# DETAILED ANATOMICAL VOLUMETRIC STUDY OF DEEP NUCLEI OF BRAIN AND OTHER STRUCTURES BETWEEN PARKINSON'S DISEASE PATIENTS WHO HAD DEEP BRAIN STIMULATION (DBS) AND CONTROL GROUP

**DR GOH CHIN HWEE**

**Dissertation Submitted In Partial Fulfilment Of The Requirement For The Degree Of Master Of Surgery (Neurosurgery)**


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**Preliminaries**

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**Content**

**Title page**

# Detailed anatomical volumetric study of deep nuclei of brain and other structures between Parkinson's disease patients who had deep brain stimulation and control group.

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**Keywords**

Volumetry, MRI, Parkinson's disease, Basal ganglia, Globus pallidus, Subthalamic nucleus

**Abstract**

***Background***: In my country, Deep Brain stimulation surgery (DBS) was pioneered by Neuroscience team Hospital Universiti Sains Malaysia (HUSM) nearly a decade ago. The treatment was mainly directed to advanced Idiopathic Parkinson's Disease (PD) patients. ***Objectives***: It is known that volume reduction occurs with age, we searched to define the degree of volume discrepancy in PD patients and attempted to correlate the anatomical volumetric changes to motor symptoms and cognitive function. ***Methods***: The research aimed to establish a baseline Magnetic resonance imaging (MRI) based volumetric analysis of the seven brain structures (Head of caudate nucleus, Putamen, Thalamus, Globus pallidus, Hippocampal head, Amygdala & Subthalamic nucleus) of selected pre-DBS advanced PD patients in comparison to matched healthy controls. *Results*: Significant atrophy and volume discrepancy were observed in PD surgical group, though thalamus and amygdala were not affected. Positive correlation of globus pallidus volume to higher mental function in the absence of cognitive or behavioural problem. ***Conclusions***: These findings might imply that structural alteration could be the early changes prior to clinical manifestation and PD involves multiple alternative pathway other than nigrostriatal circuit.

# Cover letter

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Prof,

**NEW MANUSCRIPT FOR PUBLICATION CONSIDERATION IN THE STEREOTACTIC AND FUNCTIONAL NEUROSURGERY JOURNAL**

I am pleased to inform you of the submission of an online manuscripts to be considered for publication in the Journal Stereotactic and Functional Neurosurgery, Karger.

Name of manuscript: “Detailed anatomical volumetric study of deep nuclei of brain and other structures between Parkinson’s disease patients who had deep brain stimulation and control group”.
Type of manuscript: Clinical study.
The corresponding author: Dr Goh Chin Hwee

The manuscript is original in clinical information, has not been published previously and is currently not under consideration for publication elsewhere. All the authors and individuals mentioned in the paper agree with the contents of the manuscript and the contents that are specifically attributed to them. No conflicts of interest.

The enclosed manuscript submitted using online submission consisting of this covering letter, the original manuscript, the legend for tables and figures. Thank you.

Regards

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**Introduction**

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterised by cardinal clinical symptoms of bradykinesia, resting tremor, rigidity and postural instability. It is first described by James Parkinson in his classical 1817 monograph, "An Essay on the Shaking Palsy"[1]. This disease affects around 100 per 100,000 population over age of 40 and still remains a clinical diagnosis. It is based on its distinctive clinical feasters discerned from the history and neurological assessment. Goetz et. al. published a battery of revised Unified Parkinson's Disease Rating Scale (UPDRS) criteria that require presence of motor parkinsonism (bradykinesia plus tremor or rigidity) as the central and essential feature of the disease[2].

The determination that PD is the cause of motor parkinsonism requires the presence of supportive criteria to counterbalance the presence of any "red flags" and requires absence of absolute exclusion criteria. An equivocal, beneficial response to dopaminergic therapy is an important supportive feature of the diagnosis. Other clinical features that are supportive of the diagnosis are unilateral onset, presence of a resting tremor, and a persistent asymmetry throughout the course of the disease, with the side of onset most affected.

The tremor in PD typically described as "pill-rolling", is a resting tremor at 3-7 Hertz[3], which becomes more often and apparent in about 80% of PD patients. The tremor is usually unilateral and then spread contralateral within years after the onset. It commonly involves hand and may affect legs, lips, jaw and tongue. Emotions and stressful situation can make tremor worse. Bradykinesia is

generalised slowness of movement and often present late simply this symptom is the most difficult to describe by patients, which often regarded as weakness and tiredness during initial stage[4]. This symptom is the major cause of disability in PD and it affects the speed, amplitude, rhythm and gross motor movement. Rigidity is manifested as an extrapyramidal symptoms characterised by increased and sustained resistance to passive movement about a joint in all directions. It is seen in about 90% of PD patients. A tonic smooth resistance throughout the whole range of passive movement is classically known as lead pipe rigidity. When the symptom is mixed together with tremor, a ratchety pattern of resistance and release along the passive range of movement occurred and is known as cogwheel rigidity[5]. PD patients tend to have stoop posture and classical festinant gait with reduced arm swing and shuffling. As the disease progress in later stage, postural instability appears as involvement of centrally mediated postural reflexes, leading to imbalance and tendency to fall[6]. This is tested in "pull test" where PD patients will lose balance with multiple retropulse steps.

Neuropathological study in PD has divided the brain pathology into 6 different stages in sequence. However, the classification system did not timely correlate with clinical severity. There are still no laboratory tests till date to confirm the diagnosis of PD, and neuroimaging, be it Computed tomography (CT) or Magnetic resonance imaging (MRI) is usually unrevealing. Nevertheless, MRI is performed in patient to exclude mimics of PD, such as stroke, tumour or hydrocephalus. More advanced technique including magnetic resonance volume try, MR spectroscopy (MRS), magnetisation transfer imaging, diffusion-weighted MRI, diffusion tensor MRI, and high resolution imaging (MRI at 7 Tesla), are promising methods that may offer higher sensitivity than conventional MRI for detecting the neuroimaging correlates of PD neurodegeneration and for separating idiopathic PD from secondary Parkinsonian syndromes.

**Literature review**

Traditionally, studies of brain morphology completely relied on autopsy material. In recent advances of clinical neuroscience, brain morphometry has emerged as one of the most dynamic fields with the development of scientific computation simulation, technologies, and advanced MRI resolution[7]. The era of MRI-based morphometry expansion has become a valuable tool for studying human brain plasticity in vivo. It has achieved scientific breakthroughs and changed how human think of brain. This immense advantage enables the in-vivo observation of brain morphology and the correlation with brain function physiologically[8]. Numerous studies have utilised voxel brain morphometry imaging techniques to acquire changes in the structural and function organisation of PD patients[9]. These studies have shown brain atrophy to exist in may cortical and subcortical regions, particularly in the basal ganglia (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, substantial nigra)[10]. Some studies also revealed certain brain areas (frontal lobe, temporo-parietal junction, parietal lobe, insula, anterior cingulate cortex and thalamus) had compensatory increase volume in PD patients[11,12]. However, the results of these literatures on cerebral region atrophy were rather inconsistent and such variability among the findings remained uncertained. Although PD has largely been viewed as associated with functional changes, studies had suggested that the accurate interoperation of the significance of such functional imaging studies depends on determining whether volume changes occurred in various deep nuclei of the brain[13].

**Rationale of the study**

This research aim to employ Magnetic resonant imaging (MRI) to conduct a volumetric study of the deep nuclei and brain structures in medically refractory advanced idiopathic parkinson's disease patients compared to matched controls. Little research has been directed at understanding the functional correlation of these deep nuclei and brain structures in PD. We aim to provide a baseline volumetric analysis of the studied brain structures in pre-DBS advanced PD patients in comparison to matched healthy controls. It is known that atrophy or volume reduction occurs with age, we search to define the degree of volume discrepancy in PD patients and to correlate the unadjusted mean anatomical volumetric changes to clinical severity of disease. This study serves as the first part of the future expansion study of the deep nuclei volumetric alterations in post deep brain stimulation (DBS) PD patients.

**Hypotheses**

It is hypothesised that abnormality is present in the deep nuclei and brain structures of Parkinson's disease group that is manifest in decrease in its anatomical volume including caudate head of nucleus, putamen, globus pallidus, thalamus, head of hippocampus, amygdala and subthalamic nucleus. Consequently, we hypothesised the volume alterations correspond to stages of the disease.

Null Hypothesis I: There is no significant volume discrepancy of brain structures between the DBS surgical group and control. The seven studied brain structures are head of caudate nucleus, putamen, thalamus, globus pallidus, hippocampal head, amygdala and subthalamic nucleus.

Null Hypothesis II: There is no correlation between age and volume changes of brain structures. The seven studied deep nuclei & brain structures are head of caudate nucleus, putamen, thalamus, globus pallidus, hippocampal head, amygdala and subthalamic nucleus.

Null Hypothesis III: There is no significant volume changes of brain structures between the left and right of the brain. The seven studied brain structures are head of caudate nucleus, putamen, thalamus, globus pallidus, hippocampal head, amygdala and subthalamic nucleus.

Null Hypothesis IV: There is no correlation between the volume changes of brain structures and higher mental function. The seven studied deep nuclei & brain structures are head of caudate nucleus, putamen, thalamus, globus pallidus, hippocampal head, amygdala and subthalamic nucleus.

## Methodology

### Study

This is a retrospective observational cross-sectional study, in Hospital Universiti Sains Malaysia (HUSM). There was a total of nine idiopathic parkinson's disease patients had deep brain stimulation in the University. We matched the nine cases to control group based on age for comparison. Inclusion and exclusion criteria were addressed (**Refer appendix**).

### MRI

We retrieved the MRI brain data of the studied subjects from the database of HUSM Radiology department with the permission of the head of unit. All MRI brains were conducted using 3.0 Tesla MRI system (Philips, USA), adhering the the hospital's standard imaging protocol. A series of sagittal scout images was acquired to verify head position and quality of images. All the scans used for the volumetric analysis were T1-weighted three-dimensional (3D)-fast spoiled gradient-recalled multi-planar (TR 7.6ms, TE 3.4ms, slice thickness 1mm, no gap, matrix 220x218, FOV 240mm), and T2-weighted spin echo axial and coronal (TR 3000ms, TE 80ms, slice thickness 1mm, no gap, matrix 400x255, FOV 230mm). The MR images were transferred in Picture archiving and communication system (PACS) gateway, and organised in Digital Imaging Communications in Medicine (DICOM) format. The selected data were retrieved from the PACS gateway and saved in compact disc (CD-R or DVD-R) or universal serial bus (USB) 3.0 32 gigabyte pen drive as digital copies. These digital copies were then uploaded into personal computer (MacBook Pro or Dell CPU).

This study represents the first volumetric analysis of the deep nuclei of brain using MRI in deep brain stimulation surgical patients (HUSM) with medically refractory idiopathic Parkinson's disease, it was not possible to conduct a meaningful power analysis prior to this investigation.

Given the limited resources difficulties and expenses of the surgery and MRI, preliminary studies using small sample sizes can help to determine the costs or benefits of further data collection.

Subject movement during the scan affects the quality of image, particularly in volumetric studies, which will lead to variability in the measurement tracings. Hence, difference in MR image quality between the two groups were also assessed based on the movement ratings. A neuroradiological rating system were utilised to reflect the degree of motion corruption and its effect on the clinical utility of the image. The rating system was published in journal of paediatric radiology in 2001 by Kuperman et. al.[14] The system ranged from 0 to 4.

- 0: Slice is free of motion
- 1: Curvilinear motion artifacts that are barely perceptible and occupy <50% of the surface area of the brain in the sagittal slice, or mild motion artefacts that are observed mostly in white matter.
- 2: Motion artifacts that are perceptible in >50% of the brain in the given slice and extend to visibly involve the gray matter, or cause very minimal stepladder artifact at the gray/white matter interface
- 3: Motion artifacts that involved 100% of the image surface area, encompassing both brain and soft tissues, cause moderate motion artifact bands in white and gray matter, as well as moderate stepladder artifact at gray/white matter junction.
- 4: Severe motion artifacts that render the images non-diagnostic for medical interpretation

**Volumetric analysis**

We conducted the volumetric study using The Medical Imaging Interaction Toolkit (MITK), in microsoft engine Window 7 or mac engine OS X. MITK is an open source software (C++) under a

BSD-style license, developed by the German Cancer Research Centre and recognised by the Open Source Initiative (OSI) public benefit corporation. It was validated by Fritzsche et. al.[15] in Methods Inf Med. 2012. We defined the radiological anatomy of the brain structures endorsed by consultant neuroradiologist. The volume of deep nuclei of brain (Region of interest) were studied. This included head of caudate nucleus, putamen, globes pallidus, thalamus, head of hippocampus, amygdala, subthalamic nucleus. The region of interest (ROI) is defined by using the combination of automated segmentation tool, known as "region growing tool" and manually traced by means of computer mouse-driven pointer. Manual trace is based on exact delineation of structures, and parameters such as size, contrast and brightness were adjusted to achieve sharp border of the ROI. The ROI is defined in each slice of the MRI brain from axial view, in Frankfurt plane. Coronal and sagittal views were checked on in a similar manner to improve segmentation accuracy. The compiled ROI segmented images were interpolated in 3 dimensions (**Figure 1 & 2**). The summation was processed and presented in exact cubic milimetres ($cm^3$).

We utilised Atlas of stereotaxy of human brain 2nd edition 1977 by Schaltenbrand and Wahren, and 7.0 Tesla MRI brain atlas in vivo with cryomacrotome correlation 1st edition 2015 by Zang-Hee Cho, as adjunct to enhance the accuracy of radiologically defined deep nuclei (craniocaudal, ventrodorsal, medial and lateral), based on the spontaneous contrasts between white and gray matter with appropriate sequence T1W gadolinium delineating the deep nuclei contours. The volumetric measurement was done by 2 observers, the author and co-author. Each cases were measured in separate occasions to obtain 3 sets of data and a mean values were calculated. The brain structures volumes of the matched pair were compared and analysed with parametric independent T-test to appraise the relationship in SPSS version 18 software. The flow chart of the study (**Figure 3**).

**Delineation of ROI**

*Head of caudate nucleus*

Head of caudate nucleus began on the most cranial section at genu of callosum till its body which was close to anterior limb of internal capsule. Its dorsal portion was surrounded by genu and body of callosum, with the anterior limb of internal capsule extended as the lateral border. Medially, it was bounded by anterior horn of lateral ventricle and cingulate gyrus. Corpus callosum fibre and orbital gyrus constituted the ventral portion.

*Putamen*

Putamen was situated along genu of callosum and extended caudally to posterior limb of internal capsule and thalamus. Its lateral border was surrounded by external capsule and claustrum and partly by superior temporal gyrus. Medially, anterior and posterior limb of internal capsule formed majority of it together with globus pallidus and lateral medullary lamina. The internal capsule spanned dorsally to form the roof. Orbital gyrus, amygdala and anterior commisure constituted the ventral border.

*Globus pallidus*

Globus pallidus situated medial to putamen and external medullary lamina. It began as cranial portion at anterior commisure and terminated at posterior limb of internal capsule and thalamus. The whole anterior and posterior limb of internal capsule constituted the main medial and dorsal border of the nucleus. Anterior commisure extended from the cranial portion to join the par olfactory area, subtrantia nigra and amygdala to form the ventral border.

*Thalamus*

Thalamus was the largest nucleus that began from genu and posterior limb of internal capsule in craniocaudal manner. Its dorsal boundary was constituted by body of fornix, body of corpus callosum, lateral ventricle body and caudate nucleus body. Ventral border was bounded by third ventricle, mammillary body, subthalamic nucleus, red nucleus, hippocampus and parahippocampus. Whereas midline, stria medullary thalami, third ventricle and massa intermedia formed the medial border. Lateral border was formed by posterior limb of internal capsule and transverse temporal gyrus.

*Head of hippocampus*

We took 30% of hippocampus as head, based on photographs of histological preparations by Duvernoy et al 1998, and Hackert et al 2002. The head of hippocampus first appeared cranially right next to column of fornix and ended at amygdala as caudal portion. The medial occipitotemporal gyrus constituted the ventral portion. Dorsally bounded by globes pallidus. Optic tract and mammillary bodies represented the medial border, and lateral temporal horn of lateral ventricle represented the lateral border.

*Amygdala*

Amygdala began from the temporal pole and uncut of temporal lobe along strai terminals and substantia nigra in craniocaudal manner. Its dorsal portion is bounded by anterior commisure, globus pallidus, putamen and optic tract. Ventrally, cavernous sinus wall, parahippocampus gyrus, uncut of temporal lobe and enthorhinal cortex formed the border. The medial border was represented by optic chasm and tract, hypothalamus, globes pallidus, cerebral peduncle of midbrain; while lateral border was represented by temporal horn of lateral ventricle, hippocampus, middle temporal gyrus.

*Subthalamic nucleus*

It was located in close proximity to midbrain, represented by substantial nigra red nucleus and hypothalamus in craniocaudal manner. It was bounded dorsally by ventrolateral nucleus of thalamus and ventrally by red nucleus, substantial nigra, cerebral peduncle of midbrain. Red nucleus and internal capsule constituted the lateral border. Midline mass intermedia, third ventricle and hypothalamus formed the medial border.

**Results**

We had nine sets of mean volumetric data (age-matched surgical and control group). These values were presented in cubic millimetres and rounded to zero decimal places. Sets of data were randomly chosen and analysed for intra-rater reliability. The intraclass correlation coefficient was 0.998 and Cronbach's alpha coefficient was 0.90, suggestive of good internal consistency. There was no significant difference between the same raters and strong agreement was achieved. Demographic data of surgical group was analysed (**Table 1**). All the seven structures of the brain were described in tabulated form into 2 groups, deep brain stimulation surgical and control group. (**Table 2**).

**Demographic**

The DBS surgical group age ranged 52 to 70 years old, multiracial but predominantly Malay due to the race being major population in Kelantan. The group consisted of 6 males and 3 females. Majority of them were diagnosed idiopathic Parkinson's disease less than a year. Overall, mean duration from symptoms to diagnosis was 3 years and mean age diagnosis was 47.3 years. The first DBS case was diagnosed after 10 years of symptoms at the age of 50, and progressed to stage 4 over a span of 25 years. The rest of the subjects had Hoehn & Yahr stage 4 disease progression

ranged from 6 to 25 years, mean value was 13.9 years. They did not have Parkinson plus features. All of them were on multiple combinations of Parkinson's medications prior to surgery. All of the subjects demonstrated significant improvement in Unified Parkinson's Disease Rating Score (UPDRS) motor symptoms at 3 months after surgery and drug combinations were reduced.

**Mean volume**

Overall, majority of the studied deep nuclei or brain structure was smaller in advanced Parkinson disease Surgical group. There were significant volume reduction of corpus striatum in the surgical group, in which head of caudate nucleus was the most atrophied, followed by globus pallidus and putamen. Only thalamus and amygdala were comparable in the two groups without much difference in the mean volume (**Table 3**).

**Volume discrepancy**

In this series, there were five out of seven studied deep nuclei or brain structure reduced in size. We compared the mean volume reduction of each age-matched control group to measure the degree of discrepancy. In advanced Parkinson's disease surgical group, head of caudate nucleus volume was severely reduced by one-third as compared to age-matched control group, at 32% for both left and right. The highest volume reduction (head of caudate nucleus) was observed in 52 year-old Parkinson's disease subject, at 59%. The discrepancy gradually narrowed with increasing age and the volume reduction was 12% in the eldest 70 year-old subject. However, this trend was not observed in the rest of the studied nuclei or brain structures.

Globus pallidus and subthalamic nucleus in surgical group were also reduced with significant volume discrepancy, 28% (left) and 29% (right) in the former, 25% (both) in the latter. Hippocampal head which was measured as the proximal third of the entire length according to

literature was also noted to be smaller compared to control group. Its mean volume reduction discrepancy was 26% (left) and 23% (right). Putamen was the deep nuclei of all the five structures that showed least volume discrepancy. Its mean volume reduction discrepancy was the most minimum, 18% (left) and 14% (right) (**Table 4 & 5**).

**Age**

There was no correlation between age and volume of the studied nuclei and brain structures. (**Table 6**).

**Left and Right**

There was no significant volume difference between the left and right for all the seven studied nuclei and brain structures. (**Table 7**)

**Correlation of atrophied deep nuclei and brain structures to higher mental function**

A Pearson correlation coefficient was computed to assess the relationship between each volume of deep nuclei & brain structures and higher mental function (MMSE). There was only a positive correlation between the globus pallidus and higher mental function, r=0.571, n=18, p=0.013. A scatterplot summarises the results (**Table 8 & Figure 4**). Overall, there was a moderate, positive correlation between globus pallidus and MMSE. Higher scores of MMSE were correlated with bigger volume of globus pallidus.

**Correlation of deep nuclei and brain structures to UPDRS Motor Score III**

A Pearson correlation coefficient was utilised to appraise the relationship between each volume of deep nuclei & brain structures and UPDRS Motor Score III. Low correlation was observed in head of caudate nuclei and putamen though statistically not significant. (**Table 9**)

**Discussion**

Literatures widely reported brain structures morphologic changes in PD. Lee et al. had reported loss of white matter volume occurred in early disease stages[16]. Variation of volumes in grey matter including deep nuclei was thought to be an early phenomenon of disease progression. Such grey matter volume reduction was often associated with Parkinson-plus syndrome. Brenneis et al reported significant volume loss of caudate nucleus and putamen in Multiple system atrophy (MSA). Summerfield et al. found marked hippocampus and thalamus atrophy seen in PD with dementia[17,18]. However, the study also showed PD without dementia demonstrated minimal hippocampus volume reduction. Nonetheless these results were inconsistent, cause was still uncertain and the loss of volume of brain structures in PD varies according to region.

In our series, we looked into PD patient in Hospital Universiti Sains Malaysia who had surgery DBS. Unlike previous studies, our surgical group PD patients were all advanced Hoehn & Yahr stage. Our PD series revealed volume reduction in head of caudate nucleus, putamen, globus pallidus, hippocampal head and subthalamic nucleus when compared to the age-matched control group. A significant mean volume reduction discrepancy of 25% was documented. We observed such volume change in the group of late stage PD. Only globus pallidus demonstrated positive correlation to cognition. However, none of PD patients in our series had impaired higher mental function or psychological problem. They scored mean MMSE of 26.1. Striatum is known to involve in cognitive functions, particularly globus pallidus. Saga et. al. summarised cognitive involvement of globus pallidus in attention and action inhibition[19.] Functional MRI reviewed evidence of globus pallidus distinct roles in planning and movement parameters of precision grip. This actually implied that PD might not be a disease that was solely restricted to the nigrostriatal pathway but brain structures beyond that, even at early stages. Gillies et. al. utilised natural experiment offered by DBS to compare globus pallidus interna local field potential responses in PD[20]. The

electrophysiology study suggested there was more than one mechanism to basal ganglia-dependent cognitive function, allowing Parkinsonian basal ganglia to still act as a moderator to thalamocortical circuits despite the striatonigral pathway degeneration. Jellinger et. al. reported pathological neuronal system changes other than the nigrotriatal dopaminergic pathway, causing multiple neuromediator and neurochemistry dysfunctions that accounted for the complex patterns of functional deficits[21]. He addressed the loss of nondopaminergic neurons, including cholinergic, serotonergic, peptinergic and noradrenergic systems.

Other possible explanation includes the discrimination of morphologic changes in deep nuclei might represent the early signs of disease progression ahead of neurochemistry and clinical manifestations. This is further explained by advanced neuroimaging studies including Gattellaro et. al. had incorporated diffusion tensor imaging as the analytic method and presence of wide-spread micro structural damage was seen in early stage of PD prior to progression of the cognitive dysfunction[22]. Few morphologic research studies revealed PD without dementia also demonstrated grey matter volume changes in early stage of disease. Krabbe et al. reported 10-15% volume reduction of caudate nucleus, putamen, hippocampus and amygdala in early stage PD without dementia. He concluded putamen atrophy seen in PD group as a trait of late stages of PD[23].

On the other hand, interestingly we did not observe the volume changes in thalamus and amygdala. The 2 structures play important role in cognition and affection respectively. Salsone et. al. also reported thalamus volume reduction was associated with REM sleep behaviour disorder[24]. In thalamus volumetric literature comparison, Portas et al. reported thalamus mean volume in normal adult was 4400mm$^3$ [25]. In younger age group (10-30 years old), Tsatsanis et al. found that they have larger mean volume of thalamus, ranged from 6610-7290mm$^3$ [26]. Van Der Werf et al. demonstrated thalamic size decreases with higher age following a linear relationship starting reasonable early

during the life-span[27]. He measured the mean thalamus volume of thalamus according to young subjects, middle-aged subjects and old subjects, respectively 7600 $mm^3$, 6700 $mm^3$, and 6110 $mm^3$. Larger thalamic volume is associated with better cognitive function[26]. The control group of another study showed the mean volumetric of thalamus was 5657 to 5891 $mm^3$ in male, and 5837 to 5905 $mm^3$ in female[27]. Mean volume of thalamus of our series was comparable though might be slightly smaller, this include PD patient. We did not find any decreasing trend of thalamus volume with increased age, instead our eldest PD patient and control had largest thalamic volume. In amygdala volumetric literature review, Huang et al. revealed no amygdala volume reductions even in Parkinson's disease patients with depression[28], although some other studies reported the decreased volume with histopathological evidence in PD patient[29].

This has led to possibility of the two structures might be more resistant to neurodegenerative effect and not yet reach the level to allow noticeable changes in volume even in advanced stage of PD.

**Conclusion**

Significant striatum and STN volume reduction were observed in pre-DBS advanced Idiopathic PD patients despite such structural changes were not statistically correlated to motor symptoms and cognitive function, possibly limited by the small scale volumetric study. Interestingly, thalamus and amygdala volume were not affected. We strongly believe volumetric re-evaluation may provide further information of the effect of DBS towards volume changes and relation to the motor symptoms or cognitive function.

## Tables and Figures

Fig. 1. The deep nuclei of the brain 3D reconstruction model.

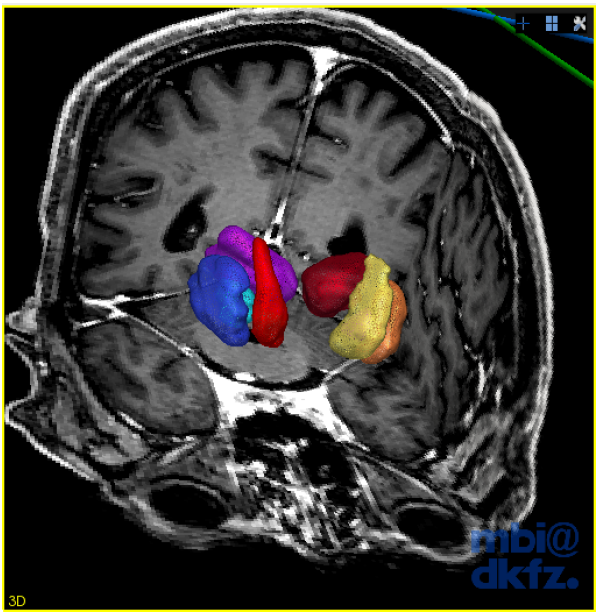


Fig. 2. Multiplanar view for delineation of the ROI and summated to 3D model.

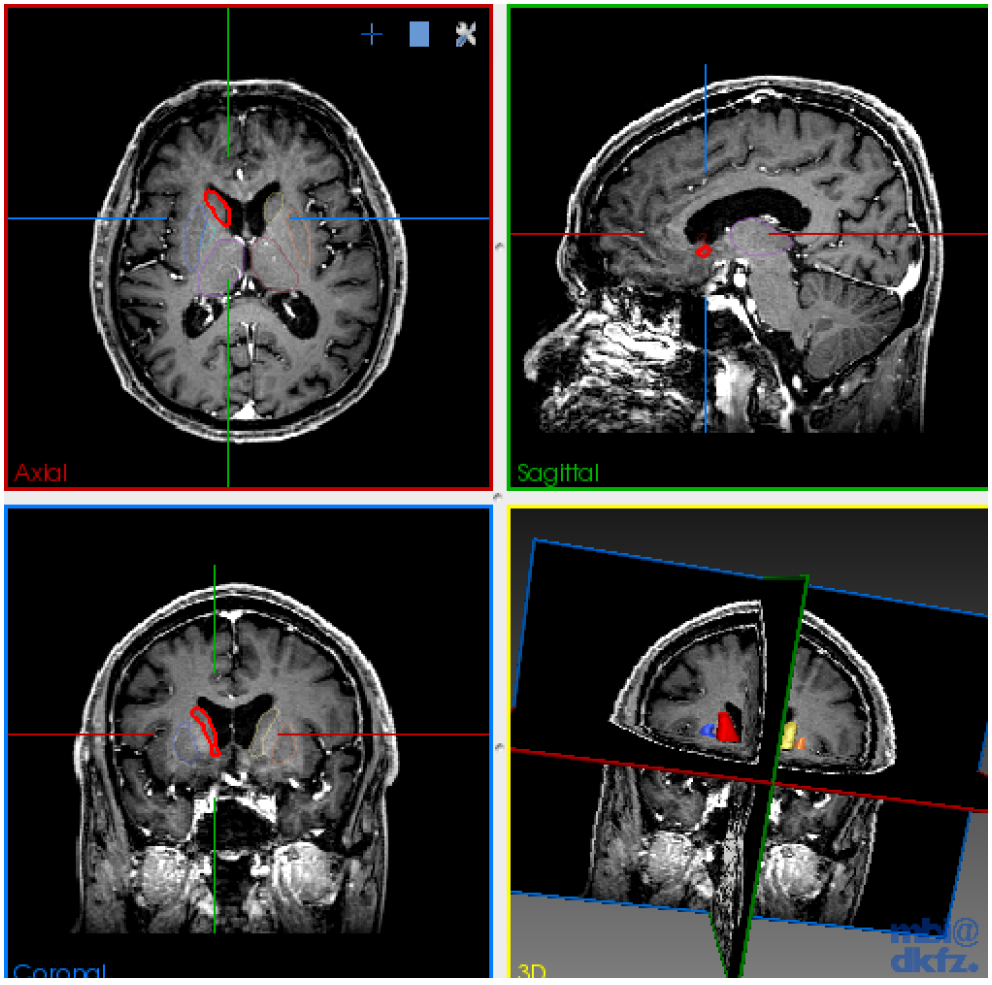

Fig. 3. Flow chart of the study

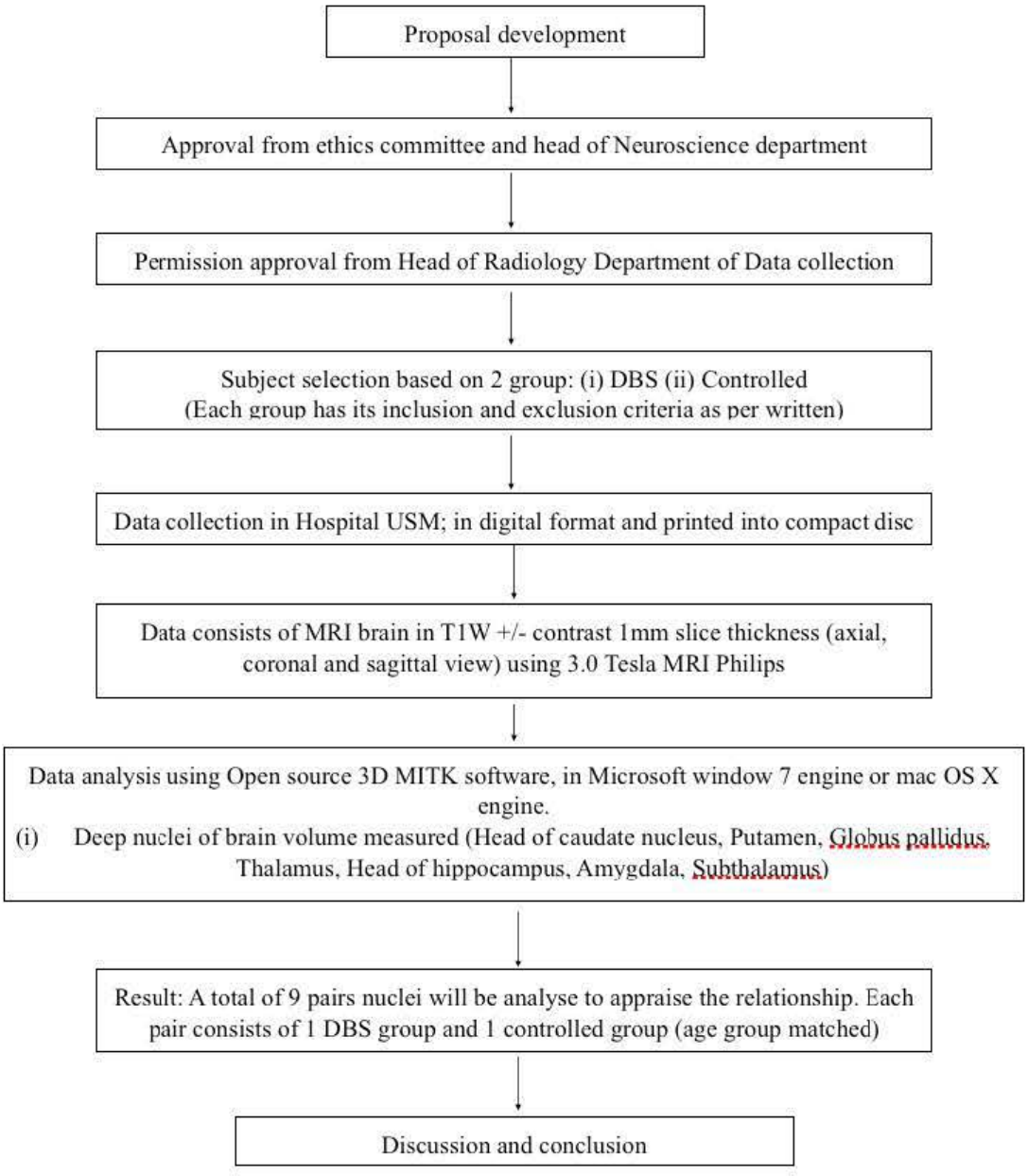

Fig. 4. Positive correlation of globus pallidus volume to higher mental function