach is occasionally unclear. Lesions causing the same symptom can occur in various parts in the brain, whereas one cerebral lesion can result in different neurological symptoms. As a result, the relationship between neurological symptoms and lesion location is not often straightforward [25–27]. Second, it is not uncommon to have patients with complex neurological and psychiatric symptoms unable to find obvious cerebral lesions from neuroimaging [27]. Therefore, it has been speculated that these neurological symptoms, instead of resulting from overt lesions in the nervous system, may be caused by disruption of anatomical and functional networks created by interacting neural elements, which are at a more microscopic level.

To study the human brain network, we have to understand the concept of human connectome. The human connectome is defined as "a comprehensive structural description of the network and connections forming the human brain." [25, 26] In general, the term "connectome" has three major components.

First, the connectome is a description of structures and studies the set of physical links between neural elements. To examine the connections between neural elements, we need to look at both *structural* and *functional connectivity*.

Structural connectivity offers a consistent anatomical description of structural connections within the nervous system. At the micro- and meso-scales, structural connectivity reveals synaptic coupling between cells or long-distance axonal projections between neuronal populations [28, 29]. On the other hand, at the macroscale, structural connectivity points to large, myelinated white matter fiber bundles, which can be visualized with diffusion-weighted MRI data using the tractography software packages [30, 31].

As for *functional connectivity*, it means correlations in activation among spatially distinct brain regions, either in a resting state or with external stimuli, and can be measured as the bivariate correlation of their activities when using functional MRI data [26, 32–34].

Second, the connectome is merely a description of brain connectivity across multiple spatial scales. However, it does not offer all the information of cells and synapses at the microscale level [26].

Thirdly and most importantly, the concept of the connectome is that it is a description of a neural network [26]. With the use of mathematical and statistical approaches, the connectome is an object that fits within a larger theoretical framework, thereby linking neuroscience to network science and complex systems [26].

3. Approach to mapping the human connectome

As discussed in last section, the human connectome is a structural description of the neural network and connections across multiple spatial scales. In general, there are three scales of organization within the human brain [26]:

- The microscale of single neurons and synapses [35, 36]

- The mesoscale of neuronal populations and their interconnecting circuitry [37–39]

- The macroscale of anatomically distinct brain regions and pathways

Mapping of the connectome at the first two levels usually occurs in animal models and is conducted in experimental trials. In this review, we will focus on the mapping of the human connectome at the macroscale.

At present, MRI has been used as a non-invasive tool for mapping of large-scale structural connections in the human brain [26, 27]. Both *structural* and *functional connectivity* need to be studied in detail.

Structural connectivity is usually assessed by diffusion-weighted MRI sequences, followed by probabilistic tractography, because water moves more freely along white matter fiber bundles than across them and so white matter pathways can be reconstructed, thereby identifying fibers that pass between various brain regions [27].

In contrast, resting state functional MRI (rfMRI) is frequently used to study *functional connectivity*. It examines the blood oxygen level dependent (BOLD) signal, which serves as an indirect marker of neuronal activity [27, 34]. When brain activity increases, blood flow and glucose consumption increase much more than oxygen consumption. Therefore, the amount of deoxygenated hemoglobin decreases in the region of increased activity and the BOLD signal is enhanced [40]. *Functional connectivity* is defined as the statistical association between time-series of anatomically distinct brain regions, which in functional MRI is typically calculated as zero-lag correlation. In other words, if two brain regions have BOLD signals that are correlated, they are functionally connected [34].

With the use of diffusion-weighted MRI and functional MRI, the functional human connectome can be mapped out at the macroscale [25, 27]. The approach to mapping the human connectome is outlined as follows (**Figure 1**) [25].

Step 1:

First, diffusion-weighted MRI, followed by probabilistic tractography of thalamocortical tracts and corticocortical interareal pathways, should be performed to aid in the parcellation of the human brain, thereby creating a voxel-wise probabilistic all-to-all *structural connectivity* matrix.

Step 2:

Second, a correlation analysis of spatially registered resting state and/or task-based functional MRI recorded in the same person is then accomplished to construct a voxel-wise all-to-all *functional connectivity* matrix for the human brain.
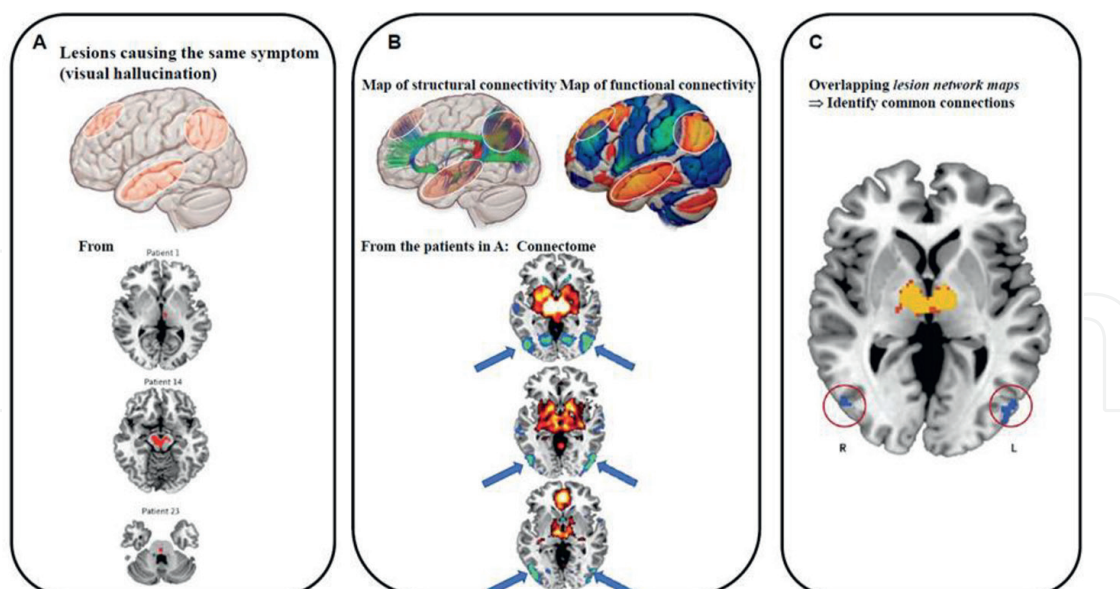
Figure 1.
Using the human brain connectome to localize symptoms [27].

Step 3:

Subsequently, a cluster analysis of correspondences between the structural and functional connectivity matrix obtained from the last two steps is carried out. With that, the human brain regions of consistent structure-function relationships can be found.

In this way, it is possible for us to map out the human connectome. To further improve the quality of the connectome, we may need to compare the mapped network with animal models to look for correspondences and deviations. Also, the predictions generated from the structural-functional connectivity matrix can be validated with specific stimulation techniques.

4. Normative connectome and the human connectome project (HCP)

Even though human connectome is a big step in enhancing localization in the nervous system, it is time-consuming, expensive and may be exhausting to the patients because they have to go through a lengthy process of image acquisitions with functional MRI and diffusion-weighted MRI. In fact, in a clinical imaging context, the human connectomes can be studied with either individual MRI data or the MRI data from a group of individuals. The latter approach gives rise to an idea known as a *normative connectome*, which is described as an average or generalized wiring diagram of the human brain [27].

Normative connectome can be useful in those who fail to obtain their own connectomes [27]. For instance, in PD patients with severe tremor or dyskinesia, they may not be able to obtain good-quality MRI images without motion artifacts. Besides, in those patients with cerebral lesions such as cerebrovascular accident, they may not be able to obtain their own connectome even if they can tolerate the long procedure of image acquisition. It is because with previous cerebral insults, that specific region(s) in the brain may have been damaged, thereby disrupting the cerebral circuitry focally and making it impossible to map out the functional connectivity accurately. Nevertheless, normative connectome, which is obtained from group MRI data, cannot

provide each individual information of connectivity of his own brain, and may not reflect his actual situation. It can vary with age, gender, body mass index and neurological diseases [41–46].

As such, research studying normative connectome of the human brain has grown in number over the last five to ten years and the Human Connectome Project (HCP) is a good example. It is a large-scale project conducted in the U.S. to examine the human brain circuits and their relationship to behavior in a large population of healthy adults at a macroscopic level [27, 47, 48]. Clinical and neuroimaging information obtained in this project were listed out as follows [47–49].

- Multimodal neuroimaging with 3 T/7 T MRI scanners: structural, functional, and diffusion-weighted MRI

- Magnetoencephalography

- Genetic analyses

- Behavioral assessment

5. Applications of normative connectome (including DBS)

As a powerful tool to study the intriguing network in the brain, normative connectome can be used in different areas.

First, normative connectome can unveil the underlying complicated pathways of various neurological and psychiatric diseases and so may bring insights to the identification of new treatment targets. Let us take **Figure 1** as an example. By mapping the connectomes of a group of patients with visual hallucination, lesions that cause the symptom were found to be connected to the occipital cortex. This aid in the discovery of novel treatment targets, as in this example, transcranial magnetic stimulation at the occipital cortex can suppress visual hallucination [50].

Second, normative connectome can enhance surgical precision and hence improve treatment outcome of different neurosurgical procedures. For instance, for glioma patients who plan for resection surgery, the application of normative connectome can help in the identification of eloquent areas and motor tracts before operation, hence reducing the number of intra-operative stimulations required to safely confirm a tract, decreasing the likelihood of disruptive seizures, lowering the risks of post-operative neurological deficits, facilitating the resection, and making patients more comfortable during the operation [51, 52]. Epilepsy surgery is another example. It has been reported that with the use of connectome, the surgical outcome of epilepsy surgery can be improved and the risks of post-operative neurocognitive sequelae, including memory and language impairment, can be reduced [53–56].

Last but not the least, normative connectome has been used widely in the field of neuromodulation, especially DBS. Theoretically, DBS works by depolarization blockade, synaptic inhibition and depression, as well as, stimulation-induced modulation of pathological network activity, of which is regarded the most important mechanism of action [57, 58]. Thus, when normative connectome allows us to map out the pathological pathways in the brain, stimulation at certain points along the circuits may restore the disrupted information flow and so alleviate patients' symptoms. Besides, DBS electrodes, which function as probes, can become *seeds* or regions-of-interest

(ROIs) when they are used to compute their connectivity profiles with normative connectome to perform network-based analyses. In this way, we can identify the optimal site for stimulation and avoid undesirable side effects, thereby facilitating DBS programming and improving surgical outcome [59].

6. How to perform connectomic analyses in patients with DBS implanted

Assuming that there is no significant difference between the patient's brain and an average brain, normative connectomic analysis can be conducted to study the patient's connectivity profile that his neurostimulator may modulate. Unlike individual connectomic analysis, either structural or functional MRI data is enough for normative connectomic analysis. In other words, either diffusion-weighted MRI with tractography or functional MRI is required for normative connectomic analysis. With this network analysis, the precision of pre-operative targeting and post-operative programming can be enhanced [23, 60, 61].

The approach to conduct connectomic analysis in a patient with DBS implanted is described as follows (**Figure 2**) [23, 60, 61].

Step 1: co-registration.

Before DBS surgery, structural MRI brain, as well as diffusion-weighted or functional MRI brain is performed. After surgery, a computed tomography (CT) of the brain is done. The post-operative CT brain is then co-registered to the pre-operative MRI brain, preferably with brain shift correction and spatial normalization.

Step 2: electrode localization.

After co-registration of pre-operative and post-operative neuroimages, the electrodes can be localized while the adjacent neuroanatomical structures are identified.

Step 3: estimation of volume of tissue activated (VTA).

The VTA is an estimate of the volume and shape of the distribution of electrical signal stimulating brain tissues when the contact on a DBS electrode is activated. It depends on the composition of settings of the electrode contacts and implanted pulse
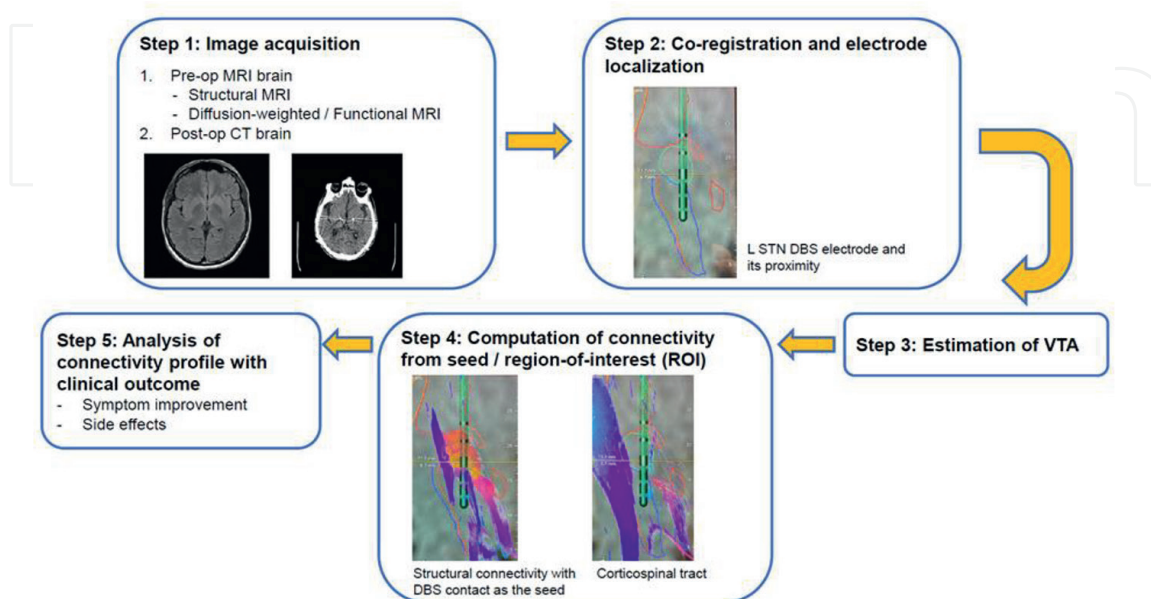

Figure 2.
The approach to perform connectomic analysis in a patient with DBS implanted.

generator, e.g., the number and locations of activated contacts, impedance, voltage, pulse width, or frequency [62, 63].

After the localization of DBS electrode, the VTA is estimated with the activated contact(s) on the DBS electrode identified. The physician can choose the electrode contact(s) stimulated with monopolar stimulation and decide the stimulation programming setting. The VAT will be estimated according to the DBS programming parameters.

Step 4: calculation of connectivity profile from seed region.

When a region-of-interest (ROI) has been identified, it can be used as a seed within specific functional or structural normative connectomes to work out its functional or structural connectivity, respectively. Usually, the VTA of a specific DBS electrode is selected as the seed.

Step 5: analysis of the relationship of DBS site connectivity with clinical outcome.

Finally, a statistical analysis is conducted to investigate if there is a relationship between DBS site connectivity and clinical outcome, which can be symptom improvement or side effects.

7. Connectomic DBS in PD

Indeed, the use of human connectome has been studied extensively in the field of DBS surgery, especially for major movement disorder indications such as PD. In general, electrode localization is important in the success of surgery. Historically, lesion-based localization at surgical targets, namely STN or GPi, is found to improve motor symptoms in PD patients. However, as increasing evidence points out that DBS works by restoring the connectivity of abnormal networks to a physiological state, [57, 58] more studies have investigated the relationship between connectivity-based localization and treatment outcome of DBS surgery. Horn et al. reported that with the use of normative connectome, structural connectivity to supplementary motor area (SMA), superior frontal gyrus and cerebellum were associated with good clinical response. Also, structural and functional connectivity were independent predictors of clinical improvement of STN DBS [45].

Next, it has been postulated that if different surgical targets would modulate the same circuit in PD patients and affect treatment response. Sobesky et al. showed that based on normative connectome atlas, connectivity profiles seeding from either STN or GPi DBS electrodes were highly similar, suggesting that irrespective of the surgical target, the network modulated by DBS largely overlaps [64]. Moreover, in both groups, functional connectivity to the frontal lobe, especially SMA and adjacent cingulate, middle and inferior temporal gyri, inferior parietal gyri and motor cerebellum were associated with good clinical outcome [64]. Nonetheless, despite the marked similarity in the circuitry modulated by both DBS, the treatment response in the two groups varied. For bradykinesia-rigidity symptoms, connectivity profile was associated with significant improvement and shared considerable similarity in both groups. In contrast, the results for tremor were different, suggesting that the networks modulated by effective neurostimulation at different targets, though similar, may have a small discrepancy [64].

Electrophysiological data has long been used as markers for lesion-based neuromodulation surgeries in PD. For example, local field potential (LFP) can serve as a

tool for brain sensing in PD patients with DBS implanted at STN, thereby facilitating DBS programming and medication titration. Increased beta activities were observed in the hypodopaminergic state when the patients suffer from bradykinesia and rigidity and could be suppressed by DBS and dopaminergic medications. On the other hand, increased gamma activities were seen in times of dyskinesia [65–69]. However, in patients with connectivity-based stimulation, will the electrophysiological data correlate with the connectivity profile? Accolla et al. described that beta oscillations were detected in the cerebral circuit projecting from the STN to the motor and premotor cortical areas in PD patients [70]. Besides, Hirschmann et al. reported that with the use of magnetoencephalography (MEG), local field potential (LFP) and electromyogram (EMG), elevated beta coherence was found between M1 and STN in PD patients, which could be suppressed with administration of levodopa [71]. These findings suggested a link between electrophysiology data and connectivity-based stimulation.

As such, connectomic DBS seems to be a reasonable and effective therapeutic option for advanced PD patients. Growing evidence has showed that depending on the symptoms, connectomic DBS can act on different circuits in the brain. In this way, the neuromodulation surgery can affect both motor and non-motor functions (**Table 2**) [23, 45, 61, 72–79].

Study	DBS target	Number of subjects	Type of connectome	Major findings
Motor effects				
Horn et al. [23]	STN	51	Structural connectivity	VTAs connecting to SMA correlated to clinical motor improvement
Treu et al. [61]	STN	51	Structural connectivity	VTAs connecting to M1 / S1 negatively correlated with motor outcome.
Horn et al. [45]	STN	95	• Structural connectivity • Functional connectivity	• VTA structural connectivity with SMA associated with clinical motor improvement • Functional connectivity with M1 associated with clinical motor improvement.
Tsuboi et al. [72]	GPi	16	• Structural connectivity • Functional connectivity	• Stimulation induced dyskinesia (SID) VTAs significantly associated with higher structural connectivity to the associative cortex and SMA / premotor cortex. • Non-SID VTAs associated with greater connectivity to the primary sensory cortex, cerebellum, subthalamic nucleus, and motor thalamus.

Study	DBS target	Number of subjects	Type of connectome	Major findings
Lofredi et al. [73]	STN	17	Structural connectivity	VTAs connecting to the pre-SMA and inferior frontal gyrus of the right hemisphere correlated with stimulation-induced movement inhibition.
de Almeida Marcelino et al. [74]	STN	20	Functional connectivity	VTAs connecting to M1 and cerebellar hemispheres correlated with motor learning improvement.
Avecillas-Chasin et al. [75]	STN	43	Structural connectivity	• Stimulation zones related to rigidity and tremor improvement involved pallidofugal pathway. • Stimulation zones related to bradykinesia improvement involved nigrofugal pathway.
Lizarraga et al. [76]	STN	1	Structural connectivity	VTAs associated with a greater degree of lateral deviation (Pisa syndrome) associated with increased white matter streamlines.
Non-motor effects				
Irmen et al. [77]	STN	116	Structural connectivity	VTAs connecting to left prefrontal cortex associated with worsening of depressive symptoms.
Cury et al. [78]	STN	32	Structural connectivity	VTAs connecting to a distributed network of sensory brain regions (prefrontal, insular and cingulate cortex, and postcentral gyrus) inversely correlated with pain intensity improvement.
Mosley et al. [79]	STN	55	Structural connectivity	VTAs connecting to the prefrontal cortex (especially the orbitofrontal cortex) related to impulsivity

Table 2.
Clinical effects of connectomic DBS in PD.

8. Conclusion

In conclusion, connectomic DBS, which makes use of circuitry-based stimulation technique rather than lesion-based stimulation technique, has revolutionized the field of neuromodulation surgery. By stimulating patient-specific circuits, this surgery enables us to offer a more precise management approach while avoiding undesirable side effects. In addition, with the advent of normative connectome obtained

by grouped data, it simplifies the complicated procedure of connectome mapping, trajectory planning and DBS programming, making it more user-friendly to the neurosurgeons and neurologists. Furthermore, connectomic mapping allows us to map out symptom-specific circuits for each patient individually and check for the overlap of these circuits. In this way, connectomic DBS surgery can be tailormade for each patient and become "bespoke surgery" that can address their own needs.

Author details

Germaine Hiu-Fai Chan
Department of Medicine, Queen Elizabeth Hospital, Hong Kong

*Address all correspondence to: chf862@ha.org.hk

IntechOpen

References

[1] Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;**386**(9996):896-912. DOI: 10.1016/S0140-6736(14)61393-3

[2] Tanner CM, Aston DA. Epidemiology of Parkinson's disease and akinetic syndromes. Current Opinion in Neurology. 2000;**13**(4):427-430. DOI: 10.1097/00019052-200008000-00010

[3] Aquino CC, Fox SH. Clinical spectrum of levodopa-induced complications. Movement Disorders. 2015;**30**(1):80-89. DOI: 10.1002/mds.26125

[4] Worth PF. When the going gets tough: How to select patients with Parkinson's disease for advanced therapies. Practical Neurology. 2013;**13**(3):140-152. DOI: 10.1136/practneurol-2012-000463

[5] Volkmann J, Albanese A, Antonini A, Chaudhuri KR, Clarke CE, de Bie RM, et al. Selecting deep brain stimulation or infusion therapies in advanced Parkinson's disease: An evidence-based review. Journal of Neurology. 2013;**260**(11):2701-2714. DOI: 10.1007/s00415-012-6798-6

[6] Williams DR, Evans AH, Fung VSC, Hayes M, Iansek R, Kimber T, et al. Practical approaches to commencing device-assisted therapies for Parkinson disease in Australia. Internal Medicine Journal. 2017;**47**(10):1107-1113. DOI: 10.1111/imj.13398

[7] Moro E, Lang AE. Criteria for deep-brain stimulation in Parkinson's disease: Review and analysis. Expert Review of Neurotherapeutics. 2016;**6**(11):1695-1705. DOI: 10.1586/14737175.6.11.1695

[8] Defer GL, Widner H, Marié RM, Rémy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Movement Disorders. 1999;**14**(4):572-584. DOI: 10.1002/1531-8257(199907)14:4<572::aid-mds1005>3.0.co;2-c

[9] Munhoz RP, Picillo M, Fox SH, Bruno V, Panisset M, Honey CR, et al. Eligibility criteria for deep brain stimulation in Parkinson's disease, tremor, and dystonia. The Canadian Journal of Neurological Sciences. 2016;**43**(4):462-471. DOI: 10.1017/cjn.2016.35. Epub 2016 May 3

[10] Okun MS, Tagliati M, Pourfar M, Fernandez HH, Rodriguez RL, Alterman RL, et al. Management of referred deep brain stimulation failures: A retrospective analysis from two movement disorders centers. Archives of Neurology. 2005;**62**(8):1250-1255. DOI: 10.1001/archneur.62.8.noc40425. Epub 2005 Jun 13

[11] Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nature Reviews. Neurology. 2019;**15**(4):234-242. DOI: 10.1038/s41582-019-0145-9

[12] Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K. Et al; German Parkinson study group, Neurostimulation section. A randomized trial of deep-brain stimulation for Parkinson's disease. The New England Journal of Medicine. 2006;**355**(9):896-908. DOI: 10.1056/NEJMoa060281

[13] Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, et al. CSP 468 study group. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: A randomized controlled

trial. Journal of the American Medical Association. 2009;**301**(1):63-73. DOI: 10.1001/jama.2008.929

[14] Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: The COMPARE trial. Annals of Neurology. 2009;**65**(5):586-595. DOI: 10.1002/ana.21596

[15] Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. CSP 468 study group. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. The New England Journal of Medicine. 2010;**362**(22):2077-2091. DOI: 10.1056/NEJMoa0907083

[16] Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, et al. CSP 468 study group. Randomized trial of deep brain stimulation for Parkinson disease: Thirty-six-month outcomes. Neurology. 2012;**79**(1):55-65. DOI: 10.1212/WNL.0b013e31825dcdc1. Epub 2012 Jun 20

[17] Odekerken VJ, van Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijssen PC, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): A randomised controlled trial. Lancet Neurology. 2013;**12**(1):37-44. DOI: 10.1016/S1474-4422(12)70264-8. Epub 2012 Nov 16

[18] Odekerken VJ, Boel JA, Schmand BA, de Haan RJ, Figee M, van den Munckhof P, et al. NSTAPS study group. GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up. Neurology. 2016;**86**(8):755-761. DOI: 10.1212/WNL.0000000000002401. Epub 2016 Jan 27

[19] Lambert C, Zrinzo L, Nagy Z, Lutti A, Hariz M, Foltynie T, et al.

Confirmation of functional zones within the human subthalamic nucleus: Patterns of connectivity and sub-parcellation using diffusion weighted imaging. NeuroImage. 2012;**60**(1):83-94. DOI: 10.1016/j.neuroimage.2011.11.082. Epub 2011 Dec 8

[20] Benarroch EE. Subthalamic nucleus and its connections: Anatomic substrate for the network effects of deep brain stimulation. Neurology. 2008;**70**(21):1991-1995. DOI: 10.1212/01.wnl.0000313022.39329.65

[21] Ewert S, Plettig P, Li N, Chakravarty MM, Collins DL, Herrington TM, et al. Toward defining deep brain stimulation targets in MNI space: A subcortical atlas based on multimodal MRI, histology and structural connectivity. NeuroImage. 2018;**170**:271-282. DOI: 10.1016/j.neuroimage.2017.05.015. Epub 2017 May 20

[22] Krack P, Fraix V, Mendes A, Benabid AL, Pollak P. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. Movement Disorders. 2002;**17**(Suppl. 3): S188-S197. DOI: 10.1002/mds.10163

[23] Horn A, Li N, Dembek TA, Kappel A, Boulay C, Ewert S, et al. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. NeuroImage. 2019;**184**:293-316. DOI: 10.1016/j.neuroimage.2018.08.068. Epub 2018 Sep 1

[24] Karnath HO, Sperber C, Rorden C. Mapping human brain lesions and their functional consequences. NeuroImage. 2018;**165**:180-189. DOI: 10.1016/j.neuroimage.2017.10.028. Epub 2017 Oct 16

[25] Sporns O, Tononi G, Kötter R. The human connectome: A structural description of the human brain. PLoS Computational Biology. 2005;**1**(4):e42. DOI: 10.1371/journal.pcbi.0010042

[26] Sporns O. The human connectome: A complex network. Annals of the New York Academy of Sciences. 2011;**1224**:109-125. DOI: 10.1111/j.1749-6632.2010.05888.x. Epub 2011 Jan 4

[27] Fox MD. Mapping symptoms to brain networks with the human connectome. The New England Journal of Medicine. 2018;**379**(23):2237-2245. DOI: 10.1056/NEJMra1706158

[28] Oh SW, Harris JA, Ng L, Winslow B, Cain N, Mihalas S, et al. A mesoscale connectome of the mouse brain. Nature. 2014;**508**(7495):207-214. DOI: 10.1038/nature13186. Epub 2014 Apr 2

[29] Markov NT, Ercsey-Ravasz MM, Ribeiro Gomes AR, Lamy C, Magrou L, Vezoli J, et al. A weighted and directed interareal connectivity matrix for macaque cerebral cortex. Cerebral Cortex. 2014;**24**(1):17-36. DOI: 10.1093/cercor/bhs270. Epub 2012 Sep 25

[30] Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magnetic Resonance in Medicine. 2000;**44**(4):625-632. DOI: 10.1002/1522-2594(200010)44:4<625::aid-mrm17>3.0.co;2-o

[31] Daducci A, Gerhard S, Griffa A, Lemkaddem A, Cammoun L, Gigandet X, et al. The connectome mapper: An open-source processing pipeline to map connectomes with MRI. PLoS One. 2012;**7**(12):e48121. DOI: 10.1371/journal.pone.0048121 Epub 2012 Dec 18

[32] Zhou D, Thompson WK, Siegle G. MATLAB toolbox for functional connectivity. NeuroImage. 2009;**47**(4):1590-1607. DOI: 10.1016/j.neuroimage.2009.05.089. Epub 2009 Jun 8

[33] Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, et al. Network modelling methods for FMRI. NeuroImage. 2011;**54**(2):875-891. DOI: 10.1016/j.neuroimage.2010.08.063. Epub 2010 Sep 15

[34] Pervaiz U, Vidaurre D, Woolrich MW, Smith SM. Optimising network modelling methods for fMRI. NeuroImage. 2020;**211**:116604. DOI: 10.1016/j.neuroimage.2020.116604. Epub 2020 Feb 13

[35] White JG, Southgate E, Thomson JN, Brenner S. The structure of the nervous system of the nematode Caenorhabditis elegans. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 1986;**314**(1165):1-340. DOI: 10.1098/rstb.1986.0056

[36] Chen BL, Hall DH, Chklovskii DB. Wiring optimization can relate neuronal structure and function. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**(12):4723-4728. DOI: 10.1073/pnas.0506806103. Epub 2006 Mar 14

[37] Micheva KD, Smith SJ. Array tomography: A new tool for imaging the molecular architecture and ultrastructure of neural circuits. Neuron. 2007;**55**(1):25-36. DOI: 10.1016/j.neuron.2007.06.014

[38] Palm C, Axer M, Gräßel D, Dammers J, Lindemeyer J, Zilles K, et al. Towards ultra-high resolution fibre tract mapping of the human brain - registration of polarised light images and reorientation of fibre vectors. Frontiers in Human Neuroscience. 2010;**4**:9. DOI: 10.3389/neuro.09.009.2010

[39] Axer M, Amunts K, Grässel D, Palm C, Dammers J, Axer H, et al. A novel approach to the human connectome: Ultra-high resolution mapping of fiber tracts in the brain.

NeuroImage. 2011;**54**(2):1091-1101. DOI: 10.1016/j.neuroimage.2010.08.075. Epub 2010 Sep 9

[40] Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature Reviews. Neuroscience. 2007;**8**(9):700-711. DOI: 10.1038/nrn2201

[41] Christova P, James LM, Georgopoulos AP. Effects of sex and age on presumed inhibitory interactions in 6 areas of the human cerebral cortex as revealed by the fMRI human connectome project. Experimental Brain Research. 2022;**240**(3):969-979. DOI: 10.1007/s00221-021-06298-z. Epub 2022 Jan 30

[42] Kim HG, Shin NY, Nam Y, Yun E, Yoon U, Lee HS, et al. MRI-visible dilated perivascular space in the brain by age: The human connectome project. Radiology. 2022;**213254**:1-9. DOI: 10.1148/radiol.213254. Epub ahead of print

[43] Chin Fatt CR, Jha MK, Minhajuddin A, Mayes T, Trivedi MH. Sex-specific differences in the association between body mass index and brain aging in young adults: Findings from the human connectome project. Psychoneuroendocrinology. 2021;**124**:105059. DOI: 10.1016/j.psyneuen.2020.105059. Epub 2020 Nov 16

[44] Wang Q, Akram H, Muthuraman M, Gonzalez-Escamilla G, Sheth SA, Oxenford S, et al. Normative vs. patient-specific brain connectivity in deep brain stimulation. Neuroimage. 2021;**224**:117307. DOI: 10.1016/j.neuroimage.2020.117307. Epub 2020 Aug 28

[45] Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, et al. Connectivity predicts deep brain stimulation outcome in Parkinson disease. Annals of Neurology. 2017;**82**(1):67-78. DOI: 10.1002/ana.24974

[46] Germann J, Elias GJB, Boutet A, Narang K, Neudorfer C, Horn A, et al. Brain structures and networks responsible for stimulation-induced memory flashbacks during forniceal deep brain stimulation for Alzheimer's disease. Alzheimer's & Dementia. 2021;**17**(5):777-787. DOI: 10.1002/alz.12238. Epub 2021 Jan 21

[47] Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E. Ugurbil K; WU-Minn HCP consortium. The WU-Minn human connectome project: An overview. NeuroImage. 2013;**80**:62-79. DOI: 10.1016/j.neuroimage.2013.05.041. Epub 2013 May 16

[48] Glasser MF, Smith SM, Marcus DS, Andersson JL, Auerbach EJ, Behrens TE, et al. The human connectome Project's neuroimaging approach. Nature Neuroscience. 2016;**19**(9):1175-1187. DOI: 10.1038/nn.4361

[49] Elam JS, Glasser MF, Harms MP, Sotiropoulos SN, Andersson JLR, Burgess GC, et al. The human connectome project: A retrospective. NeuroImage. 2021;**244**:118543. DOI: 10.1016/j.neuroimage.2021.118543. Epub 2021 Sep 8

[50] Merabet LB, Kobayashi M, Barton J, Pascual-Leone A. Suppression of complex visual hallucinatory experiences by occipital transcranial magnetic stimulation: A case report. Neurocase. 2003;**9**(5):436-440. DOI: 10.1076/neur.9.5.436.16557

[51] Henderson F, Abdullah KG, Verma R, Brem S. Tractography and the connectome in neurosurgical treatment of gliomas: The premise, the progress, and the potential. Neurosurgical Focus. 2020;**48**(2):E6. DOI: 10.3171/2019.11.FOCUS19785

[52] Chen Z, Ye N, Teng C, Li X. Alternations and applications of the

structural and functional connectome in gliomas: A mini-review. Frontiers in Neuroscience. 2022;**16**:856808. DOI: 10.3389/fnins.2022.856808

[53] Taylor PN, Sinha N, Wang Y, Vos SB, de Tisi J, Miserocchi A, et al. The impact of epilepsy surgery on the structural connectome and its relation to outcome. Neuroimage Clinical. 2018;**18**:202-214. DOI: 10.1016/j.nicl.2018.01.028

[54] Arski ON, Martire DJ, Young JM, Wong SM, Suresh H, Kerr EN, et al. Connectomic profiles and cognitive trajectories after epilepsy surgery in children. Neurology. 2022;**98**(22): e2233-e2244. DOI: 10.1212/ WNL.0000000000200273. Epub 2022 Apr 11

[55] Chen X, Wang Y, Kopetzky SJ, Butz-Ostendorf M, Kaiser M. Connectivity within regions characterizes epilepsy duration and treatment outcome. Human Brain Mapping. 2021;**42**(12):3777-3791. DOI: 10.1002/hbm.25464. Epub 2021 May 11

[56] Englot DJ, Konrad PE, Morgan VL. Regional and global connectivity disturbances in focal epilepsy, related neurocognitive sequelae, and potential mechanistic underpinnings. Epilepsia. 2016;**57**(10):1546-1557. DOI: 10.1111/ epi.13510. Epub 2016 Aug 24

[57] McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: Activation, inhibition, or both. Clinical Neurophysiology. 2004;**115**(6):1239-1248. DOI: 10.1016/j.clinph.2003.12.024

[58] Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: Current challenges and future directions. Nature Reviews. Neurology. 2019;**15**(3):148-160. DOI: 10.1038/s41582-018-0128-2

[59] Horn A, Ostwald D, Reisert M, Blankenburg F. The structural-functional connectome and the default mode network of the human brain. NeuroImage. 2014;**102**(Pt 1):142-151. DOI: 10.1016/j.neuroimage.2013.09.069. Epub 2013 Oct 4

[60] Horn A, Kühn AA. Lead-DBS: A toolbox for deep brain stimulation electrode localizations and visualizations. NeuroImage. 2015;**107**:127-135. DOI: 10.1016/j.neuroimage.2014.12.002. Epub 2014 Dec 8

[61] Treu S, Strange B, Oxenford S, Neumann WJ, Kühn A, Li N, et al. Deep brain stimulation: Imaging on a group level. NeuroImage. 2020;**219**:117018. DOI: 10.1016/j.neuroimage.2020.117018. Epub 2020 Jun 4

[62] Mädler B, Coenen VA. Explaining clinical effects of deep brain stimulation through simplified target-specific modeling of the volume of activated tissue. AJNR. American Journal of Neuroradiology. 2012;**33**(6):1072-1080. DOI: 10.3174/ajnr.A2906. Epub 2012 Feb 2

[63] Dergachyova O, Zhao Y, Haegelen C, Jannin P, Essert C. Automatic preoperative planning of DBS electrode placement using anatomo-clinical atlases and volume of tissue activated. International Journal of Computer Assisted Radiology and Surgery. 2018;**13**(7):1117-1128. DOI: 10.1007/s11548-018-1724-8. Epub 2018 Mar 20

[64] Sobesky L, Goede L, Odekerken VJJ, Wang Q, Li N, Neudorfer C, et al. Subthalamic and pallidal deep brain stimulation: Are we modulating the same network? Brain. 2022;**145**(1):251-262. DOI: 10.1093/brain/awab258

[65] Kühn AA, Fogelson N, Limousin PD, Hariz MI, Kupsch A, Brown P. Frequency-specific effects of stimulation of the subthalamic area in treated Parkinson's disease patients. Neuroreport. 2009;**20**(11):975-978. DOI: 10.1097/WNR.0b013e32832d2456

[66] Kühn AA, Kempf F, Brücke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. The Journal of Neuroscience. 2008;**28**(24):6165-6173. DOI: 10.1523/JNEUROSCI.0282-08.2008

[67] Tinkhauser G, Pogosyan A, Tan H, Herz DM, Kühn AA, Brown P. Beta burst dynamics in Parkinson's disease OFF and ON dopaminergic medication. Brain. 2017;**140**(11):2968-2981. DOI: 10.1093/brain/awx252

[68] Kühn AA, Tsui A, Aziz T, Ray N, Brücke C, Kupsch A, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Experimental Neurology. 2009;**215**(2):380-387. DOI: 10.1016/j.expneurol.2008.11.008. Epub 2008 Nov 25

[69] Kühn AA, Kupsch A, Schneider GH, Brown P. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. The European Journal of Neuroscience. 2006;**23**(7):1956-1960. DOI: 10.1111/j.1460-9568.2006.04717.x

[70] Accolla EA, Herrojo Ruiz M, Horn A, Schneider GH, Schmitz-Hübsch T, Draganski B, et al. Brain networks modulated by subthalamic nucleus deep brain stimulation. Brain. 2016;**139** (Pt 9):2503-2515. DOI: 10.1093/brain/aww182. Epub 2016 Jul 13

[71] Hirschmann J, Özkurt TE, Butz M, Homburger M, Elben S, Hartmann CJ, et al. Differential modulation of STN-cortical and cortico-muscular coherence by movement and levodopa in Parkinson's disease. NeuroImage. 2013;**68**:203-213. DOI: 10.1016/j.neuroimage.2012.11.036. Epub 2012 Dec 16

[72] Tsuboi T, Charbel M, Peterside DT, Rana M, Elkouzi A, Deeb W, et al. Pallidal connectivity profiling of stimulation-induced dyskinesia in Parkinson's disease. Movement Disorders. 2021;**36**(2):380-388. DOI: 10.1002/mds.28324. Epub 2020 Oct 1

[73] Lofredi R, Auernig GC, Irmen F, Nieweler J, Neumann WJ, Horn A, et al. Subthalamic stimulation impairs stopping of ongoing movements. Brain. 2021;**144**(1):44-52. DOI: 10.1093/brain/awaa341

[74] de Almeida Marcelino AL, Horn A, Krause P, Kühn AA, Neumann WJ. Subthalamic neuromodulation improves short-term motor learning in Parkinson's disease. Brain. 2019;**142**(8):2198-2206. DOI: 10.1093/brain/awz152

[75] Avecillas-Chasin JM, Honey CR. Modulation of Nigrofugal and Pallidofugal pathways in deep brain stimulation for Parkinson disease. Neurosurgery. 2020;**86**(4):E387-E397. DOI: 10.1093/neuros/nyz544

[76] Lizarraga KJ, Naghibzadeh M, Boutet A, Elias GJB, Fasano A. Management of Pisa syndrome with lateralized subthalamic stimulation. Journal of Neurology. 2018;**265**(10):2442-2444. DOI: 10.1007/s00415-018-8991-8. Epub 2018 Aug 3

[77] Irmen F, Horn A, Mosley P, Perry A, Petry-Schmelzer JN, Dafsari HS, et al. Left prefrontal connectivity links subthalamic stimulation with depressive

symptoms. Annals of Neurology. 2020;**87**(6):962-975. DOI: 10.1002/ana.25734. Epub 2020 Apr 30

[78] Cury RG, Teixeira MJ, Galhardoni R, Silva V, Iglesio R, França C, et al. Connectivity patterns of subthalamic stimulation influence pain outcomes in Parkinson's disease. Frontiers in Neurology. 2020;**11**:9. DOI: 10.3389/fneur.2020.00009

[79] Mosley PE, Paliwal S, Robinson K, Coyne T, Silburn P, Tittgemeyer M, et al. The structural connectivity of subthalamic deep brain stimulation correlates with impulsivity in Parkinson's disease. Brain. 2020;**143**(7):2235-2254. DOI: 10.1093/brain/awaa148