# THALAMIC PROBABILISTIC CONNECTIVITY WITH CEREBRAL CORTEX AND ITS CORRELATION WITH MOTOR OUTCOME IN SPASTIC CEREBRAL PALSY

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**DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF**

**MASTER OF SCIENCE IN CLINICAL ANATOMY**


**UNIVERSITI SAINS MALAYSIA**

**2021**

**ACKNOWLEDGEMENT**

Alhamdulillah all praise be to Allah, The Almighty God, whose great power has granted accomplishment of this research work despite challenges. I owe many people in this research journey. Thanks to Assoc. Prof. Dr Zul Izhar Mohd Ismail, my main supervisor for your great advice and encouragement. Thanks to all my co-supervisors; Dr Asma Hayati Ahmad, Prof Dato' Dr Jafri Malin Abdullah, Dr Anna Alicia Simok for your excellent guidance and fruitful contribution.

Thank you to all lecturers and staff of Anatomy Department for their good support. I would like to thank Dr Nur Asma Sapiai, the radiologist who assisted in conventional MRI images interpretation. Thanks to my friend, Aimi Nadhiah who taught me the basic steps of diffusion MRI analysis.

A big thanks to my parents for their sound prayers and support. A special appreciation I dedicated to my beloved husband and children for their endless sacrifice and love that granted me perseverance.

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**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AD | Anterodorsal |
| AXD | Axial diffusivity |
| AM | Anteromedial |
| AV | Anteroventral |
| CL | Central lateral |
| CM | Central medial |
| CP | Cerebral palsy |
| CPI | Connection probability index |
| dMRI | Diffusion Magnetic Resonance Imaging |
| DTI | Diffusion Tensor Imaging |
| DWI | Diffusion weighted imaging |
| FA | Fractional anisotropy |
| FMRIB | Functional Magnetic Resonance Imaging of the Brain |
| FSL | FMRIB Software Library |
| GMFCS | Gross Motor Function Classification System |
| GMFM | Gross Motor Function Measures |
| LD | Lateral dorsal |
| LGN | Lateral geniculate nucleus |

| | |
|---|---|
| LP | Lateral posterior |
| MD | Mediodorsal |
| MND | Mean diffusivity |
| MGN | Medial geniculate nucleus |
| MRI | Magnetic Resonance Imaging |
| Pu | Pulvinar |
| RD | Radial diffusivity |
| rTMS | Repetitive Transcranial Magnetic Stimulation |
| SCP | Spastic Cerebral Palsy |
| VA | Ventral anterior |
| VL | Ventral lateral |
| VM | Ventral medial |
| VP | Ventroposterior complex |
| VPL | Ventral posterolateral |
| VPM | Ventral posteromedial |

**KEBARANGKALIAN HUBUNGAN SARAF ANTARA TALAMUS DAN KORTEKS MOTOR SERTA HUBUNGKAIT DENGAN FUNGSI MOTOR DALAM PALSI SEREBRAL SPASTIK**

## ABSTRAK

Ketidakupayaan fizikal adalah kesan utama dalam palsi serebral spastik. Talamus adalah tempat persinggahan utama untuk hampir semua laluan ke korteks motor dan merupakan salah satu sasaran terapi rangsangan otak dalam palsi serebral. Sama ada laluan saraf antara talamus ke korteks motor dalam palsi serebral spastik terjejas adalah masih tidak jelas dan kajian tentang corak sambungannya adalah sedikit. Oleh itu, kajian retrospektif ini bertujuan untuk mengkaji kebarangkalian hubungan saraf antara talamus dan kawasan korteks motor serta menilai hubung kaitnya dengan ukuran fungsi motor kasar (GMFM) pada pesakit palsi serebral spastik.

Teknik kebarangkalian traktografi telah dilakukan ke atas data MRI sekunder untuk sepuluh subjek kawalan yang sihat dan sepuluh pesakit palsi serebral spastik yang tidak sepadan umur (purata umur 12.8 tahun). Talamus telah ditetapkan sebagai kawasan pemula manakala tiga kawasan korteks motor, terutamanya korteks motor utama, korteks premotor dan kawasan motor tambahan adalah kawasan sasaran. Indeks kebarangkalian sambungan, yang merupakan petunjuk integriti laluan saraf dalam jirim putih otak, diukur antara talamus ke setiap korteks motor. Hubungkait antara sambungan talamus-korteks motor dengan ukuran fungsi motor kasar (GMFM) dikaji pada pesakit palsi serebral spastik. Talamus telah dibahagikan lagi mengikut sambungannya dengan korteks motor tertentu.

Dapatan kajian ini menunjukkan bahawa corak hubungan saraf antara talamus dan korteks motor dalam palsi serebral spastik adalah berubah-ubah mengikut keadaan klinikal pesakit. Sesetengah indeks kebarangkalian hubungan saraf dalam palsi serebral spastik adalah lebih rendah daripada subjek kawalan tetapi ada yang lebih tinggi. Penemuan kajian ini

mendedahkan bahawa tiada hubungkait antara hubungan saraf talamus-korteks motor dengan fungsi motor GMFM. Pembahagian talamus dalam subjek kawalan menunjukkan bahawa kluster yang mempunyai hubungan saraf yang positif kepada korteks motor utama adalah dikaitkan dengan kumpulan nukleus lateral yang mempunyai nukleus motor. Ciri menarik pembahagian talamus dalam palsi serebral spastik adalah kehadiran kluster yang mempunyai hubungan saraf yang positif ke kawasan motor tambahan. Penemuan ini mencadangkan bahawa rangkaian otak palsi serebral spastik adalah unik mengikut manifestasi klinikal. Terdapat juga bukti neuroplastik sebagai mekanisme untuk membaik pulih kemerosotan fizikal dalam palsi serebral spastik.

**THALAMIC PROBABILISTIC CONNECTIVITY WITH CEREBRAL CORTEX AND ITS CORRELATION WITH MOTOR OUTCOME IN SPASTIC CEREBRAL PALSY**


**ABSTRACT**

Motor impairment is the main disabling impact of spastic cerebral palsy (SCP). Thalamus is the major relay station for nearly all pathways to cerebral cortex and is one of the targets of deep brain stimulation therapy in cerebral palsy. Whether the pathways between the thalamus to motor cortex in spastic cerebral palsy are disrupted remains unclear and the study on its pattern of connectivity is sparse. Hence, this retrospective study aims to investigate the probabilistic connectivity between the thalamus and motor areas of cerebral cortex as well as to assess its correlation with Gross Motor Function Measures (GMFM) in spastic cerebral palsy patients.

Probabilistic tractography was performed on secondary MRI data of ten healthy control and ten non aged-matched SCP patients (mean age 12.8 years old). Thalamus was set as the seed region while the three areas of motor cortex, particularly primary motor cortex, premotor cortex and supplementary motor area were the target regions. Connection probability index, which is the indication of white matter integrity, was measured between the thalamus to each motor cortex. Correlation between the thalamo-cortical connectivity with GMFM was performed in SCP patients. The thalamus was further parcellated according to its connection with specific motor cortex.

It has been found that the pattern of thalamo-cortical connectivity in cerebral palsy was varied according to the patient's clinical presentation. Some connection probability indices in SCP were lower than control but some were higher. The findings revealed that there was no correlation between the thalamo-cortical connectivity with GMFM. Thalamic parcellation in control showed that the thalamic cluster with positive connection to primary motor cortex was associated with the lateral group nuclei, which contain the thalamic motor nuclei. A striking

feature of thalamic parcellation in SCP was the presence of cluster with positive connection to supplementary motor area. The findings suggest that the SCP brain network was unique according to the clinical manifestation. There was also an evidence of neuroplasticity as a compensatory mechanism for the motor deficit in spastic cerebral palsy.

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of the study

Thalamus functions as an important structure that receives motor pathways and is a major relay station for sensory pathways. It is also an integrative centre for information passing to other areas of central nervous system including cerebral cortex, brainstem and spinal cord (Snell, 2006; Habas *et al.*, 2019). In spastic cerebral palsy (SCP), the motor function is greatly impaired. Motor disability in spastic cerebral palsy is related to the disruption of motor fibres between thalamus and cerebral cortex (Samsir *et al.*, 2018). An association has also been demonstrated between injury of the posterior thalamic radiation with the motor impairment in spastic cerebral palsy patients (Hoon *et al.*, 2009; Scheck *et al.*, 2016).

## 1.2 Problem Statement & Study Rationale

The variabilities in the clinical presentation of spastic cerebral palsy make it difficult to assess prognosis in terms of motor function, hence uncertainties in determining the mode and outcome of treatment. A review article by Sarathy *et al.,* (2019) stated that patients with CP may present with mild to severe neurological deficit, creating challenges for decision-making in the treatment of CP. The musculoskeletal deficit varies from poor muscle tone, spasticity, rigidity and selective motor control abnormalities.

A systematic review by Mailleux et al. (2020) revealed that various studies have been carried out to assess the relationship between the microstructure of white matter and

motor outcome in cerebral palsy. However, there is limited data on the specific relationship of the motor tracts between thalamus and cerebral cortex with the Gross Motor Outcome Measures (GMFM) in spastic cerebral palsy. Disruption in white matter tracts between thalamus and motor areas of cerebral cortex might reflect the specific motor impairment as measured by GMFM. Identification of the damaged structure might contribute to determining the target therapy for SCP patients.

Thalamic injury has led to 62% cases of dyskinetic cerebral palsy according to another systematic review by Aravamuthan & Waugh (2016). A recent study has generated a protocol on the parcellation of thalamic substructures using T1 weighted MRI images in healthy subjects (Liu *et al.*, 2020). More detailed study has been done on thalamic segmentation in diseased patients (Corona *et al.*, 2020). However, the researchers did not include cerebral palsy patients in their study. Hence, this study aims to investigate the thalamic probabilistic connectivity with motor cortices (namely primary motor cortex, supplementary motor area, and premotor cortex) and to assess its correlation with the Gross Motor Function Measures (GMFM) in spastic cerebral palsy patients.

### 1.3 Justification and Benefits

It is important to investigate the integrity of motor tracts between thalamus and cerebral cortex in spastic cerebral palsy patients in order to correlate with their symptoms of motor impairment. The current study would explore the microstructural changes of thalamic lesion and connectivity in spastic cerebral palsy using diffusion MRI. In the past, there have been studies on the impact of thalamic injury related to motor outcome in cerebral palsy, but only looking into the volume of thalamus, not involving mapping of the specific lesion in the thalamus (Reid *et al.*, 2015; Pagnozzi *et al.*, 2018; Craig *et al.*, 2019).

Injury involving specific group of nuclei in the thalamus may lead to disruption of specific pathways to cerebral cortex. Therefore, the identification of specific sites affected in the thalamus and cerebral cortex and the structural pathways between these structures in SCP patients would provide the neuroanatomical mapping of the pattern of lesions. The mapping of thalamic injury could also form a basis for investigation of causal pathways in cerebral palsy (Reid *et al.*, 2015; Craig *et al.*, 2019).

The relationship between thalamus-cerebral cortex connectivity and motor outcome is beneficial to provide effective therapy for the spastic cerebral palsy patients. Mapping of thalamic injury in cerebral palsy may lead to channelling the patients towards deep brain exercise to improve the motor outcomes (Aravamuthan & Waugh, 2016). Ventral intermediate thalamic nucleus is one of the targets for deep brain stimulation therapy in cerebral palsy (Jiang *et al.*, 2020). Another treatment to improve the motor outcome of the cerebral palsy patients is the repetitive transcranial magnetic stimulation (rTMS). This treatment also used thalamus as the target therapy. There was a significant increase of connectivity in the thalamus of cerebral palsy patients following rTMS therapy (Zhang *et al.*, 2021). Revelation of probabilistic connectivity between thalamus and motor areas of cerebral cortex is important for personalized rehabilitation therapy in cerebral palsy patients (Woodward et al., 2019).

### 1.4 Research Questions

i) How does the pattern of distribution of the connection probability indices between thalamus to three areas of motor cortex (primary motor area, supplementary motor area, premotor area) differ in healthy control and spastic cerebral palsy patients?

ii) What is the correlation between thalamic probabilistic connectivity with Gross Motor Function Measures (GMFM) in spastic cerebral palsy patients?

iii) How does the pattern of thalamic segmentation differ according to its connectivities to motor cortices in healthy control and spastic cerebral palsy?

## 1.5 Study Objectives

### 1.5.1 General Objective

This study aims to investigate the structural connectivity between thalamus and motor areas of the cerebral cortex using diffusion MRI and its correlation with Gross Motor Function Measures (GMFM) in spastic cerebral palsy patients

### 1.5.2 Specific Objectives

The specific objectives of the study are as follows:

1) To describe the pattern of distribution of the connection probability indices between thalamus to three areas of motor cortex (primary motor area, supplementary motor area, premotor area) in healthy control and spastic cerebral palsy patients

2) To correlate between thalamus-motor cortex connectivity (in the form of connection probabilities index) with Gross Motor Function Measures (GMFM) in spastic cerebral palsy patients

3) To parcellate the thalamus according to its connectivity to motor cortices in healthy control and spastic cerebral palsy

## 1.6 Research Hypothesis

### 1.6.1 Null Hypothesis

1) There is no difference in the pattern of distribution of connection probabilities indices between thalamus and three subdivisions of motor cortex (primary motor area, supplementary motor area, premotor area) in spastic cerebral palsy and healthy control

2) There is no correlation between thalamus-motor cortex connectivity (in the form of connection probabilities index) with Gross Motor Function Measures (GMFM) in spastic cerebral palsy patients

3) There is no difference in the pattern of thalamic segmentation according to the motor cortices in healthy control and spastic cerebral palsy

### 1.6.2 Alternative Hypothesis

1) There is a difference in the pattern of distribution of connection probabilities indices between thalamus and three subdivisions of motor cortex (primary motor area, supplementary motor area, premotor area) in spastic cerebral palsy and healthy control

2) There is a correlation between thalamus-motor cortex connectivity (in the form of connection probabilities index) with Gross Motor Function Measures (GMFM) in spastic cerebral palsy patients

3) There is a difference in the pattern of thalamic segmentation according to the motor cortices in healthy control and spastic cerebral palsy

### 1.7 Operational Definition

**a) Diffusion MRI (dMRI) images:**

MRI images derived from an imaging technique that reflects the Brownian motion whereby the water molecules move freely in all direction provided there is no restriction (isotropic diffusion) (Oishi, 2011; Minh Duc *et al.*, 2018).

In the current study, the diffusion MRI images were the secondary data of ten healthy control and ten spastic cerebral palsy subjects from the database (Samsir et al. 2018).

**b) Probabilistic tractography:**

Probabilistic tractography is a method that allows reconstruction of the white matter tracts based on the nature of water diffusivity. Tractography is a quantitative analysis using diffusion MRI that offers an objective measure of the integrity of the white matter (Johansen-Berg *et al.*, 2010; Bech *et al.*, 2018).

In the current study, probabilistic tractography was performed between the thalamus to the three areas of the motor cortices to investigate the putative structural white matter connectivity between these structures.

**c) Connection Probability Index (CPI):**

Connection probability means the chances of finding a pathway between the seed to target regions. Connection probability index is a quantitative measure of the connection strength between the seed and target regions, but does not refer to the number of axons or fibres (Boccard *et al.*, 2016)

In the current study, connection probability index was measured between the thalamus ('seed') to the three areas of motor cortices ('targets') namely primary motor cortex, premotor cortex and supplementary motor area.

**d) Gross Motor Function Measures (GMFM)**

Gross Motor Function Measures is a tool to measure the patients' gross motor function which consists of five dimensions related to movements during lying/rolling, sitting, crawling/kneeling, standing, walking/running/jumping (Park *et al.*, 2014; Lee, 2017).

In the current study, GMFM score was measured in the ten spastic cerebral palsy patients that represent their motor ability or impairment.

**e) Thalamic Parcellation:**

Thalamic parcellation, also known as segmentation is a method that allows the thalamus to be divided into areas corresponding to their connection to the specific cortical areas. It is an analysis available in the FMRIB's Software Library, FSL (Johansen-Berg *et al.*, 2005a; Middlebrooks *et al.*, 2018)

In the current study, the thalamus was parcellated according to its connection to the three areas of the motor cortices which are the primary motor cortex, premotor cortex and supplementary motor area.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Cerebral Palsy

Cerebral palsy (CP) is the primary cause of motor disability in children, some of whom need physical assistance for their daily activities (Dean, 2017). William Little and Sigmund Freud first introduced cerebral palsy as a clinical syndrome in the 19th century (Korzeniewski *et al.*, 2008). Over the last two decades, the definition of cerebral palsy is evolving (Richards & Malouin, 2013; Shevell, 2019). Cerebral palsy (CP) is defined as a group of permanent neurodevelopmental disorder that affects motor skills, movement and posture due to the non-progressive lesions in the developing brain (Cans, 2007; Monbaliu *et al.*, 2017). This condition may also involve other functions including communication, cognition and behavior depending on the area of brain injury (Richards & Malouin, 2013; Monbaliu *et al.*, 2017).

Looking into the risk factor of CP, some children may have perinatal events such as neonatal encephalopathy or neonatal stroke leading to the condition (Morgan *et al.*, 2018). A study by Monokwane *et al.*, (2017) reported that the risk factor for CP includes serious neonatal infection, perinatal complications, and maternal human immunodeficiency virus (HIV) infection. In term infants, small for gestational age (SGA) is a known risk factor for cerebral palsy (Freire *et al.*, 2015). Moderate to late preterm infants with small for gestational age also have higher risk of developing CP according to a meta-analysis by Zhao *et al.*, (2016). Preterm babies are highly likely to suffer from white matter disruptions due to the hypoxic ischaemic events (Korzeniewski *et al.*, 2008; Schneider & Miller, 2019). Amongst the antenatal condition associated with small-for-gestational-age infants with CP are gestational hypertension and intrauterine infection (Freire *et al.*, 2015). White matter

damage, including periventricular leukomalacia, is the most common cause in all cerebral palsy patients. Periventricular leukomalacia is a specific type of white mater abnormality in patients with “ventriculomegaly with irregular outlines of the trigone and body of the lateral ventricle, a small amount of periventricular white matter, deep prominent cerebral sulci, and periventricular signal defects of low intensity on T1-weighted images and high intensity on T2-weighted MRI images” (Korzeniewski *et al.*, 2008; Gotardo *et al.*, 2019). Bilateral spastic CP children have more white matter abnormalities while the hemiplegic CP patients are associated with combined grey and white matter disruptions (Korzeniewski *et al.*, 2008; Gaberova *et al.*, 2018).

Based on a few studies in developing countries, the prevalence of cerebral palsy is two to three per 1000 births and remains static for the last 40 years (Wimalasundera & Stevenson, 2016). Patients with cerebral palsy are characterised by abnormal muscle tone, posture and balance. The symptoms may vary between individuals depending on the specific region of brain injury. Classification of cerebral palsy can be based on the number of limbs affected and the type of motor presentations of the patients (Korzeniewski *et al.*, 2008; Monbaliu *et al.*, 2017). Monoplegic CP affects only one limb usually arm while diplegic CP involves two limbs either upper or lower limbs. Hemiplegic CP affects upper and lower limb on one side of the body whereas quadriplegic CP affects all four limbs (Hallman-Cooper & Rocha Cabrero, 2021).

According to The Surveillance of Cerebral Palsy in Europe, based on the motor disorder, cerebral palsy can be classified into three predominant subtypes namely: spastic, ataxic and dyskinetic. Spastic CP can be unilateral or bilateral and is characterized by abnormal posture/movement, hypertonia, and hyperreflexia. Ataxic CP is described as having abnormal pattern of posture/movement and loss of orderly muscular coordination. Dyskinetic CP is characterised by abnormal pattern of posture/movement with uncontrolled

stereotyped movements. Dyskinetic CP is further subdivided into dystonic or choreo-athetotic. Dystonic CP is dominated by both hypokinesia and hypertonia while choreo-athetotic CP is characterised by hyperkinesia and hypotonia (Cans, 2007; Monbaliu *et al.*, 2017). The current study focused on spastic CP as it is the most common presentation among patients (Bangash *et al.*, 2014; Blumetti *et al.*, 2019).

Based on a systematic review of neuroimaging in cerebral palsy by Korzeniewski *et al.* (2008), the majority of the cerebral palsy patients (83%) have some abnormal radiological findings with the white matter disruption being the most common cause. However, about 17% of the patients have no abnormal findings on MRI or computed topography (CT) scan. Other common radiological findings in cerebral palsy include ventriculomegaly, cerebrospinal fluid space abnormalities, and brain atrophy whereas a solely grey matter damage is the rarest. The diagnosis of cerebral palsy is primarily based on the patients' clinical presentation. Neuroimaging is not mandatory to diagnose cerebral palsy however it provides significant values in the study of the aetiology and pathogenesis of the disease. Neuroimaging, which includes MRI or CT scan, was suggested by The American Academy of Neurology for all cases of cerebral palsy of unknown cause. (Korzeniewski *et al.*, 2008; Novak *et al.*, 2017)

Variability of clinical presentation of cerebral palsy reflects different regions of brain injury related to its function. Hence, the study of the impaired brain structures is vital because the anatomical connectivity in brain reflects the motor functions in CP (Passingham *et al.*, 2002; Ferre *et al.*, 2020). The rehabilitation treatment must be tailored to the specific condition in order to achieve successful improvement (Tornberg & Lauruschkus, 2020).

## 2.2 Gross Motor Function Classification System (GMFCS) and Gross Motor Function Measures (GMFM)

Cerebral palsy can also be classified according to Gross Motor Function Classification System (GMFCS), which was developed to provide an objective classification of motor disability in CP (Palisano *et al.*, 2008; Park, 2020). GMFCS focuses on the patient's self-initiated movement such as sitting, walking and use of mobility devices. Patients' current gross motor function is classified into five levels whereby level I indicates the highest level of independency and Level V is the lowest. (Wood & Rosenbaum, 2007; Park, 2020)

Cerebral palsy patients in GMFCS Level I category can walk or run independently but with slower speed and some limitation in balance and coordination. CP patients in GMFCS Level II category can walk in most circumstances with some challenges to keep balance on uneven ground. For a long-distance walk, they may need to use walking aid. They may need to hold the railing while climbing stairs and they have limited ability to run or jump. (Wood & Rosenbaum, 2007; Park, 2020)

CP patients in GMFCS Level III category can walk indoor with hand-held walking aid. In outdoor setting, they might need the wheeled mobility. They may self-propel for a short-distance walk. However, for a long-distance journey, they need assistance to operate the wheelchair. Those in the GMFCS Level IV category need the wheeled mobility for both indoor and outdoor settings. With the aid of a powered wheelchair, they can attain self-mobility. CP patients in the GMFCS Level V category have to be transported in a wheelchair due to their physical impairment. They have limited ability to maintain antigravity body postures as well as to control upper and lower limb movement. (Wood & Rosenbaum, 2007; Park, 2020)

Gross Motor Function Measures (GMFM) is a tool to measure the patients' gross motor function which consists of five dimensions related to movements during lying/rolling,

sitting, crawling/kneeling, standing, walking/running/jumping (Park *et al.*, 2014; Lee, 2017). To distinguish between the two confusing terms, GMFCS classifies the CP patients into classes according to their motor abilities while GMFM is the score of the patient's ability to perform the itemised movements at the time of the test. A literature review by Alotaibi *et al.*, (2014) on the efficacy of GMFM in cerebral palsy suggests that it is effective to detect changes in gross motor function in children with CP undergoing interventions. A systematic review by Ferre-Fernández *et al.*, (2020) and a clinical study by Ko & Kim (2013) in CP patients across all Gross Motor Function Classification System criteria showed that relative reliability and responsiveness of GMFM is outstanding (cronbach alpha >0.95).

### 2.3 Thalamus

Thalamus is the largest subcortical grey matter of central nervous system that forms a major constituent of diencephalon. Galen in 2$^{nd}$ century first used the Greek word "thalamos" in an anatomical context during dissection of the optic tract. Back then, Galen referred the thalamus to a region in between the lateral ventricles, at the posterior part of diencephalon and near the lateral geniculate bodies (Jones, 1985; Serra *et al.*, 2019). Thalamus is located deep to the white matter of each cerebral hemisphere. This grey matter mass consists of right and left thalami, connected via the inter-thalamic adhesion (Patestas & Gartner, 2006; Singh, 2018). The inter-thalamic adhesion is a grey matter structure that traverses through the third ventricle. The information from the basal ganglia and cerebellum will also pass through the thalamus before reaching the cerebral cortex (Tanaka *et al.*, 2018).

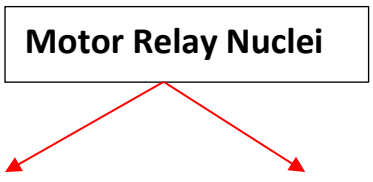
Thalamus consists of various nuclei that possess specific functions and connections to various parts of central nervous system including cerebral cortex (Iglehart *et al.*, 2020a).

Thus, injuries at particular parts will exhibit different clinical presentation of motor impairment. Thalamus consists of mainly grey matter and a small amount of white matter. The white matter part consists of external and internal medullary lamina. The external medullary lamina covers the lateral surface of the thalamus. The internal medullary lamina divides a thalamus into anterior, lateral and medial parts (Chaurasia, 2015; Singh, 2018). The grey matter part of thalamus contains various nuclei. The nuclei in the thalamus can be subdivided according to their functions and connections. Karl-Friedrich Burdach in 1822 had made a clear delineation of subdivision of the thalamic nuclei (Jones, 1985; Serra *et al.*, 2019). He had noticed that the internal medullary lamina divided them into anterior, lateral and medial nuclei. However, Burdach had not associated the thalamic nuclei with their connection and function. Later in 1865, Luys had referred that the thalamic nuclei as foci or centres, that were made up of a group of cells linked with a specific afferent fibres. Upon dissecting the cerebral cortex, he discovered that the distinct regions of the cerebral hemisphere were interconnected with the specific centers in the thalamus with some exemptions (Jones, 1985; Serra *et al.*, 2019).

Functional subdivision of the thalamic nuclei is based on connections between the nuclei and the cerebral cortex. Functionally, the thalamic nuclei can be divided into specific relay nuclei, sensory relay nuclei, motor relay nuclei, and association nuclei. The motor relay nuclei of the thalamus are the ventral anterior (VA) and ventral lateral (VL) nuclei (Figure 2.1). Information from the somatic motor system, basal ganglia and the cerebellum will relay at these VA and VL nuclei before reaching to the motor cortical areas. Ventral anterior nucleus receives afferent fibres from globus pallidus of basal ganglia and send the efferent fibres to premotor cortex, which is important for motor planning. Ventral lateral nucleus receives afferent fibres from the cerebellum and basal ganglia and send the efferent fibres to

frontal cortex and primary motor cortex, which is important for movement and motor planning. (Patestas & Gartner, 2006; Singh, 2018)

The sensory relay nuclei consist of the ventral posterior medial (VPM) and ventral posterior lateral (VPL) nuclei, the medial geniculate nucleus (MGN), and the lateral geniculate nucleus (LGN) (Figure 2.1). Somatosensory information from the orofacial region will relay at VPM whereas the information from the body will relay at VPL. The MGN is responsible to process sensory information related to hearing, while the LGN is important for vision. Specific relay nuclei comprise of the ventral tier of the lateral nuclear group. Specific relay nuclei have reciprocal connections with sensory or motor cortex. Association nuclei receive the sensory and motor information indirectly via a relay in other thalamic nuclei and various brain regions. Association nuclei consist of dorsomedial (DM), lateral dorsal (LD), lateral posterior (LP), and pulvinar nuclei. (Patestas & Gartner, 2006; Singh, 2018)



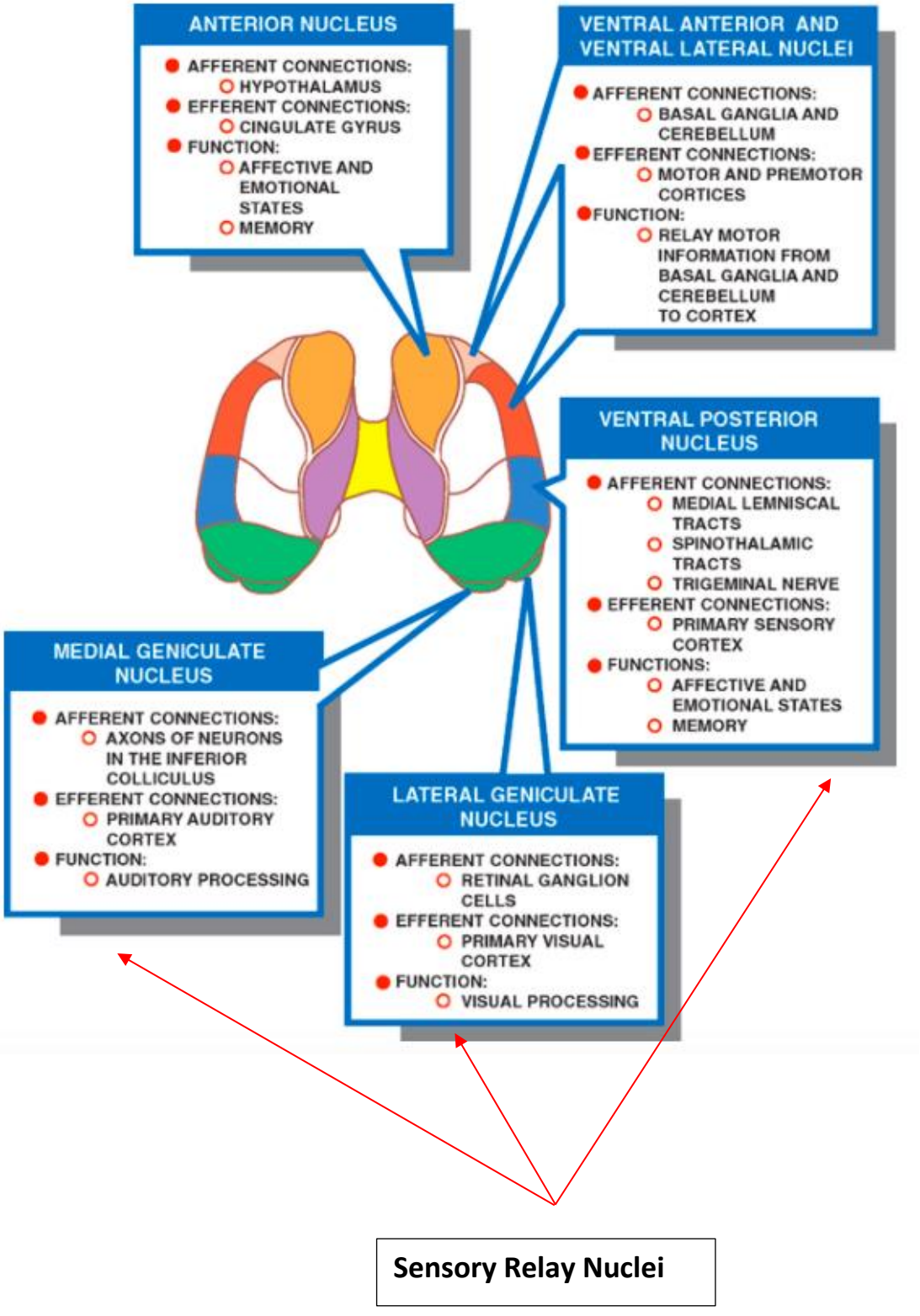



Figure 2.1 Motor and sensory relay nuclei of thalamus (adapted from https://neupsykey.com/thalamus-2 and Patestas & Gartner (2006))

It is important to know the relation of thalamus with regard to the adjacent structures to locate it in the MRI imaging. The thalamus is located medial to the internal capsule and the lentiform nucleus of the basal ganglia. A thalamus is located lateral to the wall of the third ventricle and the medial surface of another thalamus (via interthalamic adhesion). The superior surface of thalamus forms the floor of the lateral ventricle. The inferior surface of thalamus is related to the hypothalamus and subthalamus. The interventricular foramen (Foramen of Monro) is found rostral to the thalamus. Four structures located caudal to thalamus are the lateral geniculate body, medial geniculate body, superior colliculus, and superior brachium. (Chaurasia, 2015; Serra *et al.*, 2017)

## 2.4 Cerebral Cortex

Cerebral cortex plays a vital role in various brain activities including planning the motor activity, sensory perception and awareness, comprehension, memory, thinking and awareness of emotions (Patestas & Gartner, 2006; Fernández *et al.*, 2016). Cerebral cortex is divided into three main types of functional areas namely motor areas, sensory areas and association areas. This study will focus on the motor areas of cerebral cortex as the motor function is greatly impaired in cerebral palsy (Samsir *et al.*, 2018). The motor area of cerebral cortex is subdivided into primary motor cortex, supplementary motor area and premotor cortex (Donoghue & Sanes, 1994; Ninomiya *et al.*, 2019).

Primary motor cortex is important for specific movement of individual parts of the body. It is located in the precentral gyrus and extended to the anterior part of paracentral lobule in the medial surface of frontal lobe. It corresponds to Brodmann's area 4 (Chaurasia, 2015; Ninomiya *et al.*, 2019). Stimulation of primary motor cortex will produce the movement on the contralateral side due to the crossing over of the motor pathways e.g. the corticospinal tract. Majority of the motor fibres will cross over to the other side in the medulla oblongata at

the level of decussation of pyramid (Bech *et al.*, 2018). There is a somatotopic organization of the motor homunculus in the primary motor cortex, with some variations between individuals (Roux *et al.*, 2020). The superior part of precentral gyrus gives a control on the thigh and toes musculature. The lateral part of the homunculus regulates the movement of hand and face. The inferior parts represent the areas of tongue, mouth and larynx. Leg, foot and perineum areas of homunculus are located in the medial surface in the paracentral lobule (Emos & Agarwal, 2019). Damage to the primary motor cortex may contribute to a great impact of motor impairment in the contralateral side of the body. The patient may suffer from paralysis of upper limb and/or lower limbs depending on the extent of injury. Upper motor neuron syndrome including spasticity, clonus and hyperreflexia might also be observed in these patients because a majority of the upper motor neurons of the pyramidal tracts reside in the primary motor cortex and the premotor cortex (Emos & Agarwal, 2019).

The premotor cortex is crucial in the planning phase of motor execution and its activity is slowly reduced after the movement has been initiated (Patestas & Gartner, 2006; Li *et al.*, 2016). It is located in the posterior parts of superior, middle and inferior frontal gyri, anterior to primary motor cortex. It corresponds to the lateral surface of Brodmann area 6 (Singh, 2018). It is important that the premotor area has reciprocal connection with the primary motor cortex and the supplementary motor area to establish a smooth motor function. It is also involved in adjusting the body parts mainly axial and proximal limbs towards the intended movement based on the input from the cerebellum and basal ganglia. The premotor cortex receives fibres from the cerebellum via a relay in ventral lateral nuclei of the thalamus (Snell, 2006; Guo *et al.*, 2017). It also has a special connection with the primary sensory cortex, hence receiving the sensory information needed in programming the motor tasks. The fibres from the premotor area is sent to the cerebellum, corticospinal and corticonuclear tract. Injury to premotor cortex may cause an impairment of skilled movement (Singh, 2018).

Supplementary motor area plays an important role for organising the activity sequence of a complex movement by an input from the basal ganglia (Tanji, 1994; Mohebi *et al.*, 2019). It is located in the medial frontal gyrus, anterior to the paracentral lobule, on the medial surface of the frontal lobe. It corresponds to the medial surface of Brodmann's area 6. Supplementary motor area can modulate some simple motor activity to compensate for injury of the primary motor cortex (Singh, 2018). It receives fibres from the globus pallidus and the substantia niagra via a relay in the ventral lateral thalamic nucleus. It is also involved in ensuring a coordination between the right and left limbs by controlling the contractions of the axial and proximal limbs musculatures (Patestas & Gartner, 2006; Welniarz *et al.*, 2019). Supplementary motor area syndrome may occur following a resection of brain tumour in this area. Patients with the supplementary motor area syndrome might experience transient paralysis that take one to nine week to recover depending on the severity of the injury (Nakajima *et al.*, 2020).

### 2.5 Pathways between Thalamus and Cerebral Cortex

Thalamus is connected anatomically and functionally with cerebral cortex with various white matter tracts traversing between them. In the last four decades, the connection between the thalamus and the cerebral cortex was debated. Protomap and Protocortex theories emerged in the history. Protomap theory hypothesized that the functions of the cells in the cerebral cortex have been predetermined at birth. However, the Protocortex theory proposed that all neurons in the cerebral cortex were initially homogenous and multipotent. Protocortex theory further postulated that the afferent axons (mostly thalamic input) encode the cortical area identification via the biochemical activities in the pathways (Antón-Bolaños *et. al.*, 2018).

Thalamus represents a gate for the pathway to the cerebral cortex and responsible for upregulating or downregulating the information (Sherman, 2017). It is important to investigate the integrity of motor tracts between thalamus and cerebral cortex in cerebral palsy patients to correlate with their symptoms of motor impairment. Regarding the motor pathway involving thalamus, the ventral anterior and ventral lateral thalamic nuclei will relay the motor information from the deep cerebellar nuclei and basal ganglia to the cerebral cortex (Sheridan & Tadi, 2020).

In order to understand the circuit between the thalamus and cortex, it is convenient to divide the thalamus into dorsal and ventral regions according to its embryonic derivation. The dorsal division consists of the nuclei within which are the relay cells projecting onto the cerebral cortex. The ventral division of the thalamus comprise of the reticular nucleus and the ventral part of lateral geniculate nucleus, which both do not project onto the cerebral cortex. However, the dorsal part of the lateral geniculate nucleus is included in the dorsal division of the thalamus and does have a connection with the cerebral cortex. The thalamic reticular nucleus gives out fibres to the thalamic relay cells in the dorsal divison of the thalamus (Sherman, 2017). So, only the relay nuclei in the dorsal division of thalamus have a direct connection with the cerebral cortex. There are three types of relay cells in the thalamus, namely core, intralaminar and matrix cells (Harris *et al.*, 2019).

The reciprocal connection between thalamus and motor cortex is vital in a complex motor movement (Antón-Bolaños *et al.*, 2018). Pathways between the thalamus and the cerebral cortex are divided into the cortico-thalamic (CT) and thalamo-cortical (TC) pathways (Figure 2.2). CT and TC pathways are further classified into two classes, which are driver (feedforward) and modulator (feedback) projections. The driver pathways transport the input between the neurons while the modulator pathways regulate the driver information accordingly (Sherman, 2017).

Cerebral cortex is organized into six layers that contain specific types of neurons according to their pathways (Agirman *et al.*, 2017). Cortico-thalamic (CT) pathways are associated with layer V and VI of the cerebral cortex. Cortico-thalamic pathway from layer V is considered as feedforward (driver) whereas the CT pathways from the layer VI is described as feedback (modulator) route. However, the other layers of cerebral cortex may also contain some input from the thalamus depending on the cortical area and the thalamic nuclei involved in that circuit (Harris *et al.*, 2019).

Besides that, the thalamo-cortical (TC) pathways involve three classes of neurons in the thalamic relay nuclei namely: core, intralaminar and matrix neurons. Core TC pathway is known as driver (feedforward) while the matrix TC pathway is considered as modulator (feedback) projection (Harris *et al.*, 2019). Core neurons project into the middle layers of cortex and innervate a single or several cortical regions. Matrix neurons project diffusely to superficial cortical layers including layer I (Sherman, 2017).

One of the feedforward pathways includes the cortico-thalamo-cortical (transthalamic corticocortical) pathways. In the transthalamic corticocortical circuit, there are two types of thalamic relay nuclei which are first order nuclei and higher order nuclei. The first order nuclei receive information from the subcortical course whereas the higher order nuclei receive input from a cortical area. The examples of first order nucleus and the higher order nucleus are lateral geniculate nucleus and pulvinar, respectively (Sherman, 2017). Thalamic motor nuclei, namely ventral anterior and ventral lateral nuclei, are organised in a mosaic pattern by the input from basal ganglia and deep cerebellar nuclei. First order nuclei zones receive the input from the cerebellum while the higher order nuclei zones receive the innervation from layer V of the motor cortex and also from the basal ganglia.

The feedback pathway from the cerebral cortex to the thalamus involves two types of corticothalamic neurons, distinctively as the neurons from layer VI and layer V of the cerebral

cortex. Corticothalamic neurons from layer VI are small, pyramidal cells with narrow vertical dendrites. Upon leaving the cortex, their axons give off a few branches that surround the dendritic area of the cell in the same layer VI. Their main axons descend subcortically to reach the thalamus only. They enter a confined area of the dorsal thalamic nucleus in a topographic manner, according to the related cortical region. In contrast, the corticothalamic neurons from layer V are large, pyramidal cells with a thick dendrite. Their axons give off collaterals that can initially ascends up to the cortical level III and IV, then descend subcortically. Their subcortical target structures do not only include thalamus, but also the brain stem and spinal cord (Jones, 2009; Guo *et al.*, 2020). The morphological differences of these neurons could also explain the unique relation between the cells in the thalamic nuclei and the associated individual areas of the cortex.

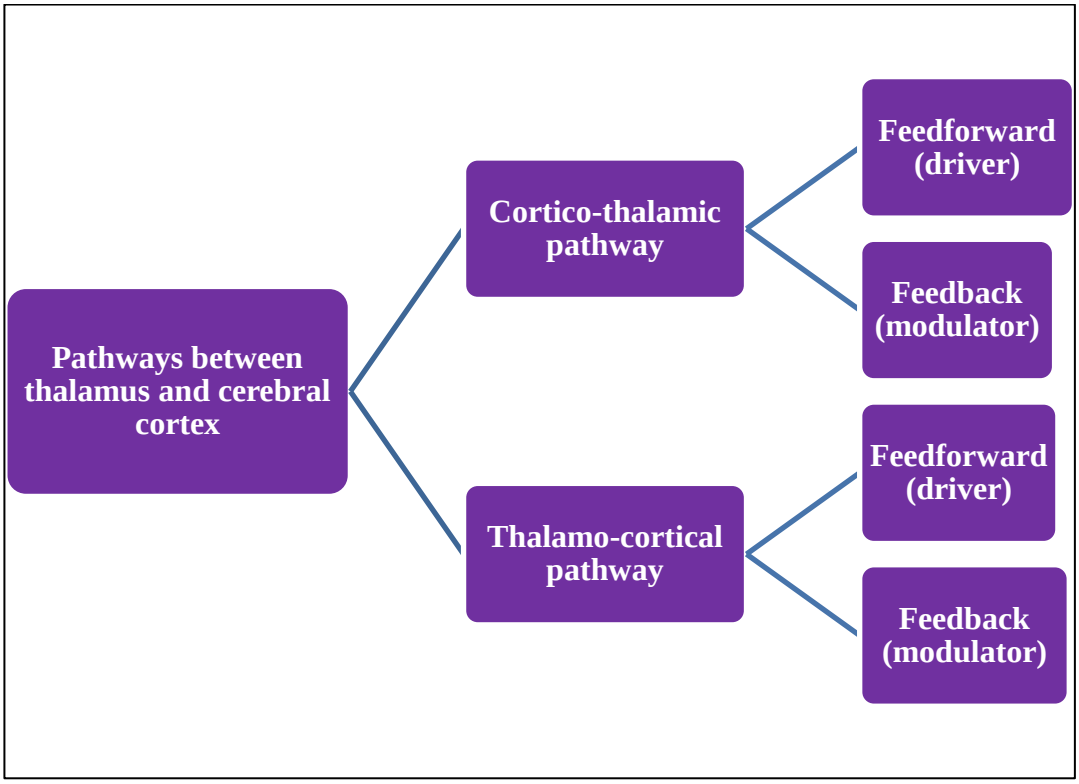


Figure 2.2 Summary of the pathways between thalamus and cerebral cortex

(adapted from Sherman, 2017)

On another note, there is a difference in the amount and types of the calcium-binding proteins (calbindin / parvalbumin / calretinin) in the thalamic nuclei. Even though the biochemical implication of these protein is unknown, they portray some significant association. Parvalbumin is associated with the sensory and motor pathways and highly targeted to a distinct cortical region. However, the calbindin is related to the subcortical pathways and less specific to the cerebral cortices. Pathways associated with parvalbumin sink deep into the layer III and IV of the cerebral cortices, whereas the pathways containing the calbindin protein project onto the superficial cortical layers of I, II and III. Thalamic nuclei with an abundance of calbindin are found to be lacking of parvalbumin and vice versa. Intralaminar neurons however contain a mixture of calbindin and parvalbumin. These findings are beneficial in the study of the synchronization between thalamo-cortical circuit. (Jones, 2009; Żakowski, 2017)

Pathways between the thalamus and cerebral cortex can also be classified according to the neurotransmitter involved. Thalamo-cortical pathway is also known as glutamatergic pathway, which is the feedforward route (Sherman, 2017). Glutamate is the main excitatory neurotransmitter in the human central nervous system. Cortico-thalamic pathway is also known as GABAergic pathway, which is the feedback track. Gamma aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the mammalian central nervous system. Thalamic relay cells are glutamatergic whereas the reticular cells and interneurons are GABAergic (Sherman, 2017). Interneurons and reticular cells provide inhibitory information to the relay cells. Neurodegenerative disorder could be due to the impact of some disturbance in the receptor activities. Hence, modulating the pathways involving the glutamate receptor might be a therapeutic approach to these diseases (Tomita, 2016). The balance between excitatory and inhibitory activities is critical for a normal neuronal function.