UMEÅ UNIVERSITY

FUNCTIONAL BRAIN IMAGING OF SENSORIMOTOR DYSFUNCTION AND RESTORATION

Investigations of Discomplete Spinal Cord Injury and Deep Brain Stimulation for Essential Tremor

Amar Awad

Department of Integrative Medical Biology, Physiology section

Umeå 2022

Dissertation for PhD

ISBN: 978-91-7855-837-7 (print)

ISBN: 978-91-7855-838-4 (pdf)

ISSN: 0346–6612

New Series Number 2194

Cover design created by Emy Eklånge

Electronic version available at: http://umu.diva-portal.org/

Printed by: Cityprint i Norr AB

Umeå, Sweden 2022

To Emy

Table of Contents

Abstract

The nervous system exists to generate adaptive behaviour by processing sensory input from the body and the environment in order to produce appropriate motor output, and vice versa. Consequently, sensorimotor dysfunction is the basis of disability in most neurological pathologies. In the current thesis, I explore two conditions with different types and degrees of sensorimotor dysfunction by means of functional magnetic resonance imaging (fMRI). In part 1, I assess residual sensory connections to the brain in clinically complete spinal cord injury (SCI) with seemingly complete loss of sensorimotor function below the injury level. In part 2, fMRI is combined with deep brain stimulation (DBS) to investigate interventional mechanisms of restoring dysfunctional sensorimotor control in essential tremor (ET).

Part 1: SCI disrupts the communication between the brain and below-injury body parts, but rarely results in complete anatomical transection of the spinal cord. In studies I and II, we demonstrate somatosensory cortex activation due to somatosensory (tactile and nociceptive) stimulation on below-level insensate body parts in clinically complete SCI. The results from studies I and II indicate preserved somatosensory conduction across the spinal lesion in some cases of clinically complete SCI, as classified according to international standards. This subgroup is referred to as sensory discomplete SCI, which represents a distinct injury phenotype with an intermediate degree of injury severity between clinically complete and incomplete SCI.

Part 2: ET is effectively treated with DBS in the caudal zona incerta, but the neural mechanisms underlying the treatment effect are poorly understood. By exploring DBS mechanisms with fMRI, DBS was shown to cause modulation in the activity of the sensorimotor cerebello-cerebral regions during motor tasks (study III), but did not modulate the functional connectivity during resting-state (study IV).

fMRI is a valuable tool to investigate sensorimotor dysfunction and restoration in SCI and DBS-treated ET. There is evidence for sensory discomplete SCI in about half of the patients with clinically complete SCI.

DBS modulates DBS modulation of the activity in the sensorimotor cerebello-cerebral circuit during motor tasks, but not during resting-state, is action-dependent.

Key words: Sensorimotor control, fMRI, discomplete spinal cord injury, essential tremor, deep brain stimulation, cerebello-thalamo-cerebral circuit

Sammanfattning på svenska

Nervsystemet är till för att möjliggöra ett ändamålsenligt beteende. Sensorisk information från kropp och omgivning bearbetas som en förutsättning för optimerade motoriska handlingar, vilka i sin tur genererar nya sensoriska intryck. Detta sensorimotoriska kretslopp definierar allt målinriktat beteende, och följaktligen utgör bristfällig sensorimotorisk funktion grunden till funktionsstörningar till följd av neurologiska sjukdomar och skador.

I denna avhandling använder jag funktionell magnetresonanstomografi (fMRI, *"functional magnetic resonance imaging"*) för att undersöka hur hjärnan arbetar vid två tillstånd med olika typer av sensorimotorisk dysfunktion. I del 1 undersöks kvarvarande somatosensorisk funktion efter kompletta ryggmärgsskador och i del 2 kartläggs mekanismerna bakom djup hjärnstimulering (DBS, *"deep brain stimulation"*) för att återställa sensorimotorisk funktion vid sjukdomen essentiell tremor.

Del 1: Ryggmärgsskador bryter förbindelsen mellan hjärnan och resten av kroppen, och resulterar därmed i varierande grad av sensorimotoriska bortfall nedanför skadeområdet. Klassifikationen av ryggmärgsskador inom såväl klinisk praxis som forskning baseras på en klinisk undersökning, där viljemässig muskelstyrka och rörelseförmåga samt rapporterad medveten känsel noteras för att bestämma skadans nivå och allvarlighetsgrad. I denna avhandling studeras kompletta ryggmärgsskador (ASIA impairment scale (AIS) grad A), det vill säga den mest allvarliga graden av ryggmärgsskador med bortfall av all viljemässig rörelseförmåga och känsel nedanför skadenivån, inklusive de nervförbindelser som försörjer underlivet och dess viljemässiga funktioner. I studie I och II undersöks förekomsten av eventuellt kvarvarande somatosensorisk funktion efter kliniskt kompletta ryggmärgsskador genom känselstimulering av kroppsdelar nedanför skadenivån med samtidig mätning av hjärnans aktivitet med fMRI.

Vi visar här att somatosensorisk stimulering av kroppsdelar innerverade nedanför skadenivån aktiverar motsvarande hjärnregioner (somatosensorisk cortex) hos hälften av personerna med kliniskt kompletta

ryggmärgsskador, trots avsaknad av känselupplevelse från dessa kroppsdelar. Denna skadefenotyp som vi döpt till *sensoriskt diskomplett ryggmärgsskada*, utgör en intermediär allvarlighetsnivå mellan kompletta och inkompletta skador. Detta kan tala för behov av en revision av rådande klassifikationssystem, och kan utgöra en förutsättning för nya funktionsförbättrande interventioner.

Del 2: DBS är en etablerad och effektiv behandling vid essentiell tremor men hur den utövar sin effekt för att dämpa tremor (skakningar) är fortfarande oklart. Genom experiment som kombinerar DBS i ett hjärnområde som kallas kaudala zona incerta och fMRI hos 16 patienter har vi kunnat belysa hur DBS påverkar hjärnans aktivitet under motoriska uppgifter (studie III) och under vila (studie IV). Experimenten genomfördes med DBS av och på, medan hjärnans aktivitet analyserades och jämfördes i dessa två lägen.

Studie III visar att DBS påverkar aktiviteten i det sensorimotoriska cerebello-cerebrala nätverket. Vi visar signifikanta interaktionseffekter mellan DBS och motoriska uppgifter i kontralaterala motorcortex samt ipsilaterala cerebellum. Vi fann även signifikanta huvudeffekter (main effects) av DBS i dorsala premotorcortex i form av ökad aktivitet under alla motoriska betingelser. Studie IV visar att DBS inte påverkar funktionell konnektivitet (samvariation i aktivitet) mellan olika hjärnregioner under vila (s.k. resting-state). Sammantaget talar resultaten från studie III och IV för att DBS-effekter är aktivitetsberoende och mer komplexa än man tidigare trott, med både ökad och minskad aktivitet i hjärnregioner bortom det stimulerade området runt elektroden.

fMRI är en värdefull metod för att studera kliniska populationer såsom personer med ryggmärgsskador och patienter med DBS. Med hjälp av fMRI har vi kunnat beskriva sensoriskt diskompletta ryggmärgsskador, en specifik skadefenotyp med tecken på bevarad överföring av somatosensoriska impulser trots avsaknad av (medveten) perception, samt belysa hur DBS påverkar aktiviteten i det cerebello-cerebrala nätverket vid essentiell tremor.

Abbreviations

ASIA	American Spinal Injury Association
AIS	ASIA impairment scale
BA	Brodmann area
BOLD	Blood-oxygenation-level-dependent
cZi	Caudal zona incerta
DBS	Deep brain stimulation
ET	Essential tremor
fMRI	Functional magnetic resonance imaging
GLM	General linear model
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
LFP	Local field potential
M1	Primary motor cortex
PAS	Perceptual awareness scale
RF	Radiofrequency
ROI	Region of interest
Rs-fMRI	Resting-state fMRI
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SCI	Spinal cord injury
SMA	Supplementary motor area
Vim	Ventral intermediate nucleus (in ventrolateral thalamus)
VLa	Ventrolateral anterior nucleus of the thalamus
VLp	Ventrolateral posterior nucleus of the thalamus
VPI	Inferior nucleus of the ventroposterior thalamus
VPL	Lateral nucleus of the ventroposterior thalamus
Zi	Zona incerta
ZPP	zone of partial preservation

List of Papers

This doctoral thesis is based on the following studies:

I. **Awad, A.**, Levi, R., Lindgren, L., Hultling, C., Westling, G., Nyberg, L., Eriksson, J., 2015. **Preserved somatosensory conduction in a patient with complete cervical spinal cord injury**. *J. Rehabil. Med.*

II. **Awad, A.**, Levi, R., Waller, M., Westling, G., Lindgren, L., Eriksson, J., 2020. **Preserved somatosensory conduction in complete spinal cord injury: Discomplete SCI**. *Clin. Neurophysiol.*

III. **Awad, A.**, Blomstedt, P., Westling, G., Eriksson, J., 2020. **Deep brain stimulation in the caudal zona incerta modulates the sensorimotor cerebello-cerebral circuit in essential tremor**. *Neuroimage*

IV. **Awad A.**, Grill F., Blomstedt P., Nyberg L., and Eriksson J. (Submitted) **Deep brain stimulation does not modulate fMRI resting-state functional connectivity in essential tremor**

1 Background

We are motor actions guided by our senses. Generating optimal sensorimotor function is ultimately the major reason why we have brains, which essentially act as sensorimotor processors. We perceive our environment via our senses, and make use of such information to guide our behaviour in terms of motor output (**Figure 1**). This perception-action cycle consists of a flow of information from the environment to the sensory system, to the motor system, back again to the environment, and so on during the process of goal-directed behaviour (Fuster, 2000). Sensorimotor dysfunction in this cycle is the basis of disability in most neurological pathologies.

In the current thesis, I use functional magnetic resonance imaging (fMRI)[1] to address the issue of sensorimotor dysfunction in two conditions with different types and degrees of sensory or motor dysfunction. In part 1 of the thesis, I study the extent of sensorimotor deprivation caused by spinal cord injury, with focus on residual subclinical somatosensory function. In part 2, I investigate interventional mechanisms of restoring dysfunctional sensorimotor control, specifically invasive electrical stimulation to treat pathological brain circuits in essential tremor. These questions are undoubtedly of a rather complex nature, and in order to put them in their proper context, I believe that a thorough review of the background, including basic concepts, is of value. Thus, in the following sections, I will give an overview of relevant background divided into three main parts. In part 1, the somatosensory system is briefly described beginning with peripheral coding of sensory input in the skin, followed by transmission of the sensory signals in the spinal cord up to the cerebral cortex where they are further processed to generate perception. Next, I describe how the somatosensory system is variably disrupted by traumatic lesions in the

[1] fMRI is described in more detail in section "1.3 functional magnetic resonance imaging". In brief, fMRI is a non-invasive functional neuroimaging method where brain activity is indirectly captured by measuring regional, time-varying changes in deoxyhaemoglobin concentration as a consequence to task-induced changes or spontaneous fluctuations during rest.

spinal cord. In part 2, the motor system is briefly described, focusing on motor cortex and cerebellum, as well as their interconnections. Next, I describe the consequences of a dysfunctional motor system in essential tremor, and how it is restored by means of electrical stimulation. Lastly, I describe fMRI which is the method used in all the studies in this thesis.

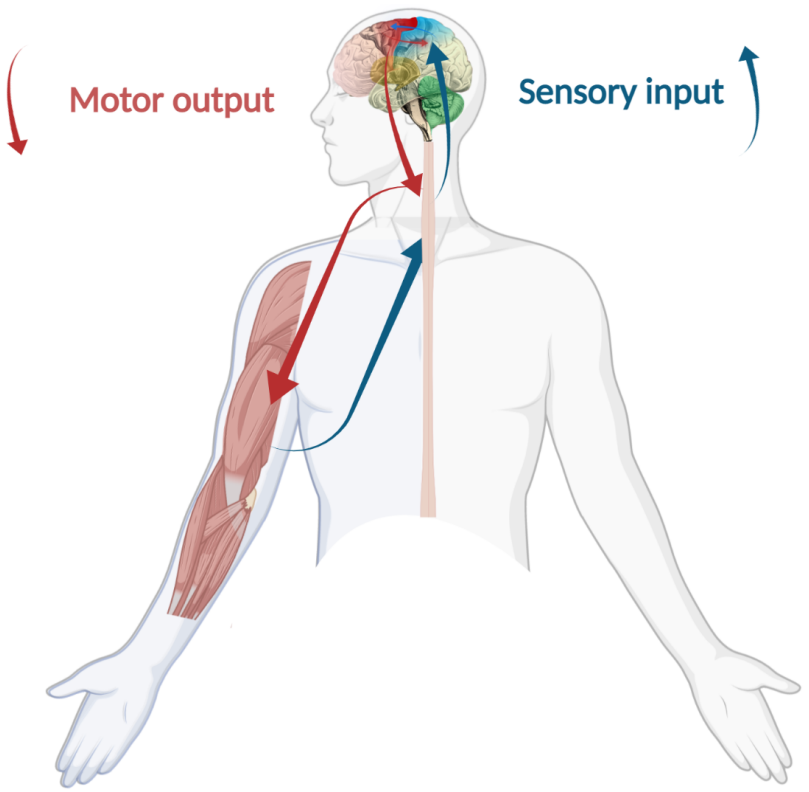


Figure 1. General organisation of the sensorimotor system: The nervous system is devoted to the processing of sensory input from our senses to create a representation of the body and the external environment. Here, the sensory system is exemplified by somatosensory input (depicted in blue) from the periphery to the spinal cord, brainstem and ultimately the cerebral cortex. The processing of sensory input is aimed to guide the generation of purposeful motor behaviour. The motor system (depicted in red) generates goal-directed motor behaviour by sending descending motor commands from motor cortex to the brainstem and spinal cord, and ultimately the muscles. →

→ ***Figure 1. cont.*** The sensorimotor cortex is hierarchically organised. Simple/automatic actions in response to elementary sensory input are processed in primary sensorimotor cortices. More complex actions as guided by complex and temporally distant sensory input are integrated in higher-order sensorimotor areas along both the perceptual (association cortex) and motor hierarchies (premotor and prefrontal cortex) (Fuster, 2004). According to Fuster, the prefrontal cortex (pink) is located at the top of the perception-action hierarchy and is fundamental for the temporal organisation of behaviour especially when perception and action are remote in time (Fuster, 2000). Our behaviour, as generated by the cerebral cortex, is supported by two important circuits involving the cerebellum (green) and basal ganglia (yellow). The cerebellum streamlines and fine-tunes the behaviour in order to reach the goals, while the basal ganglia make sure that a specific behaviour indeed accomplishes the goals. Although frequently separated, the sensory and motor system are, in reality, a single integrated system with extensive communication back and forth at multiple levels ranging from the spinal cord, cerebellum, basal ganglia, up to the cerebral cortex. *Partly created with BioRender.com*

1.1 The disruption of the somatosensory system in spinal cord injury (Part 1)

In this section, I will give an introduction to the somatosensory system and the extent of sensory deprivation in this system caused by lesions to the spinal cord.

1.1.1 The somatosensory system

Here, I will give a brief overview of the somatosensory system regarding the perception of tactile (touch) and nociceptive (pain) stimuli from the extremities, with emphasis on cerebral somatosensory processing. Generally, the somatosensory pathway consists of afferent projections from the peripheral receptors (mechanoreceptors, thermoreceptors and nociceptors) to the spinal cord, brainstem, thalamus and ultimately the somatosensory cortex.

The body is equipped with different somatosensory receptors that deliver a great spectrum of information about the current state of the body and the surrounding environment to the brain. Mechanoreceptors, nociceptors and thermoreceptors embedded in the skin detect and code mechanical

deformation or temperature changes of the tissue by converting them into neural signals. The sensation of touch is mediated by four different classes of myelinated and rapidly conducting mechanoreceptor afferents that respond to different stimuli or stimuli parameters (Johansson and Flanagan, 2009; Delhaye et al., 2018). Depending on their adaptation to stimulation, they provide the central nervous system with complementary information, for example, fast-adapting receptors code for on/off input while slow-adapting receptors provide continuous monitoring of a constant stimulus. Nociceptive or noxious stimuli, i.e. comprising actual or potential tissue-damaging events, are coded by high-threshold nociceptors in free nerve endings (Van Hees and Gybels, 1981).

After coding by peripheral receptors, somatosensory signals are transmitted through different fibres/axons; fast-conducting thick myelinated Aβ fibres for conduction of light touch, thin-myelinated Aδ fibres for conduction of sharp nociceptive and thermal stimulation, and slow-conducting unmyelinated C-fibres for conduction of nociceptive, thermal and light touch stimulation. The cell bodies of the 1st order somatosensory neurons reside in the dorsal root ganglia adjacent to the spinal cord, from which they send an axonal branch into the spinal cord via the dorsal roots.

Tactile and nociceptive signals ascend in spatially distinct tracts wihin the spinal cord. The dorsal column–medial lemniscus pathway conveys tactile, proprioceptive and vibratory information, while the spinothalamic pathway conveys nociception, temperature, crude touch and pressure (see **Figure 2** for details).

The somatosensory cortex

The somatosensory cortex can be viewed as a network with increasing hierarchy at the organisational and functional level (**Figure 3**).

The primary somatosensory cortex (s1): is divided into four cytoarchitecturally distinct Brodmann areas (BA) (Brodmann, 1909); 3b, 3a, 1, and 2. The S1 contains complete maps for the contralateral body (somatotopic organisation) proceeding from the foot in the medial cortex to the face and tongue in the lateral cortex, with each subdivision having its

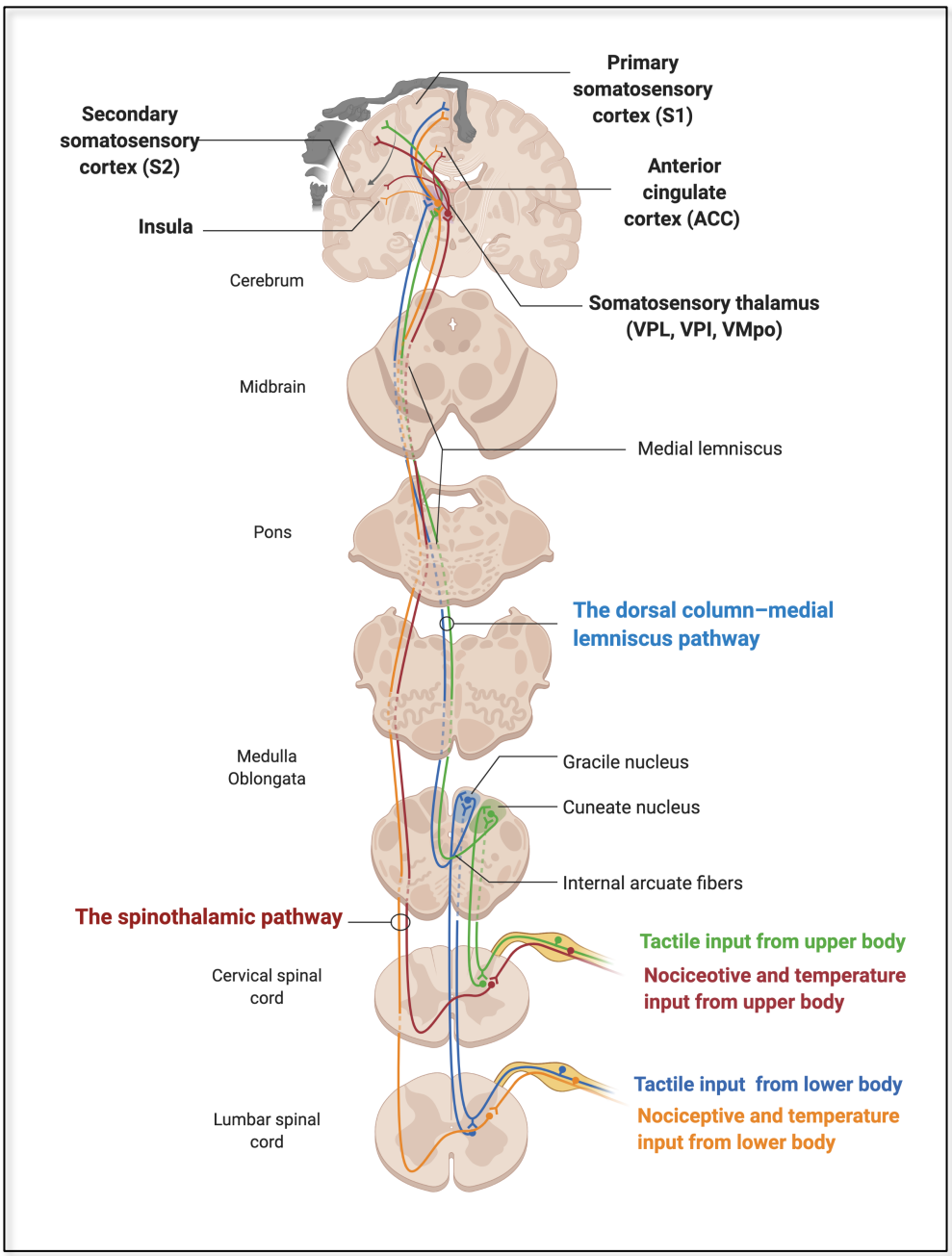
own somatotopic map of the body (**Figure 2**) (Kaas et al., 1979).

The body is not proportionally represented, i.e. body regions that are densely innervated such as the hands and the mouth occupy a disproportionally larger cortical area than less densely innervated regions e.g. proximal parts of the extremities and trunk (Penfield and Boldrey, 1937; Eickhoff et al., 2008; Akselrod et al., 2017; Catani, 2017). Accordingly, the somatotopic representation of S1 can be visualised as a distorted human-like figure "homunculus" (**Figure 2**).

Area 3b is referred to by some as "S1 proper" based on the prominence of its thalamocortical input (Qi et al., 2008). Most of the thalamocortical projections to area 3b originate in the ventroposterior thalamus and it responds mainly to cutaneous stimulation (Iwamura et al., 1993, 2002), but it also receives thalamo-cortical somatotopically-organised nociceptive input (Omori et al., 2013; Treede, 2020). Area 3a responds mostly to proprioceptive muscle spindle inputs and also receives some nociceptive projections (Vierck et al., 2013). Area 1 responds mostly to cutaneous stimulation and receives projections from area 3b. Area 2 exhibits both cutaneous and proprioceptive responses and receives projections from area 3b and area 1 and may, thus, constitute a third level of cortical processing (Qi et al., 2008; Padberg et al., 2009; Delhaye et al., 2018; Zilles and Palomero-Gallagher, 2020).

The secondary somatosensory cortex (S2) in the parietal operculum on the upper bank of the Sylvian fissure has been divided into three subregions; parietal operculum 1, 3 and 4 (Eickhoff et al., 2006b, 2006a) that contain bilateral and mirror-reversed representations of the body. S2 receives main thalamo-cortical projections from the VPI (**Figure 2**) (Stevens et al., 1993; Disbrow et al., 2002), and reciprocal cortico-cortical projections from S1 (Disbrow et al., 2003). S2 (and insula) has been considered the primary receiving area for nociceptive input, and noxious stimulation has been shown to directly activate S2 in humans (Apkarian and Shi, 1998; Lenz et al., 1998). Processing in S2 exhibits more complex properties as it shows larger receptive fields, decreased modality specificity and bilateral activation to ipsilateral and bilateral stimulation (Delhaye et al., 2018; de Haan and

Dijkerman, 2020). Moreover, the activity of S2 seems to be modulated by the relevance of the task, and by the attentional state (higher responsiveness for attended versus unattended trials) (Meftah et al., 2002; Delhaye et al., 2018).



← Figure 2. The somatosensory system for touch and nociception from the upper and lower extremities:

The dorsal column–medial lemniscus pathway conveys tactile, proprioceptive and vibratory information from the one side of the body. Upon entering the spinal cord, the 1st order afferent fibres branch and send ascending collaterals to the brainstem (Kaas, 2012). The ascending tract has two major divisions: the medial gracile fasciculus containing afferents from the lower trunk and extremities below T6; and the cuneate fasciculus containing afferents from the upper extremities and trunk. These fasciculi ascend ipsilaterally and terminate by synapsing with neurons in gracile and cuneate nuclei of the lower medulla oblongata. From these nuclei, the internal arcuate fibres originate and cross the midline to ascend in the medial lemniscus, and then terminate in the contralateral ventroposterior thalamus (Kaas, 2008; Delhaye et al., 2018). The ventroposterior thalamus is divided into a lateral nucleus (VPL, projections from the trunk and extremities), medial nucleus (VPM, projections from the face), superior nucleus (VPS, proprioceptive afferents), and inferior nucleus (VPI). The VPL is the major recipient for tactile input from the body and sends projections mainly to the primary somatosensory cortex (S1) (Kaas, 2008; Padberg et al., 2009).

The spinothalamic pathway conveys nociception, temperature, crude touch and pressure. Upon entering the spinal cord, the 1st order afferent nociceptive fibres make synaptic connections in the dorsal horn (Rexed layer I), and the 2nd order neurons from layer I decussate in the anterior white commissure at the same segmental level before ascending in the contralateral anterolateral quadrant of the cord (Apkarian and Hodge, 1989). The spinothalamic tract (nociceptive) projects mainly to the VPI which then sends projections to the secondary somatosensory cortex (S2) and S1 (Stevens et al., 1993; Stepniewska et al., 2003). Further, there are spinothalamic projections to the posterior insula (via the posterior ventromedial nucleus, VMpo), and the anterior cingulate cortex (Craig, 2004; Dostrovsky and Craig, 2020). *Created with BioRender.com*

Somatosensory cortical regions beyond S1 and S2

The posterior parietal cortex, including BA 5 and BA 7, receives projections from S1 and thalamus (Disbrow et al., 2003) and is involved in higher-order somatosensory processing that is relevant for sensorimotor control (Gardner, 2020). The somatosensory system of the posterior parietal cortex is part of the dorsal stream involved in stimulus location, which together with visual information, generates supportive spatial information for sensorimotor control. The **insula** receives nociceptive thalamocortical

projections (Apkarian and Shi, 1998; Frot and Mauguière, 2003). Direct electrical stimulation of the insula is painful and with a strong affective component (Ostrowsky et al., 2002). The insula is thought to be involved in the affective aspects of touch and pain. The **anterior cingulate cortex** receives nociceptive thalamocortical projections (Vogt et al., 1979; Apkarian and Shi, 1998; Treede, 2020). Also, unmyelinated tactile c-fibres conveying light (affective) touch afferents have been shown to project to the insula and anterior cingulate cortex (Sugiura et al., 1986; Olausson et al., 2002; Lindgren et al., 2012). It has been proposed that the cingulate cortex contributes to the affective-motivational dimension of pain.

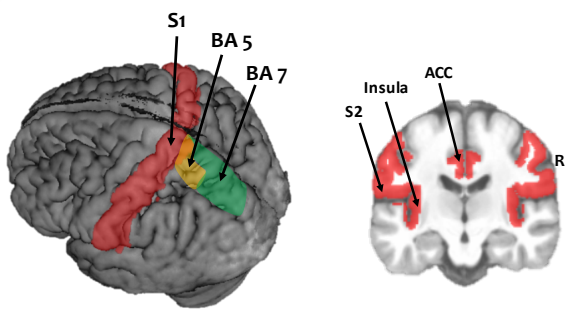


Figure 3. Somatosensory cortical regions involved in tactile and nociceptive processing. S1 = primary somatosensory cortex, BA 5 and 7 = Brodmann areas 5 and 7 respectively, S2 = secondary somatosensory cortex, ACC = anterior cingulate cortex

The somatosensory cortex is hierarchically organised which implies serial (correspondingly hierarchical) processing of the incoming afferent signals from the body (Pons et al., 1987; Delhaye et al., 2018). Most of the somatosensory information begins its cerebral processing journey in S1 where relatively simple "feature processing" occurs. Indeed, lesions in S1 lead to impairment in tactile discrimination, perception of shapes, size and texture (Dijkerman and de Haan, 2007; Kaas, 2012). The processed signals are then being subject to further, more complex, processing in different networks that make sense of the signal in a task-relevant manner (Dijkerman and de Haan, 2007). For example, somatosensory signals used for sensorimotor control are processed in posterior parietal-premotor networks, while affective processing of pleasant or noxious stimuli takes place in the insula, cingulate cortex and prefrontal cortex (de Haan and Dijkerman, 2020).

Bottom-up versus top-down processes in the somatosensory cortex

The somatosensory cortex, as depicted above, is activated by external afferent somatosensory stimulation, i.e. as a bottom-up process (when a physical stimulus actually is present). However, somatosensory cortex activity can also be enhanced or driven by other mechanisms such as top-down and/or cross-modal processes in the absence of modality-specific external stimulation (Meyer, 2011; Ruff, 2013). These processes may include:

* Selective attention, as mediated via frontoparietal regions, that includes attentional modulation of ongoing sensory processing during directed attention, or increased preparatory activity in the absence of external afferent stimulation (preparing for upcoming stimulation) (Macaluso et al., 2003; Langner et al., 2011; Ruff, 2013). In other words, increased somatosensory cortex activity by the attention to or anticipation of touch or pain.
* Somatosensory cortex activation during tactile imagery (Schmidt and Blankenburg, 2019). Merely imagining your leg being touched activates the somatosensory cortex in a somatotopic manner.
* Somatosensory cortex activation driven by vision, i.e. cross-modal modulation (Dionne et al., 2010; Meyer et al., 2011; Kuehn et al., 2018). In other words, seeing a body part apparently being touched (without actually being touched) also activates the somatosensory cortex.

Top-down mechanisms up- or downregulate the input to somatosensory regions in order to optimise their behavioural harvest, i.e. optimised sensorimotor control. Without top-down mechanisms such as attention, the sensory inputs to the brain can be overwhelming and even disruptive for behaviour.

1.1.2 Traumatic spinal cord injury (SCI) disconnects the body from the brain

SCI disrupts the communication between the brain and body, and is a devastating life-changing event. This disruption leads to consequences in

nearly all body organs. The spinal cord may be damaged by congenital or acquired diseases, as well as by trauma. Traumatic injuries are typically locally circumscribed (focal), and are often seen as model lesions both clinically and experimentally. The incidence rate of traumatic SCI is 19 cases per million (Joseph et al., 2017), but with considerable worldwide variation ranging from 8 to 58 cases per million (Singh et al., 2014). It is 4 times more common in males than females (Jackson et al., 2004), and the age at injury shows a bimodal distribution: one peak between 15 - 29 years and a smaller but growing peak in people > 55 years of age (Ahuja et al., 2017). Blunt trauma due to transport-related events and falls is the main cause of traumatic SCI (Ahuja et al., 2017; Joseph et al., 2017).

Here, by using fMRI, I address the degree of somatosensory disruption in people with the most severe (i.e. clinically complete) injuries.

The pathophysiology of SCI

Traumatic SCI is pathophysiologically divided into primary and secondary mechanisms. Primary injury includes the initial trauma that produces immediate mechanical disruption and dislocation of the vertebral column, which in turn, compresses and may transect the spinal cord. This primary insult triggers a complex progressive cascade of harmful cellular and molecular events comprising the secondary injury, which leads to further chemical and mechanical damage to the spinal tissue (Ahuja et al., 2017; Hachem and Fehlings, 2021). The secondary injury has been further subdivided into acute, subacute and chronic stages:

* The acute-to-subacute stage is characterised by ischemia, oedema and haemorrhage which lead to the release of pro-inflammatory cytokines, and intracellular influx of sodium and calcium. This causes a subsequent pathological release of the excitatory and neurotoxic neurotransmitter (glutamate) and reactive oxygen species, all of which contribute to further cell damage and death. Subsequently, this process leads to neuronal apoptosis, demyelination, retrograde axonal (Wallerian) degeneration and glial scar formation.
* The chronic stage is characterised by further axonal degeneration and remodelling of spared circuits. The glial scar with cystic cavity

formation matures to constitute a mechanical barrier to regeneration.

The classification of SCI

SCI is classified according to the widely adopted International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) system, which assesses the neurological consequences of the injury to determine 1) the level of injury[2], and 2) the degree of infralesional sensorimotor deprivation/preservation (Kirshblum et al., 2011, 2020; American Spinal Association, 2019) (see the appendix). The ISNCSCI is based on clinical examination and contains three neurological summary scores: American Spinal Injury Association (ASIA) sensory score which assesses light touch

Table 1: ASIA Impairment Scale		
A	**Complete**	Compete loss of sensory and motor function below the neurological level of injury, including absent function in the lowest sacral segments S4-S5 (that is absent sacral sparing: no voluntary anal contraction or deep anal pressure sensation).
B	**Sensory Incomplete**	Sensory but not motor function is preserved below the neurological level and include sacral segments. No motor function is present more than three segments below the neurological level, on either side of the body.
C	**Motor Incomplete**	Motor function below the neurological level of injury (including the lowest sacral segments) is preserved, with more than half of the key muscles having a grade of <3 on the ASIA motor score (against gravity without additional resistance).
D	**Motor Incomplete**	Motor function below the neurological level of injury (including the lowest sacral segments) is preserved, with more than half of the key muscles having a grade of ≥3 (antigravity) on the ASIA motor score.
E	**Normal**	Neurologically intact patient (who previously had SCI-related deficits).

[2] The neurological level of injury denotes the lowest spinal segment with normal sensorimotor function bilaterally, while the skeletal level describes the level of spinal column fractures. The discrepancy between neurological (spinal cord) and vertebral (spinal column) increases more inferiorly along the spine (higher discrepancy in low thoracic than in cervical levels).

and pinprick sensation in 28 dermatomes[3] from C2 to S4/S5; ASIA motor score which assesses and grades muscle strength in each myotome; and finally, ASIA impairment scale (AIS) which determines the overall grade/completeness of SCI (**Table 1**). Notably, the examination of the sensory function is based on reported evaluations about how the light touch and pinprick stimuli are perceived by the patient (normal, absent, or altered sensation). Likewise, the motor function in testable myotomes is scored based on muscle strength or observed muscle contractions. The AIS is a measure of injury severity and ranges from AIS grade A denoting the most severe injury with complete sensorimotor loss below the injury level including sacral segments, to grade E being the least severe injury with no residual sensorimotor deficits. For example, a C6 complete SCI represents the lowest spinal segment (6th cervical) with normal sensorimotor function on both sides, and a severity of clinically complete sensorimotor deprivation below the injury including sensorimotor loss in the lowest sacral segments, i.e. no sacral sparing (Waters et al., 1991). In this thesis, I focus on clinically complete SCI (AIS grade A) which represent the most severe lesion with complete loss of sensorimotor function below the injury level, and relatively limited recovery potential (Waters et al., 1991; Kirshblum et al., 2016).

The spinal cord is rarely severed in SCI (neuropathological foundations)

In SCI caused by blunt trauma, the spinal cord is contused, crushed and/or lacerated, but rarely transected (Kakulas, 1999, 2004; Dimitrijevic and Kakulas, 2020). Comprehensive neuropathological post-mortem examinations in traumatic SCI have been conducted by Byron Kakulas who has consistently reported the preservation of tissue continuity across the SCI even in patients with clinically complete lesions. The nature of the central necrotic injury makes such preservation more likely to be located in the white, rather than in the grey, matter (Kakulas, 2004; Brown and Kakulas, 2012). The existence of tissue continuity across the lesion,

[3] Dermatome is an area of skin innervated by one spinal nerve root. Myotome is a group of muscles innervated by one spinal nerve root.

regardless of severity, seems to be a rule rather than an exception (**Figure 4**). Recently, Freund et al. demonstrated that such spinal tissue continuities (tissue bridges) are visible and quantifiable by means of structural MRI. The width and location of those tissue bridges can predict long-term functional recovery (Freund et al., 2019; Pfyffer et al., 2019).

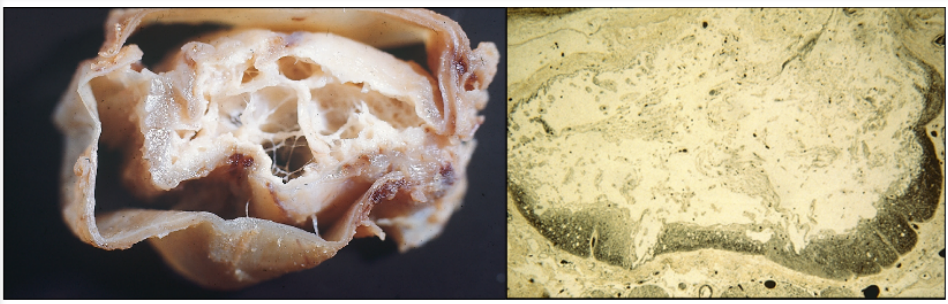


Figure 4. Neuropathology in spinal cord injury: (Left) A cross-section through a clinically complete cervical spinal cord injury demonstrating a multilocular central cavity, and more importantly, a significant amount of retained white matter at the periphery. (Right) A corresponding microscopical image over the cross-section with myelin staining depicting residual white matter that has survived the injury. *Taken from Brown and Kakulas, 2012, with permission from Elsevier conveyed through RightsLink.*

Residual motor fibres may exhibit residual function (Motor discomplete SCI)

The residual fibres that have survived a severe clinically complete SCI may still convey neural signals to and from the brain. By adopting electrophysiological methods, Dimitrijević et al. have repeatedly shown residual descending transmission demonstrated as supraspinal control on spinal motor circuits below the spinal lesion (Dimitrijevic, 1987; Dimitrijević, 1988; Sherwood et al., 1992). They coined the term "*discomplete SCI*" to describe a subset of patients who, although suffering clinically complete SCI with no infralesional voluntary movements, had subclinical neurophysiological evidence of residual motor control. They used polyelectromyography (EMG) recordings during a motor protocol called Brain Motor Control Assessment (BMCA), and showed that patients with motor discomplete SCI (about 65 % of patients with clinically complete SCI) exhibited one or more of the following (Sherwood et al., 1992; McKay et al., 2004): 1) Presence of tonic vibratory response (vibration of below-

injury muscles elicits tonic vibratory response), a reflex that is thought to be mediated from the brainstem (Matthews, 1966); 2) Plantar reflex suppression (volitionally being able to suppress the reflex response to plantar surface stimulation), indicating preserved descending inhibitory function that can be recruited voluntarily; and 3) Reinforcement manoeuvre response, indicative of a voluntary excitatory supraspinal control. Further, recent studies have demonstrated volitional EMG signals due to attempted movement of paralysed muscles (Heald et al., 2017).

In conclusion, there is substantial evidence for motor discomplete SCI in a subset of patients with clinically complete SCI, demonstrated by neurophysiological measures as brain-driven modulation on spinal motor circuits below the injury level. The existence of this entity is supported by anatomical data derived from neuropathological examinations revealing preserved white matter tracts traversing the spinal lesion (Dimitrijevic and Kakulas, 2020).

The extent of somatosensory deprivation in clinically complete SCI

An obvious question emerging from the aforementioned evidence is whether there is a somatosensory counterpart to motor discomplete SCI. I eventually came to realisation that there was no clear answer to this issue for several reasons. Somatosensory function following SCI has not been a subject for detailed studies as compared to the motor function, perhaps due to obvious reasons related to the association of SCI primarily with paralysis. Furthermore, assessing residual sensory transmission to the brain is not as straightforward as the neurophysiological methods for studying motor function, which are relatively more available and objective. Dimitrijević et al. examined a large number of SCI patients with somatosensory cortical evoked potentials (SSEPs) and found no correlation between sensory perception presence/absence and SSEPs on a case-by-case basis (Dimitrijevic et al., 1983). Moreover, SSEPs were lacking in some cases where perception of somatosensory stimulation (incomplete SCI) was evident, indicating the low sensitivity of the method. This is unlikely to have been resolved with technical development or refinement of electrophysiological methods. Indeed, in a recent study, no SSEPs could be recorded in a group of patients

with discomplete SCI (and in some cases no SSEPs from the upper extremity where sensation might have been preserved) (Wahlgren et al., 2021).

Thus, it was not until the development of advanced functional brain imaging methods, such as fMRI and magnetoencephalography (MEG)[4], that this issue was possible to address in a feasible manner. Nevertheless, despite the technical feasibility for assessing somatosensory function in SCI, the few previous studies performed had neglected crucial conceptual aspects of somatosensory processing, rendering the findings rather hard to interpret (Ioannides et al., 2002; Sabbah et al., 2002). I elaborate on these limitations below.

As I described in the previous section "Bottom-up versus top-down processes in the somatosensory cortex", activation of the somatosensory cortex can be driven by cortico-cortical (top-down) mechanisms even in the absence of peripheral afferent stimulation. Subsequently, to assess afferent-driven activation of the somatosensory cortex, cortico-cortical confounding mechanisms, such as anticipation and vision, must be controlled for. Ioannides et al. used MEG recordings during electrical stimulation on the wrists (innervated above the lesion) and ankles (innervated below the lesion) in three participants with complete SCI (Ioannides et al., 2002). Electrical stimulation on the ankle in one participant was accompanied by activation behind the contralateral central sulcus, presumably S1. During the experiment, the participants were not blinded to the stimulation, and thus, were aware of when stimulation was delivered and not (Ioannides et al., 2002). In the study of Sabbah et al., fMRI was used to study sensorimotor cortical activity in 8 patients with clinically complete SCI (and one with sensory incomplete SCI) during active/attempted and passive toe movements (Sabbah et al., 2002). With eyes closed, the patients' feet were inflected by the experimenter during the passive-movement trials, which elicited weak activation "posterior to the central sulcus" in 2 out of 8 patients. Interestingly, 2 additional patients showed sensory cortex activity when the movement was performed with eyes open, demonstrating

[4] MEG measures the fluctuations in the magnetic field generated by the electrical activity of neurons.

visually-driven somatosensory cortex activation. While the possibility of residual spinal sensory fibres conducting somatosensory signals to the cortex was plausible in those studies, sensorimotor cortex activity could also have been driven by unaccounted-for top-down (cortico-cortical) mechanisms. Again, seeing or anticipating touch can drive somatosensory cortex activity (Langner et al., 2011; Meyer et al., 2011; Kuehn et al., 2018).

In part I, we investigate, and provide a proof of concept for, *sensory* discomplete SCI while accounting for putative top-down modulation effects. We conclude that sensory discomplete SCI is evident in a subset of patients with clinically complete chronic SCI.

1.2 Mechanisms of sensorimotor restoration in essential tremor by electrical stimulation (Part 2)

In this section, I will give an introduction to the motor system, its dysfunction in essential tremor, and how it is restored by deep brain stimulation.

1.2.1 Organisation of the motor system with focus on the cerebello-cerebral circuit

The motor system generates voluntary movements by converting sensory information about the current state of the body and the environment into plans for action, and eventually, muscle activity that is required to execute the desired movements with minimal or correctable errors (**Figure 5**). The commands to execute movements are generated by motor cortex, and transmitted via pyramidal projections (the corticospinal tract) to circuits of motoneurons in the spinal cord, that in turn activate the muscles. Multiple cortical and subcortical areas communicate with spinal motoneurons, either by direct monosynaptic connections or through multi-synaptic connections via interneurons in the ventral horn of the spinal cord.

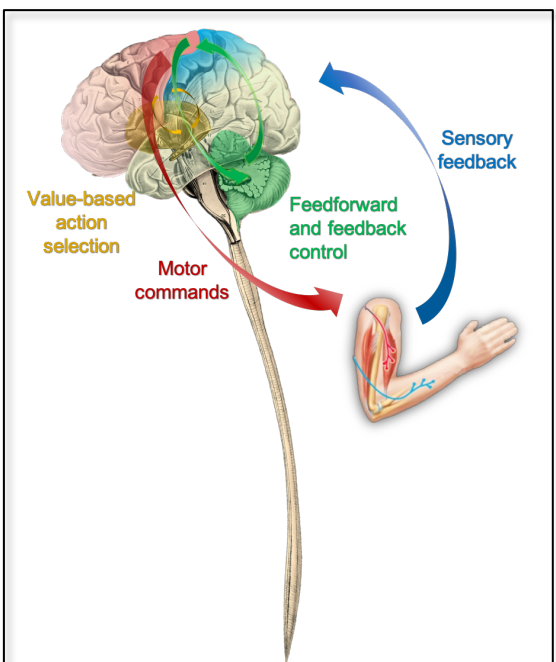


Figure 5. The general organisation of the motor system

The motor behaviour is modulated by two "extrapyramidal" circuits involving the cerebellum (overviewed below) and the basal ganglia. The basal ganglia are a group of interconnected nuclei of particular importance in supporting the cerebral cortex to choose the most optimal action and inhibit inappropriate actions, based on the internal and external environmental states. They are also involved in reinforcement learning by incorporating reward-related information into action selections. The basal ganglia will not be further discussed in this thesis since they do not seem to be involved in essential tremor pathophysiology.

Motor cortex

"The entire cortex of the primate's frontal lobe seems dedicated to organismic action. It can, thus, be considered, as a whole, 'motor' or 'executive' cortex in the broadest sense"
Joaquín M. Fuster

In the 19th century, the prevailing view was that all movements were entirely generated in the brainstem and spinal cord. One of the major events in the history of neuroscience was Fritsch and Hitzig´s discovery in 1870 that electrical stimulation of the precentral cortex in dogs produced movements in specific parts of the contralateral body. This experiment was highly significant because it showed that: 1) the cortex was not just an insignificant "rind" as was the dominant view of the "anticortex ideology" at the time, 2) the cortex was electrically excitable, and 3) cerebral cortex was somatotopically arranged. Fritsch and Hitzig´s discovery was replicated by David Ferrier who also expanded the experiments by applying longer stimulation durations and, therefore, could elicit more complex movements as compared to muscle twitches (Gross, 2007). These results were further replicated in nonhuman primates by Lyton and Sherrington in 1917, and subsequently, in humans by Penfield et al. (Penfield and Boldrey, 1937; Chouinard and Paus, 2006; Gross, 2007). These events marked the birth of the concept that a distinct part of the frontal cerebral cortex is electrically excitable and responsible for generating movements, i.e. the motor cortex.

In essence, the whole frontal cortex is engaged in the hierarchical control of actions and can, therefore, be considered an executive/motor cortex

(Fuster, 2000) (**Figure 6**). Indeed, it has been argued that the whole frontal cortex (including the prefrontal cortex) is a premotor cortex (Fine and Hayden, 2022). As a motor chauvinist myself (Wolpert et al., 2001), I do not have any conceptual objections to this view. However, here I adhere to the more common division of the frontal cortex and focus on the primary and premotor cortex.

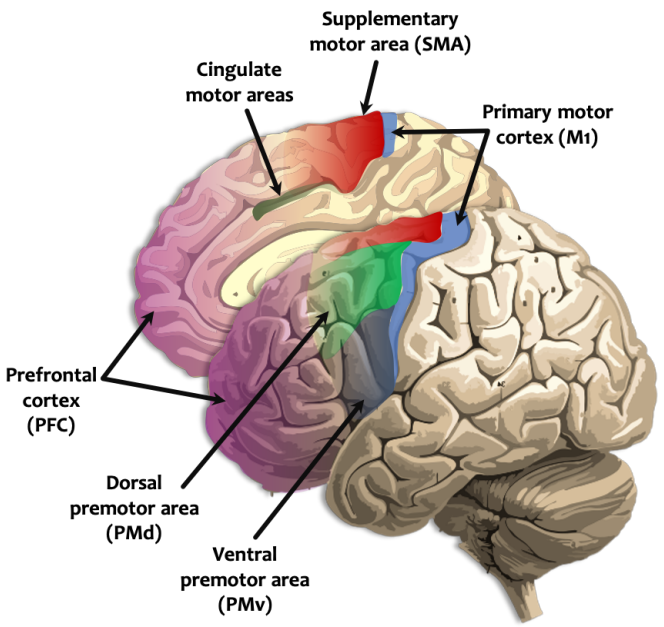


Figure 6. The executive/motor cortex in the frontal lobe. The frontal lobe is hierarchically organised along its anteroposterior (or rostrocaudal) axis where more anterior regions are involved in more abstract forms of action control than posterior areas. At the top of the cortical hierarchy is the prefrontal cortex (**PFC**) that mediates action control when perception and action are temporally remote, and in situations marked by novelty, ambiguity and complexity. The primary motor cortex (**M1**), at the bottom of the cortical hierarchy, controls our motor actions directly via sending motor commands to spinal motoneurons. The premotor areas (**SMA**, **PMd**, **PMv** and **the cingulate motor areas**), at an intermediate hierarchical level, can be considered as mediators that provide multiple access points to M1 from prefrontal, posterior parietal, and limbic regions.

Based on cytoarchitectural features, Brodmann distinguished two motor areas in the frontal lobe; area 4 and area 6 anterior to it (Brodmann, 1909;

Geyer et al., 2000) but it was Fulton who proposed the division into a primary motor (area 4) and premotor area (area 6) (Fulton, 1935). This was based on evidence from experimental cortical ablations in monkeys where the premotor cortex was viewed as functionally distinct from the primary motor cortex (M1) and as a centre for integration of complex skilled movements. Premotor lesions caused *"a disorganisation of more highly integrated voluntary movements producing a state akin to apraxia in man"*, as Fulton stated (Fulton, 1935).

The primary motor cortex (M1): M1 is located in the anterior portion of the central sulcus and the adjacent posterior part of the precentral gyrus. It is characterised cytoarchitecturally by the presence of giant pyramidal (Betz) cells in layer V, and the fact that electrical stimulation thresholds needed to elicit limb movements are significantly lower here than in any other cortical region (Dum and Strick, 2004). Close to the midline, the anterior border of M1 lies on the exposed cortical precentral surface, but recedes posteriorly when moving inferolaterally toward the Sylvian fissure, and eventually disappears into the depth of the central sulcus (**Figure 6**) (White et al., 1997; Geyer et al., 2012). Movements in different body parts are represented somatotopically in M1 similar to, but less precise than, the somatotopic organisation in S1. One-third of the corticospinal tract fibres originate from M1, the remaining two-thirds originate from frontal premotor areas and the parietal cortex (Dum and Strick, 1991). In humans, M1 has direct access (monosynaptic connections) to spinal motoneurons, bypassing interneurons, which may constitute the neuroanatomical basis of our dexterity (Strick et al., 2021).

Whether "muscles" or "movements" are represented in M1 has long been a controversy (Kakei et al., 1999). It was shown that both "low-level" parameters such as muscle force as well as more abstract parameters such as the direction of movement are represented in M1 (Kakei et al., 1999). However, Graziano observed complex, behaviourally relevant movements when M1 was stimulated with longer, half-second stimulation trains (Graziano et al., 2002b). He proposed that M1 contained an action map with behaviourally relevant actions (Graziano, 2016).

Premotor cortex: The premotor cortex encompasses all areas that directly participate in motor control through connections to M1 and/or the motoneurons in the spinal cord. Transsynaptic tracing studies, using neurotropic viruses in nonhuman primates, have revealed six frontal premotor areas that send direct projections to M1 as well as to the motoneurons in the spinal cord (Dum and Strick, 1991, 2002). Two of these reside on the lateral surface of the hemisphere: dorsal premotor area (PMd) and ventral premotor area (PMv). The remaining four lie on the medial wall of the hemisphere; supplementary motor area (SMA), and dorsal, ventral and rostral cingulate motor areas (**Figure 6**) (Picard and Strick, 2001; Dum and Strick, 2002, 2004). The premotor cortex is thought to be engaged in more abstract and "high-level" motor functions as compared to M1, such as motor preparation, action planning, and sensory guidance of movement. The modulatory role of the premotor cortex on motor output is diverse and oftentimes difficult to pinpoint on a conceptual level (Chouinard and Paus, 2006).

While **PMd and PMv** share many functional and anatomical features, they seem to be involved in distinct networks which may indicate distinct functions, to some extent (Hoshi and Tanji, 2007). The PMd forms a network with the superior parietal cortex and is involved in movement selection based on previously learned associations and spatial cues (Chouinard and Paus, 2006). Furthermore, the PMd together with the cerebellum has been implicated in arm reaching and online movement corrections (Tanaka et al., 2009; Battaglia-Mayer et al., 2014). The PMv is implicated in the control of hand movement required for manipulation of objects, such as the transformation of visual representation of the object and the hand into motor commands. Further, the PMv, together with the inferior parietal lobule, form the network known as "mirror neurons" that are active during the execution and observation of motor acts (Geyer et al., 2012; Rizzolatti and Fogassi, 2014).

The **SMA** is located on the medial wall of the frontal lobe extending anteroposteriorly between the lines crossing the anterior and posterior commissures (Picard and Strick, 1996; Geyer et al., 2012). It has been implicated in a wide range of motor behaviours, from planning and

execution of simple and complex movements, to motor imagination. SMA seems to be more involved in internally-generated (self-generated) actions, than actions directly instructed by external cues; complex sequential movements; and motor learning (Roland et al., 1980; Halsband et al., 1993; Nachev et al., 2008). Sjöberg et al. have suggested that the SMA might be involved in executive (or cognitive), rather than only motor, control (Sjöberg et al., 2019). However, a sharp distinction between "executive" and "motor" is not that clear from a conceptual point of view, at least not for me. The cingulate motor areas, within the mid-cingulate sulcus/region, have been shown to exist both in monkeys and humans (Dum and Strick, 2004; Amiez and Petrides, 2014). They appear hierarchically organised along the rostro-caudal (anteroposterior) axis and have been implicated in internally-generated actions (Debaere et al., 2003; Loh et al., 2018).

The sensorimotor cerebello-cerebral circuit streamlines the cerebral output

The cerebellum comprises about 10 % of the mass of the brain but contains upward of 75 % of its neurons (Herculano-Houzel, 2012). It is located in the posterior cranial fossa and connects to the rest of the brain via the pons through three cerebellar peduncles (superior, middle and inferior). The cerebellar hemisphere is divided by the primary fissure into an anterior and posterior lobe, while the posterolateral fissure separates the body of the cerebellum from the smaller flocculonodular lobe (Herrup and Kuemerle, 1997). It consists of the cerebellar cortex and deep cerebellar nuclei that constitute the only output structures of the cerebellum. The deep cerebellar nuclei include the fastigial, interpositus and dentate nuclei. The dentate nuclei are the largest and constitute the major output channel to the ventrolateral thalamus and ultimately the cerebral cortex. The cerebellar cortex is intricately folded and has been divided into ten lobules separated by identifiable fissures. Roughly, sensorimotor functions are represented twice and somatotopically in each cerebellar hemisphere: lobules I-VI in the anterior cerebellum, and lobule VIII in the posterior cerebellum (Grodd et al., 2001; Habas et al., 2004; King et al., 2019).

The cerebellum has complex connectivity with multiple subcortical structures such as the vestibular nuclei and basal ganglia for controlling

vestibulo-ocular functions, balance and posture. However, the focus in this thesis is on the sensorimotor cerebello-cerebral circuit that connects the cerebellum with the cerebral cortex (D'Angelo, 2018). Below, I elaborate more on the anatomy of this circuit.

Anatomy and function of the sensorimotor cerebello-cerebral circuit

*Anatomy of the sensorimotor cerebello-cerebral circuit (**Figure 7**):*
The main connections between the cerebral cortex and cerebellum are depicted in **Figure 7**. The input pathway to the cerebellum consists of cortico-cerebellar projections, originating from multiple areas in the cerebral cortex, descending down the internal capsule into the cerebral peduncle and then synapsing in the basal nuclei of pons before forming the pontocerebellar mossy fibre projections to the contralateral cerebellar cortex via the middle cerebellar peduncle (Schmahmann, 1996; Benagiano et al., 2018). Anatomical tracing studies have revealed extensive connections between the cerebellum and cerebrum. Multiple areas from almost the entire cerebral cortex send inputs to the cerebellum and the same areas receive (feedback) outputs from the cerebellum (Bostan et al., 2013). The output pathway from the cerebellum consists of cerebello-thalamic projections. Purkinje cells, the only neurons responsible for efferents from the cerebellar cortex, project to the deep cerebellar nuclei, mainly the dentate, to make a GABAergic (inhibitory) connection (D'Angelo, 2018). The dentate constitutes the main output nucleus from the cerebellum through the dentato-thalamic glutamatergic fibres that cross the midline in the mesencephalon before terminating in the "cerebellar" ventrolateral thalamus (Benagiano et al., 2018). Before reaching the ventrolateral thalamus, the cerebello-thalamic (or dentato-thalamic) tract passes through the posterior subthalamic area (PSA). As described by Blomstedt et al., the PSA is situated below the thalamus and bordered by the subthalamic nucleus (STN) (anterolaterally), the substantia nigra (inferiorly), the red nucleus (medially) and the medial lemniscus (postereolaterally) (Blomstedt et al., 2009). The PSA contains cerebello-thalamic fibres, pallido-thalamic fibres, the zona incerta (Zi) and prelemniscal radiation (Raprl) (Blomstedt et al., 2009; Gallay et al., 2008; Guridi and Gonzalez-Quarante, 2021).

The cerebello-thalamic tract ascends in the PSA lateral and anterior to the red nucleus (which also receives some collaterals from the tract) before terminating primarily in the posterior ventrolateral thalamus (VLp), partly corresponding to Hassler´s Vim, with minor extension to the anterior ventrolateral thalamus (VLa) (**Box 1**) (Gallay et al., 2008; Benagiano et al., 2018).

Box 1: The motor thalamus

Diving into different anatomical subdivisions of the motor thalamus is a well-known source of confusion and despair. There are multiple and diverse atlases derived from anatomical and physiological studies in monkeys on one side and equally diverse atlases derived from studies in humans. They parcellate and label the thalamus into diverse subdivisions and nuclei with scarcely any agreement among them (Macchi and Jones, 1997; Hamani et al., 2006; Mai and Majtanik, 2019). However, the thalamus consists of several nuclei that process and relay information from and to the cerebral cortex. The nuclei important for sensorimotor control reside in the ventral part of the thalamus. The ventrolateral thalamus can be divided into an anterior nucleus (VLa) that receives pallidal inputs, and a posterior nucleus (VLp) that receives cerebellar inputs (Macchi and Jones, 1997). Most neurosurgeons, however, use Hassler´s nomenclature. According to Hassler, the ventrolateral thalamus can be divided into oral (Voa and Vop, ventralis oralis anterior and posterior), caudal (Vc, ventralis causalis), intermediate (Vim, ventralis intermediate) and lateropolar. The Vop is thought to receive cerebellar fibres, and the Vim receives spindle afferents. Here I adopt the nomenclature from the Morel atlas, based on the nomenclature of Jones (Macchi and Jones, 1997), which is more harmonised with the nomenclature from nonhuman primates (Morel, 2007).

Our knowledge about the anatomy of the thalamo-cortical projections is derived mainly from anatomical tracing studies in monkeys, and a few diffusion-based MRI studies in humans. Although a substantial projection is sent to M1 (Holsapple et al., 1991), these fibres occupy only 30 % of the dentato-thalamic tract, which implies cerebellar projections to multiple areas of the cerebral cortex alongside M1 (Dum and Strick, 2003; Bostan et

al., 2013; Benagiano et al., 2018). Indeed, thalamo-cortical fibres project to multiple cortical areas including the premotor cortex (both PMd and PMv); SMA and preSMA; prefrontal cortex; and posterior parietal cortex (Schell and Strick, 1984; Sakai et al., 2000; Behrens et al., 2003; Kelly and Strick, 2003; Fang et al., 2006; Akkal et al., 2007; Stepniewska et al., 2007; Hashimoto et al., 2010; Palesi et al., 2015).

The dentato-olivo-cerebellar loop: there are reciprocal connections between the cerebellum and the contralateral inferior olive that regulate the activity of the cerebellar cortex. The inferior olive receives GABAergic (inhibitory) projections from the cerebellum as well as reafferent sensory and proprioceptive signals. It gives rise to excitatory projecting neurons (olivocerebellar fibres) that constitute the climbing fibres input to the cerebellum (Benagiano et al., 2018). Further, the inferior olive receives excitatory inputs from the red nucleus, and thus, forms the so-called "Guillain-Mollaret triangle" with the dentate as apex (Kakei et al., 2021).

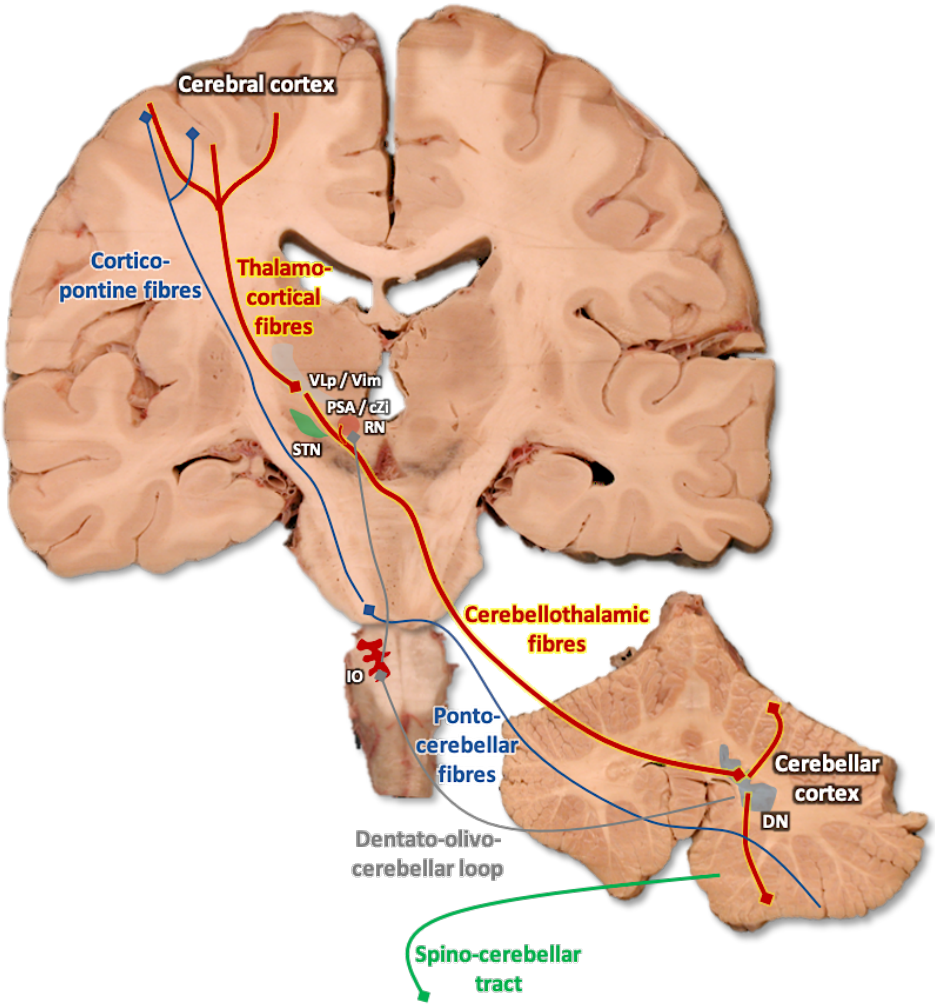


Figure 7. The cerebello-thalamo-cerebral circuit. The cerebral cortex sends input to the cerebellum for computation/transformation and gets feedback projections from the cerebellum. Input projections from the cerebral cortex synapse in the ipsilateral pons (cortico-pontine fibres), and then cross to the contralateral cerebellar cortex through the middle cerebellar peduncle. The output pathway (cerebello-thalamic fibres) synapses in the dentate nucleus, exits the cerebellum via the superior cerebellar peduncle, crosses the midline in the mesencephalon to synapse in the contralateral thalamus. The ventrolateral thalamus (incl. VLp) projects ultimately back to the cerebral cortex (thalamo-cortical fibres). This double crossing of fibres results in ipsilateral control of the body, i.e. the right cerebellum controls the right side of the body and vice versa. The cerebellum is reciprocally connected with the contralateral inferior olive (IO) through the dentato-olivo-cerebellar loop. DN = dentate nucleus, RN = red nucleus, PSA = posterior subthalamic area, cZi = caudal zona incerta), VLp = posterior ventrolateral thalamus, Vim = ventralis intermediate VL, STN = subthalamic nucleus, IO = inferior olive.

Function of the sensorimotor cerebello-cerebral circuit:

The cerebellar cytoarchitecture and circuitry are highly uniform across the entire cerebellar cortex, which is contrary to the unique cytoarchitectural features of the cerebral cortex enabling Brodmann and others to create cortical maps based on such features. Because of the uniform cerebellar circuitry, a prevailing theory about its function proposes a uniform computation across the cerebellar cortex, i.e. it performs the same operation in all areas, and the diversity in function only derives from the variety in information delivered from different input channels from the cerebral cortex (Schmahmann, 1996; Ramnani, 2006).

One of the major problems in motor control is the delay of sensory feedback providing the brain with "outdated" information about the ongoing movement and, thus, restricting the ability to correct the movement based on these data. The cerebellum has been proposed to solve this issue by maintaining internal models (forward and inverse) for motor control. The *forward* internal models transform a motor command into prediction of its sensory consequences and *inverse* models provide a motor command that will cause the desired change in the state of the body (Wolpert et al., 1998; Ishikawa et al., 2016). Based on motor-command information from motor cortex (so-called *efference copy*), the cerebellum anticipates what muscular contractions are needed to bring a movement smoothly and accurately to the desired state (D'Angelo, 2018; Kandel et al., 2021). For example, the cerebellum is proposed to provide accurate motor timing about the agonist and antagonist muscle contraction and relaxations during movements (Vilis and Hore, 1980). A movement is initiated by the contraction of agonist muscle and terminated by an appropriately timed contraction of the antagonist, the timing of which is provided by the cerebellum. If the antagonist muscle is not active enough or active too late for the agonist burst, the arm will overshoot the target and tremor oscillations appear. This type of cerebellar (intention) tremor is a hallmark for cerebellar dysfunction, and is explained by the sole reliance on sensory feedback, in the absence of forward predictive signals (Bastian, 2006).

Beyond sensorimotor control: there is an ample amount of evidence of the cerebellum's involvement in a wide range of cognitive and affective

functions along with its more well-known motor function. This is supported by anatomical tracing studies revealing connections to "nonmotor" areas, clinical evidence from patients with cerebellar damage exhibiting cognitive/affective deficits, and functional imaging studies showing cerebellar activation during cognitive tasks (Kelly and Strick, 2003; King et al., 2019; Schmahmann et al., 2019).

1.2.2 Essential tremor: Dysfunctional cerebello-cerebral circuit causing disabling tremor

Essential tremor: A common and potentially disabling movement disorder

Tremor is an involuntary, rhythmic, and oscillatory movement of a body part. Tremor can be an isolated feature of a disease such as in essential tremor (ET), or it can be part of other neurological conditions (Bhatia et al., 2018; Welton et al., 2021). ET is characterised by bilateral upper limb postural and/or kinetic tremor, and occasionally tremor of the head and voice (Bhatia et al., 2018; Hopfner and Deuschl, 2018). Thus, tremor in ET is action tremor, i.e. it is predominately present during movements as opposed to resting tremor in Parkinson´s disease. Action tremor can manifest as postural tremor (when voluntarily maintaining a position against gravity), and kinetic tremor (during a variety of voluntary movements) (Deuschl et al., 2008). Moreover, about one-third of ET patients exhibit intention tremor, i.e. tremor increases in amplitude when approaching a target at the termination of the movement (Deuschl et al., 2000).

The diagnosis of ET is based solely on clinical features, i.e. there are no ancillary radiological or laboratory tests to confirm or exclude the diagnosis. The new classification system defines ET as an isolated tremor syndrome of bilateral upper limb action tremor of at least 3 years duration, with or without tremor in other body locations such as head, voice or leg tremor, and with the absence of neurological signs such as ataxia, dystonia or parkinsonism (Bhatia et al., 2018). For ET patients exhibiting neurological signs of uncertain abnormality or relevance "AKA soft neurological signs", a new label "ET-plus" has been introduced the new classification system. Such

mild neurological signs may be resting tremor, impaired tandem gait, questionable dystonic posturing, memory impairment, etc. (Bhatia et al., 2018). New studies indicate that ET-plus might be more common than classical ET (Bellows and Jankovic, 2021).

ET is one of the most common movement disorders. Its prevalence is approximately 1 % of the population worldwide, and the prevalence increases significantly with age to reach a prevalence of circa 5 % for people older than 64 years, and circa 10 % above 80 (Louis and Ferreira, 2010; Louis and McCreary, 2021). Overall, there is no difference in the prevalence of ET between men and women (Meoni et al., 2020). The typical onset age in ET shows a bimodal distribution with peaks occurring in the twenties and sixties. There is some support for distinguishing between early- versus late-onset ET, i.e. patients with early-onset ET more often reported family history of tremor, as well as better response of tremor to alcohol (Hopfner et al., 2016). ET is often familial, with an autosomal dominant inheritance pattern with a variable estimated rate of inheritance of 20 % to 90 % between studies. Linking studies of affected families found few mutations in some families but not in others. However, genome-wide genotyping identified several genes linked to ET, such as the LINGO1-gene (Hopfner and Helmich, 2018).

Currently, there is an ongoing debate and controversy about the new classification that mostly, and not surprisingly, concerns the concept of ET-plus (Deuschl et al., 2018; Louis et al., 2019). The term ET-plus has been regarded as confusing and controversial, and merely a placeholder for disorders waiting for a more solid diagnosis (Fasano et al., 2018). Furthermore, many of the features that result in an ET-plus sub-diagnosis have been argued to represent features related to the disease stage rather than being a distinct entity (Louis et al., 2019). The heterogeneity of clinical, aetiological and pathophysiological features has given rise to the debate on whether ET is a single disease, a syndrome or a family of diseases (Louis, 2021; Louis et al., 2021b).

Beyond tremor in ET: Alongside action tremor, ET may be associated with a variety of comorbidities including gait disturbances, cognitive impairment,

psychiatric symptoms, hearing impairment, and sleep disorders (Louis and Okun, 2011; Louis, 2016a; Welton et al., 2021). Many ET patients suffer from gait disturbances such as tandem gait ataxia and impaired balance, especially during the advanced stages of the disease (Stolze et al., 2001; Fasano et al., 2010). Mild cognitive impairment, especially in the domain of executive function and memory, is significantly more likely in ET patients than in age-matched controls (Sengul et al., 2015). Likewise, psychiatric features such as depressive and anxiety disorders, and certain personality traits have been associated with ET (Louis, 2016a). It has been hypothesised that non-motor comorbidities also are manifestations of cerebellar dysfunction (Tröster et al., 2002; Passamonti et al., 2011)

Non-surgical treatment options

Currently, there is no curative treatment for ET. For patients with disabling ET, there are pharmacological and surgical treatment options. The focus of this thesis is on surgical treatment (below). Pharmacologically, beta-blockers (especially propranolol), primidone and topiramate, among others, are the most effective pharmacological agents, although many patients choose to discontinue these medications because of their limited efficacy and side effects (Deuschl et al., 2011; Ferreira et al., 2019; Hopfner and Deuschl, 2020). Alcohol (ethanol) is surprisingly effective in temporarily relieving the tremor in two-thirds of the patients. Its regular use is, however, inadvisable for other obvious reasons (Bellows and Jankovic, 2021).

Pathophysiology of ET: Dysfunctional cerebello-thalamo-cerebral circuit.

It is now widely accepted that ET results from pathological oscillations in the sensorimotor cerebello-thalamo-cerebral circuit (Raethjen and Deuschl, 2012; Helmich et al., 2013; Madelein van der Stouwe et al., 2020). The issue awaiting further elucidation is, however, where and why tremor oscillations originate. Studies addressing the pathophysiology of ET are numerous and diverse, ranging from animal model studies, neuropathological investigations to human electrophysiology and advanced neuroimaging. Here, I will attempt to write a harmonizing account based on available hypotheses with a focus on functional imaging studies.

Regions within the cerebello-thalamo-cerebral circuit exhibit dysfunctional activity during active motor tasks and during rest (Bhalsing et al., 2013; Sharifi et al., 2014; Holtbernd and Shah, 2021; Pietracupa et al., 2021). Electroencephalography (EEG)[5] and MEG studies showed that all regions within the circuit oscillate coherently with tremor frequency during motor tasks in ET (Schnitzler et al., 2009; Raethjen and Deuschl, 2012; Muthuraman et al., 2018; Pan et al., 2020). As will be elucidated below, there is now an ample amount of evidence pointing toward a central role for cerebellar dysfunction in the pathophysiology of ET.

Functional brain imaging studies have repeatedly reported involvement of abnormally increased activation in multiple regions along the circuit during tremor-inducing motor tasks. Task-based fMRI studies revealed abnormally increased activity in the primary sensorimotor cortex, premotor cortex, SMA, thalamus and cerebellum during tremor-inducing motor tasks (Bucher et al., 1997; Buijink et al., 2015a; Broersma et al., 2016). The most consistent finding is increased activation in the cerebellum during motor tasks, which seems to be bilaterally engaged even when unilateral tremor tasks are performed (Bucher et al., 1997; Broersma et al., 2016). Interestingly, an early positron emission tomography (PET)[6] study showed decreased cerebellar activation after alcohol intake in a group of patients with "alcohol-responsive" ET (Boecker et al., 1996).

Some fMRI studies analysed the coupling between regions within the cerebello-thalamo-cerebral circuit in terms of functional (correlation) or effective connectivity. For example, the posterior cerebellum showed decreased functional connectivity with M1, which also correlated with tremor severity during motor tasks (Buijink et al., 2015b). Comparable findings were reported by another fMRI study during a grip force task, which showed reduced connectivity between cerebellar lobule V and M1 as compared to healthy controls and patients with Parkinson´s disease (Neely

[5] EEG is an electrophysiological method that measures electrical field fluctuations on the scalp as generated by neuronal activity.

[6] PET is a minimally invasive imaging method that measures brain activity by using radioactive substances (radiotracers) to capture differences in blood flow, glucose metabolism, neurotransmitter activity etc.

et al., 2015).

Early functional imaging studies, using PET, compared brain activation in ET patients versus controls during motor tasks and rest (Colebatch et al., 1990; Hallett and Dubinsky, 1993; Jenkins et al., 1993; Wills et al., 1994; Boecker et al., 1996). They gave some indications about increased blood flow or glucose metabolism in the cerebellum and/or the cerebral cortex, as well as the inferior olive and red nucleus in ET patients. However, these studies suffered from low resolution and limited field of view making them unable to scan the cerebral cortex and cerebellum at the same time (Boecker and Brooks, 2008). Moreover, the differences reported during motor tasks were based on visual inspection without formal statistical testing, and actual comparisons were only conducted during resting conditions (Colebatch et al., 1990; Hallett and Dubinsky, 1993; Jenkins et al., 1993; Wills et al., 1994; Boecker et al., 1996).

Although ET predominantly causes action tremor, functional imaging studies indicate abnormalities in the activity of the cerebello-thalamo-cerebral circuit not only during motor tasks but also **during rest** when the circuit is not engaged and tremor not present (for review see: Holtbernd and Shah, 2021; Pietracupa et al., 2021). This has been examined by means of the correlational coupling, i.e. functional connectivity, between different brain regions with resting-state fMRI (rs-fMRI). Functional connectivity was shown to be decreased between the cerebellum and the sensorimotor cortex, decreased between primary and premotor sensorimotor cortices, and increased between the cerebellum and thalamus (Lenka et al., 2017; Nicoletti et al., 2020; Tikoo et al., 2020). Furthermore, regions outside the sensorimotor network, such as the default mode and frontoparietal network, have been reported to be altered in ET (Benito-León et al., 2015; Fang et al., 2015)

In summary, functional imaging in ET patients has shown abnormally increased activation in cerebello-thalamo-cerebral regions, which additionally exhibit dysfunctional connectivity both during motor tasks and rest. Consistent across many studies is the increased cerebellar activity during tremor-inducing motor tasks, and its dysfunctional connectivity with

the rest of the circuit both during tasks and rest.

Evidence for a **primary involvement of the cerebellum** in ET pathophysiology is further evident from animal, clinical, lesion, post-mortem (discussed below) and intervention studies (Berardelli et al., 1996; Benito-León and Labiano-Fontcuberta, 2016; Handforth, 2016; Louis, 2016b; van den Berg and Helmich, 2021). Clinical evidence is derived from the fact that a subset of patients with ET exhibit intention tremor, gait and balance disturbances, oculo-motor abnormalities, eye-hand incoordination, all of which are classical signs of cerebellar dysfunction (Fasano et al., 2010; Benito-León and Labiano-Fontcuberta, 2016). Furthermore, strokes in the cerebellum have been reported to result in the disappearance of ET (Dupuis et al., 1989).

There is emergent evidence that tremor oscillations may originate in the cerebellum. A recent multimodal study, which examined brain tissue from ET patients and used mouse models, reported that synaptic pruning deficits of climbing-to-Purkinje cells synapses (that are related to glutamate receptor delta 2 protein insufficiency) cause excessive cerebellar oscillations (Pan et al., 2020). They further validated the finding by demonstrating cerebellar tremor oscillations in ET patients as recorded via cerebellar EEG. Cerebellar oscillations are then conveyed via the cerebello-thalamo-cerebral circuit to the ventrolateral thalamus and sensorimotor cortex. Indeed, tremor-related oscillations were recorded in the cerebellar-receiving part of the thalamus (VLp), prior to inducing a lesion in ditto for tremor relief (Hua and Lenz, 2005; Milosevic et al., 2018; Pedrosa et al., 2018). Eventually, tremor oscillations were, as outlined above, also recorded over the sensorimotor cortex in ET patients (Schnitzler et al., 2009; Raethjen and Deuschl, 2012; Muthuraman et al., 2018).

Other pathophysiological aspects regarding the neurodegenerative, inferior olive and GABA hypotheses in ET are outlined below:

The inferior olive hypothesis: The inferior olive nucleus was previously (during the 70s) considered the single oscillator causing ET (Llinás and Volkind, 1973). This hypothesis was derived from the known rhythmic properties of the nucleus, and also from its role in driving tremor in the

harmaline-induced animal model for tremor. Harmaline enhances the rhythmic activity within the inferior olive, which then is transmitted to the cerebellar cortex through climbing fibres (Louis and Lenka, 2017). In humans, however, no structural, neurophysiological or reasonable imaging studies have been able to demonstrate the involvement of inferior olive in ET.

Is ET a neurodegenerative disease? Louis has repeatedly advocated that ET is a family of neurodegenerative diseases based on the progressive nature of the disease as well as post-mortem findings (Louis, 2010; Louis and Faust, 2020). Louis reported loss of Purkinje cells, presence of Lewy bodies, Purkinje cell axonal swellings and other findings mostly related to Purkinje cells and their connections (Louis et al., 2007, 2015; Louis and Faust, 2020). Other studies from different groups could not replicate these findings (Shill et al., 2008; Rajput et al., 2012). Rajput et al. discarded pathological changes in ET as being within the normal range when accounting for age and comorbidities (Rajput et al., 2012). Structural MRI studies enable the examination of in-vivo structural alternations in the brain, both in terms of volumetric grey matter differences (voxel-based morphometry, VBM), or white matter changes (as measured with diffusion-based MRI). While some studies showed diverse cerebellar and cerebral grey, as well white, matter reductions, others did not show differences as compared to age-matched controls (Luo et al., 2019; Ågren et al., 2021; Holtbernd and Shah, 2021). The heterogeneity of the findings is perhaps because many studies are underpowered and/or because of the heterogeneities of the patient population.

The GABA hypothesis: Abnormalities in the inhibitory neurotransmitter GABA have been pointed out as a potential explanation for the emergence of tremor in ET. As described previously, Purkinje cells are the sole output channel from the cerebellar cortex and they form GABAergic synapses with the dentate nucleus cells to regulate their intrinsic activity. Dysfunctional GABAergic neurotransmission, as shown by increased ^{11}C-flumazenil binding to GABA-receptors, has been observed in the dentate, ventrolateral thalamus and premotor cortex in ET patients (Boecker et al., 2010). Furthermore, a post-mortem study showed decreased levels of GABA

receptor density in the dentate nucleus of the cerebella from ET patients as compared to controls and patients with Parkinson's disease (Paris-Robidas et al., 2012). An explanation for these findings, that seem at odds, is that ET patients may have both reduction in GABA receptor density and functional receptor abnormality (Helmich et al., 2013). There are several drugs that increase GABAergic transmission such as primidone, Gabapentin and Ethanol can be effective in treating ET. However, as these drugs generally lack sufficient efficacy in ET, it may be seen as evidence against the GABA hypothesis

1.2.3 Deep brain stimulation (DBS) alleviates tremor

A brief history of tremor surgery

Historical as well as current efforts to alleviate tremor through invasive brain surgery testify to the potential disability of this ailment. Historically, the surgical treatment of tremor (and other neuropsychiatric disorders) can be divided into pre-stereotactic and stereotactic eras. Prior to the development of stereotactic frames for human use (the stereotactic era), tremor was surgically treated through non-stereotactic, open brain surgery (Hariz et al., 2010). Mostly, those operations aimed to make lesions at different locations along the pyramidal system, ranging from motor cortex extirpation (area 4 and 6) (Horsley, 1909; Bucy and Case, 1939; Klemme, 1940; Bucy, 1948), section of the pyramidal tract at the cerebral peduncle level (Walker, 1949) or cervical spinal level (Putnam, 1940). Those procedures resulted in relief of tremor (and other involuntary movements) but at the cost of variable degrees of contralateral hemiparesis.

Stereotactic surgery is based on the Cartesian coordinate system, introduced by René Descartes (1596-1650), which enables the identification of a point in the three-dimensional space by employing x, y and z coordinates in relation to a fixed point or landmark(s). Horsley and Clark developed the first stereotactic frame to study brain functions in animals (Horsley and Clarke, 1908). However, the first frame used for human stereotaxy was developed by Spiegel and Wycis in 1947 (Spiegel et al., 1947) after the introduction of air ventriculography by Walter Dandy 1918 (using the ventricular system as a landmark). This event marked the birth of human

stereotactic neurosurgery. In regard to tremor surgery, the ability to reach deep brain structures via stereotactic surgery made it more feasible to target deep subcortical regions instead of the pyramidal system. Hence, tremor had come to be effectively treated through lesions in the ventrolateral thalamus (Vim thalamotomy) as introduced by Hassler and colleagues in 1954 (Hassler et al., 1960; Gildenberg, 2003). Although Vim was, and still is, the target of choice for thalamotomy and DBS, the subthalamic area (including the cerebello-thalamic fibres) was also explored and lesioned to alleviate tremor (Wertheimer et al., 1960; Spiegel et al., 1963; Mundinger, 1965; Velasco et al., 1972).

What is deep brain stimulation (DBS)

Even if earlier attempts had been made (Blomstedt and Hariz, 2010), it is generally recognised that Benabid et al. pioneered the use of chronic high-frequency stimulation in the ventrolateral thalamus to treat tremor (Benabid et al., 1987). This landmark publication founded the idea to alter the function of a brain region with high-frequency stimulation rather than to destroy it. Currently, DBS is an established treatment for movement disorders including ET, Parkinson´s disease and dystonia. Furthermore, it has been investigated for the treatment of other disorders such as obsessive-compulsive disorder, epilepsy, chronic pain, Gilles de la Tourette syndrome, and depression (Lozano et al., 2019). DBS involves implanting electrodes into specific areas in the brain by means of stereotactic surgery, and delivering electrical currents through these electrodes to alleviate various symptoms. The main components of conventional DBS systems are shown in **Figure 8**.

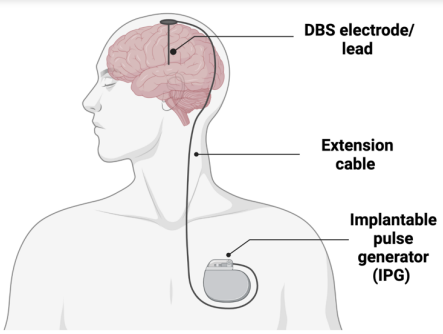


Figure 8. The components of the DBS system. The DBS system consists of three implanted components: electrodes (leads), an implantable pulse generator (IPG) or the pacemaker, and an extension cable connecting the IPG to the electrode. *Created with BioRender.com*

At the tip of the electrode, there are typically four equally spaced metal contacts (thus quadripolar) in contact with the neural tissue. The DBS system can generate and transmit electrical impulses at a specific frequency, amplitude and pulse width. The current can either be delivered between one contact and the implantable pulse generator (IPG) (monopolar stimulation), or between two adjacent contacts (bipolar stimulation). Most commonly, the current is delivered with a high frequency (rate for pulse delivery) of around 130 Hz, magnitude of the current (or the voltage delivered) of 1 – 3 V, and pulse width (length of the stimulation pulse) of 60 μs. These parameters are adjustable and can be optimised to achieve the best clinical effect (such as tremor reduction) with no or minimal side effects (such as speech or sensory disturbances).

DBS as a treatment for ET: where is the optimal target?

Currently, there are two main surgical options to treat tremor; DBS in the PSA or ventrolateral thalamus ("Vim"), or thalamotomy in the ventrolateral (VLp or "Vim") thalamus. Thalamotomy can, in most cases, only be conducted unilaterally, and is created by means of radiofrequency thermocoagulation, Gamma knife radiosurgery, or MR-guided focused ultrasound (Dallapiazza et al., 2019). However, DBS is the procedure of choice in ET, and the focus here.

DBS is a well-established and effective treatment for ET. Tremor improvement due to DBS is quick and appears within minutes once the stimulation is turned on. Traditionally, the VLp (or Vim as more commonly reported) has been targeted for stimulation with short- and long-term tremor reduction of 60-75 % (Schuurman et al., 2000; Blomstedt et al., 2007; Dallapiazza et al., 2019). However, stimulation in the PSA including the caudal zona incerta (cZi) is becoming more common and has been suggested to be superior to Vim DBS in alleviating the tremor (90-95 % reduction) (**Figure 9**) (Plaha et al., 2008; Blomstedt et al., 2009a, 2010; Deuschl et al., 2011; Plaha et al., 2011; Fytagoridis et al., 2012; Sandvik et al., 2012; Barbe et al., 2018; Kvernmo et al., 2022). It is generally believed that tremor relief results from modulating the cerebello-thalamic fibres in the PSA or Vim (Fytagoridis et al., 2016; Akram et al., 2018; Nowacki et al., 2022), which also has been shown by MRI tractography, revealing a correlation

between favourable tremor control and nearness to the cerebello-thalamic tract (Klein et al., 2012; Coenen et al., 2014; Groppa et al., 2014; Coenen et al., 2020).

The Zi is a heterogeneous diencephalic structure located within the PSA and has extensive afferent and efferent connections with the cerebral cortex, thalamus, cerebellum, basal ganglia, brainstem and spinal cord (Mitrofanis, 2005; Blomstedt et al., 2009b). In this thesis, I may often use the term cZi because it is the structure we target during the procedure. It should, however, be noted that the PSA contains other structures than the cZi, many of which, most notably the cerebello-thalamic tract, are affected by the electrical field of the DBS because of the limited volume of the PSA and the assumed spread of electrical current.

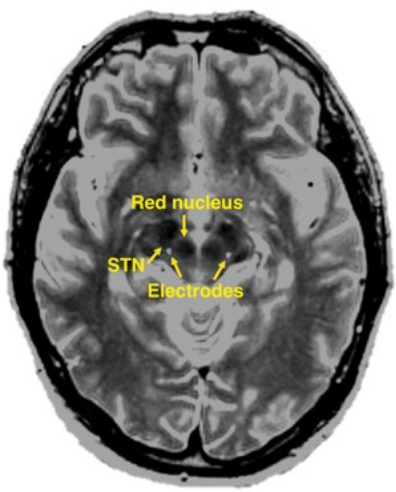


Figure 9. The DBS target for tremor in Umeå (cZi/PSA): A preoperative axial MR-image fused with a postoperative CT for a representative patient, demonstrating the localisation of the tips of the DBS electrodes in the caudal zona incerta (cZi) within the posterior subthalamic area (PSA); posteromedial to the subthalamic nucleus (STN) at the level of the maximal diameter of the red nucleus.

The mechanisms of actions of DBS are poorly understood

The expansion of the clinical utility of DBS has not been paralleled with an understanding of its mechanisms of action. DBS mechanisms of action are still poorly understood despite numerous theories on this issue, some of which I will briefly describe below.

Since the clinical effects of DBS many times resemble the effects of an anatomical lesion (such as in thalamotomy, pallidotomy or subthalamotomy), DBS mechanisms were initially thought to cause a "*functional lesion*" that blocks the neuronal output of whatever structure that was "stimulated" (Udupa and Chen, 2015; Lozano et al., 2019). Nonetheless, subsequent clinical, neuroimaging and electrophysiological evidence were difficult to reconcile with the functional lesion hypothesis.

At the most basic ionic and cellular level, the electrode contact creates an electrical field that opens voltage-gated ion channels. The cells in which Na^+-channels are opened by means of DBS can generate action potentials. With conventional DBS parameters, DBS most likely generates action potentials in axons rather than in cell bodies, which require much higher stimulation amplitudes and pulse widths to activate (Kringelbach et al., 2007). Inducing repetitive action potentials would produce a continuous state of depolarisation known as *depolarisation block* during which subsequent firing of action potentials is not possible. Indeed, electrophysiological recordings from the internal segment of globus pallidus in patients with Parkinson´s disease showed blocked spiking of the cell bodies due to DBS (Dostrovsky et al., 2000).

However, a state of confusion shortly arose as experimental recordings in parkinsonian nonhuman primates showed increased firing in downstream pallidal structures due to stimulation in the subthalamic nucleus (Hashimoto et al., 2003). Further, an early PET study also showed that thalamic stimulation was associated with increased blood flow locally in the thalamus as well as distally in the cortex (Perlmutter et al., 2002). Moreover, it is well-known that a laterally misplaced subthalamic nucleus-electrode can evoke muscle contractions due to effects on the corticospinal tract. If the DBS mimicked a lesion, then it should cause muscle paresis rather than contractions. Thus, it seemed paradoxical that DBS causes inhibition of the firing in the stimulated target, but increased activity in downstream structures.

This issue was partly resolved by McIntyre et al. who implemented a finite element model of the DBS-induced electric field which took into account the

effects on axons as well as cell bodies. This model predicted that extracellular electrical stimulation could directly activate the axons while simultaneously suppressing the cell bodies through activation of inhibitory synaptic terminals (McIntyre et al., 2004). This model can explain how DBS acts through *both excitation and inhibition*, whereby the cell body and the axon are decoupled. Another model is the *"information lesion"* hypothesis, according to which DBS is proposed to override irregular pathological activity by replacing it with stimulation-induced activation patterns (Hashimoto et al., 2003; Miocinovic et al., 2013). The information content of the stimulation-induced signal is effectively zero because of the constant frequency delivered by DBS (Grill et al., 2004; Lozano et al., 2019).

Currently, DBS is thought to exert its effects through *local as well as distant mechanisms*, and thus, it is likely that DBS acts upon modulating the whole pathological circuit, not only inducing a local functional lesion (McIntyre and Hahn, 2010). Indeed, the few available functional imaging studies indicate distant, as well as local, effects of DBS in the thalamus and subthalamic nucleus (Ceballos-Baumann et al., 2001; Perlmutter et al., 2002; Haslinger et al., 2003; Kahan et al., 2012, 2014; Gibson et al., 2016).

In the case of DBS-treated ET, the DBS-contact exerting the therapeutic effect is most often placed within the white matter in the PSA (Blomstedt et al., 2009a; Sandvik et al., 2012). Therefore, the effects are likely achieved through modulating white-matter fibre tracts that project from the cerebellum to the ventrolateral thalamus, passing through the PSA (Herzog et al., 2007; Groppa et al., 2014). How DBS modulates the activity of the cerebello-thalamo-cerebral regions is, however, largely unknown.

Functional neuroimaging of DBS

Studying DBS mechanisms by means of fMRI has been particularly limited due to safety concerns and technical challenges resulting from MRI interaction with the DBS system (discussed in detail in section "3.2.1 Combining DBS and fMRI: safety concerns and technical challenges"). As a result, exploring the effects of thalamic DBS in ET has been limited to few studies either adopting PET imaging (Ceballos-Baumann et al., 2001; Perlmutter et al., 2002; Haslinger et al., 2003) or fMRI in combination with

externalised DBS systems (Rezai et al., 1999; Gibson et al., 2016). All these previous reports were conducted in a small number of patients with thalamic electrodes alternated between On and Off during resting conditions or intraoperatively during general anaesthesia.

PET studies (comparing On and Off stimulation) showed increased blood flow in the thalamus, motor cortex and SMA due to thalamic DBS (Ceballos-Baumann et al., 2001; Perlmutter et al., 2002; Haslinger et al., 2003). Interestingly, the increase in relative blood flow in the thalamus and motor cortex varied depending on the amplitude and the frequency of the stimulation (Haslinger et al., 2003). While thalamic blood flow increased linearly with increased stimulation amplitude, the sensorimotor cortex exhibited a non-linear u-shaped correlation as amplitudes were increased. The pattern of blood flow increase was the opposite with increasing stimulation frequency (Haslinger et al., 2003). Gibson et al. conducted fMRI during general anaesthesia in 10 ET patients after being implanted with DBS in Vim (Gibson et al., 2016). They alternated between On and Off stimulation with different electrode-contact configurations. Overall, DBS resulted in increased BOLD signal in all regions within the cerebello-thalamo-cerebral circuit, which correlated with tremor reduction 3 months postoperatively. Moreover, BOLD-signal increase in S1 was found to correlate with unwanted paraesthesias (Gibson et al., 2016).

In summary, the available sparse literature regarding the combination of functional brain imaging and DBS in ET indicates network-level effects of thalamic DBS, but does not provide insight regarding how DBS actually reduces tremor. The studies were either performed during resting conditions or general anaesthesia, apparently without motor tasks and subsequently without tremor provocation. Since tremor in ET is predominantly present during actions and not during rest (Bhatia et al., 2018), it is critical to investigate DBS effects during different motor tasks, in the presence and absence of tremor. In conclusion, DBS effects on the cerebello-thalamo-cerebral circuit during different motor tasks in awake and behaving ET patients are unknown, especially in cZi DBS which, to date, has not been explored by functional neuroimaging. DBS effects on resting-state functionality connectivity in ET have not been approached with fMRI either.

1.3 Functional magnetic resonance imaging (fMRI)

"The brain, an organ of unparalleled sophistication, seems to have a fundamental design glitch: it consumes a large amount of energy but lacks a reservoir to store fuel for use when needed"
Costantino Iadecola

The lack of energy reserves in the brain necessitates the delivery of oxygen and glucose through increased blood flow at the right time and place when needed. Functional brain imaging techniques take advantage of this phenomenon to (indirectly) capture neural activity, e.g. fMRI measures differences in blood oxygenation that accompany neural activity. Despite providing an indirect measure of brain activity, fMRI is one of the most powerful methods in neuroscience that has enabled us to non-invasively image brain function in awake and behaving humans with relatively high spatiotemporal resolution, and with a whole-brain coverage.

1.3.1 A brief history of functional neuroimaging

Brain activation is oversupplied locally with oxygenated blood

In 1881, Angelo Mosso monitored the brain pulsations through skull defects and observed an increase in pulsations when the subjects engaged in tasks such as mathematical calculations. His foresighted conclusion was that local blood flow is intimately related to brain function (Raichle, 2009; Sandrone et al., 2014). Roy and Sherrington, 10 years later, provided experimental evidence of the activity-flow coupling by demonstrating increased blood flow locally due to brain activation in animals (Roy and Sherrington, 1890). Although based on indirect measures, those observations raised the possibility that brain activity could elicit changes in cerebral blood flow and perfusion. This concept was dismissed and forgotten at the time. The notion of the brain regulating its own blood supply did not re-emerge until decades later when John Fulton, in 1928, described a case of a man with vascular malformation over the visual cortex who experienced a noise (i.e. bruit) in the back of his head during visual stimulation (Fulton, 1928).

Quantitative measurements of the human brain´s blood flow were not available until the end of the 40s when Kety and Schmidt developed a method to measure whole-brain blood flow and metabolism (Raichle, 2009; Iadecola, 2017). The aforementioned method could only measure global, and not local, changes in blood flow. Regional blood-flow measurements were developed by Ingvar and Lassen, who demonstrated that blood flow changes locally during task performance (Lassen et al., 1978).

Marcus Raichle and Peter Fox demonstrated that regional increases in blood flow were disproportionate to the oxygen consumption rate (i.e. an active brain region is oversupplied with oxygenated blood beyond its needed oxygen consumption) (Fox and Raichle, 1986; Fox et al., 1988). The increase in blood flow following neuronal activation is due to dilatation of local capillaries and arterioles as mediated by glutamate, nitric oxide, astrocytes and pericytes (Attwell and Iadecola, 2002; Iadecola, 2017). The mechanisms that describe such vascular changes due to neuronal activation, i.e. the neurovascular coupling, are complex, poorly understood, and outside the scope of the thesis.

Blood oxygenation is captured by MRI… A bold discovery

In 1936, Pauling and Coryell found that oxygenated and deoxygenated haemoglobin had significant differences in their magnetic properties, i.e. magnetic susceptibilities (Pauling and Coryell, 1936). Importantly, deoxygenated haemoglobin is paramagnetic due to the exposed iron in the haemoglobin molecule, and thus, disrupts the homogeneity of the magnetic field. Oxygenated haemoglobin, on the other hand, is weakly diamagnetic and has little effect on the magnetic field (**Box 2**).

The magnetic field inhomogeneities caused by deoxyhaemoglobin were noticed by Seiji Ogawa et al. through experimentations on manipulating the concentration of deoxygenated blood in the rat brain by altering breathing from room air to 100 % oxygen. The anatomy of the venous system was easily visible as dark structures when the animals were breathing room air, whereas on 100 % oxygen, the venous structures disappeared (Ogawa et al., 1990b, 1990a). Ogawa described this finding as "blood oxygen level-dependent contrast", i.e. BOLD, and realised its future potential as a

technique to map the functions of the human brain (Ogawa et al., 1990b). Soon after Ogawa´s discovery of BOLD fMRI, its potential was recognised in 3 independently conducted studies demonstrating BOLD fMRI responses in humans during motor and visual tasks (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). Shortly before that, Belliveau et al. also demonstrated the feasibility of fMRI to capture brain function in humans but based on the exogenous paramagnetic agent gadolinium (Belliveau et al., 1991). These notable achievements started the astonishing journey of fMRI as a tool to non-invasively map the functions of the human brain.

Box 2: The physical basis of magnetic resonance imaging (MRI)

Broadly, MRI is based on the magnetic excitation of body tissue and the reception of returned electromagnetic signals from the body. Hydrogen atoms (protons), the dominant source of protons in the body, have a magnetic moment due to spin (rotating around an axis). When exposed to the MRI system's strong static magnetic field, the hydrogen protons align with the main magnetic field vector (either parallel "low-energy state" or antiparallel "high-energy state"). They continue to *precess* around the direction of the field at a frequency that is determined by the type of atom (hydrogen in this case) and directly proportional to the strength of the external magnetic field, *Larmor frequency* (Logothetis, 2002). Electromagnetic waves of radiofrequency (i.e. RF pulses) with the same (Larmor) frequency are applied. Some protons get excited by absorbing the transmitted energy (according to the *resonance* principle). Once excited, some hydrogen spins change from a low-energy to a high-energy state. After the excitation pulse ceases, some of the "high-energy" spins return to the low-energy state and release the absorbed energy as a radiofrequency wave. This wave is then received by a receiver coil. The process, during which some spins/nuclei return to a low-energy state and cause a change in net magnetisation over time, is called relaxation. There is a recovery of the longitudinal magnetisation (T_1 relaxation), and also a decay of the transverse magnetisation (T_2 relaxation). Relaxation times differ between different tissues (such as grey and white matter, cerebrospinal fluid, and fat) and tissue properties (such as tissue oxygenation) (Huettel et al., 2009). Specifically important for fMRI is a special type of T_2 relaxation, called T_2^*, that also depends on the local field inhomogeneities, which in turn, depend on the local physiological state (especially the local blood oxygenation).

1.3.2 Physiological basis of blood oxygen level-dependent (BOLD) signal

Neuronal activation is accompanied by elevated oxygen and glucose consumption which are met by increased blood flow to the activated region, i.e. *haemodynamic response*. This subsequently alters the local levels of oxygenated and deoxygenated haemoglobin. The BOLD contrast takes advantage of the paramagnetic properties of deoxygenated haemoglobin that cause inhomogeneities in the magnetic field which dephase proton spins and subsequently decrease the MR signal intensity. Thus, an increase in the concentration of deoxygenated haemoglobin would cause a decrease in MR-image signal intensity, whereas a decrease in its concentration would cause an increase in image intensity. Activation in a brain region is accompanied by an elevated oxygen extraction from the blood, which causes an increase in the concentration of deoxygenated haemoglobin. This effect results in a small and brief decrease of BOLD signal (called initial dip). Shortly after that, the neurovascular coupling causes a large and prolonged increase in the blood flow and volume within 2-3 s, bringing more oxygenated haemoglobin, and causing a net decrease in the levels of deoxygenated haemoglobin resulting in an increased BOLD signal within a few seconds (Heeger and Ress, 2002). Thus, the large increase in BOLD signal is due to drop in the levels of deoxygenated haemoglobin caused by disproportionately large delivery of blood to active brain regions (Fox and Raichle, 1986).

Electrophysiological correlates of BOLD signal

BOLD signal directly reflects the local increase in neural activity. To characterise the electrophysiological basis of BOLD signal, Logothetis et al. simultaneously acquired electrophysiological recordings and BOLD fMRI from the visual cortex of anaesthetized and alert monkeys (Logothetis et al., 2001; Goense and Logothetis, 2008). The electrophysiological recordings included single-unit activity, multiunit activity and local field potentials (LFPs). Multiunit activity records fast, high-frequency aggregated field potentials that mostly reflect spiking activity in a population of neurons; single-unit activity reflects action potentials of large principal neurons next to the microelectrode tip; and LFPs record slow events representing local

averaged excitatory and inhibitory postsynaptic potentials, which in turn, reflect the input to a given cortical area as well as its local intracortical processing (Kayser and Logothetis, 2013). While it was found that both multiunit activity and LFPs made significant contributions to the BOLD response, it was LFPs that mostly correlated with BOLD and best predicted it (Logothetis, 2008). This implies that BOLD, to a greater extent, reflects the input to a given area as well as its local intracortical processing, rather than its output (Logothetis, 2008; Kayser and Logothetis, 2013).

1.3.3 A brief introduction to fMRI methodology

In general, neuroscientific methods may be described based on their invasiveness, spatiotemporal resolution, spatial coverage, and what signal they measure (Sejnowski et al., 2014). In that regard, fMRI provides a non-invasive measure of brain activity based on haemodynamic changes that accompany neural activity at a temporal resolution of seconds (a peak occurring 5-6 s after a brief neutral stimulus). It offers a high spatial resolution, depending on the voxel (smallest spatial unit) size, of 1-3 mm in each dimension, and provides a whole-brain coverage. The spatial resolution of fMRI is very good when compared with electrophysiological methods such as EEG and MEG (>10-20 mm for scalp measurements). It also offers better spatial resolution than PET which typically has > 5-10 mm's resolution. The temporal resolution of fMRI is relatively poor (several seconds) as compared with EEG and MEG that offer a temporal resolution of milliseconds, but is better than PET (minutes).

Experiment design, image pre-processing and analysis

A general overview of fMRI methodology is described in **Figure 10**. Typically, fMRI experiments can be divided into task-based and resting-state studies (**Figure 10 A**). In task-based fMRI studies, differential BOLD responses to various stimuli or task performance are assessed by comparing BOLD signal between periods with task and periods with a control task, e.g. comparing blocks of finger tapping with blocks with a resting control task. rs-fMRI, on the other hand, is acquired in the absence of a stimulus or a task (i.e. at "rest") and aims to investigate intrinsic brain activity. In fMRI, BOLD signal exhibits slow (<0.1 Hz) spontaneous fluctuations that initially were regarded

as noise, but were later found to reflect the functional organisation of the brain (Snyder and Raichle, 2012).

Prior to statistical analysis, fMRI data need undergo several pre-processing steps (**Figure 10 B**) that commonly include: i) slice-time correction (correcting for differences in slice acquisition times), ii) head motion detection and realignment (aligning all the functional volumes/images to a reference image), iii) co-registration of fMRI images to a high-resolution structural image, iv) spatial normalisation to a standard (such as the MNI, Montreal Neurological Institute) space to enable the conduction of group analysis, and v) spatial smoothing by convolving the data with a 3D Gaussian kernel (Huettel et al., 2009).

Analysis of task-based fMRI: Task-based fMRI data are typically analysed through multiple regression, in which statistical tests are used to evaluate the relative contributions of independent variables (experimental conditions/evoked responses) to a dependent variable (observed BOLD data) (**Figure 10 C**). The main statistical tool used is the *general linear model* (GLM). GLM assumes that the observed data are composed of the linear combination of different model factors as well as uncorrelated noise. A GLM equation is shown below (Huettel et al., 2009).

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon$$

y represents the measured BOLD data; β_0 represents the constant contribution of each voxel through the experiment; x represents the design matrix where model factors (experimental conditions) are specified; β represents the parameter matrix where the relative contribution of each model/factor and voxel is calculated; ε represents the residual unexplained error

The GLM fits the created model to the data independently for each voxel which provides beta values that estimate the effect of each condition (after convolving predicted neuronal activity with the canonical haemodynamic response function). This process generates a set of estimated values from each voxel that, subsequently, can be used for statistical inference by comparing different tasks/conditions at the subject "first-level analysis" and group level "second-level analysis".

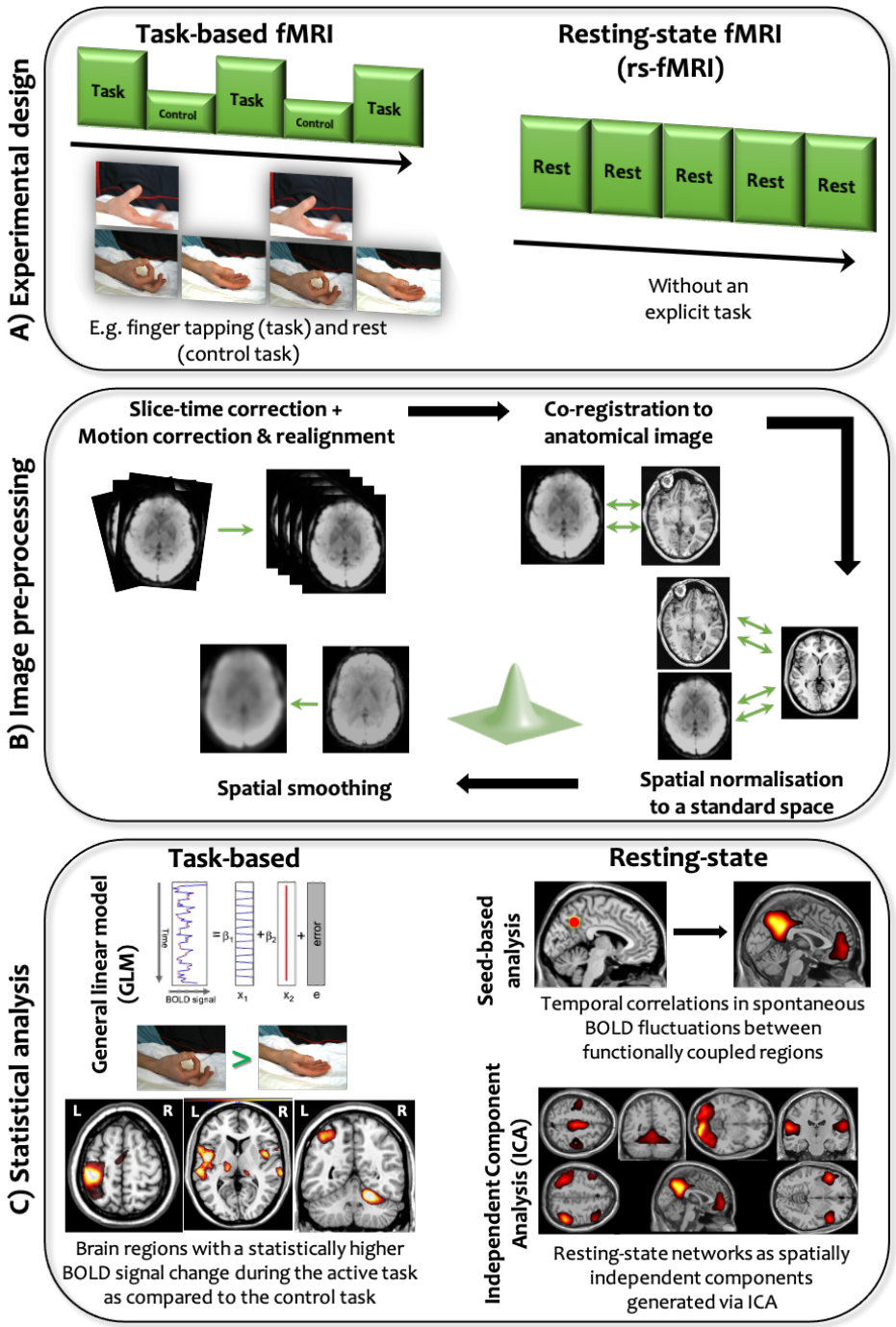


Figure 10. Typical fMRI workflow: the most common fMRI experiment designs (A), pre-processing steps (B), and statistical analysis (C). See the main text for details.

The resultant statistical maps consist of values generated by statistical tests conducted independently for each voxel. Because of the large number of voxels (~100,000) and, subsequently, the large number of independently conducted tests, there is a high risk of obtaining false positive findings because of the multiple comparison problem. Therefore, it is common practice to adopt a statistical threshold that corrects for the number of voxels studied. There are several methods used to control the false-positive rate, e.g. family-wise error (FWE), false discovery rate (FDR) and cluster-based thresholding.

Rs-fMRI can be analysed via several different approaches, two of which are shown in **Figure 10 C**. In seed-based analysis, the temporal correlation in BOLD-signal fluctuations is calculated between a predefined region of interest (ROI) and other brain regions. Functionally coupled regions seem to exhibit higher correlations in their BOLD fluctuations at rest (Biswal et al., 1995). Correlated BOLD fluctuations are commonly referred to as functional connectivity, and thus, are a measure of inter-regional connectivity based on temporal dependence in BOLD signal. Based on the same principle, several networks have been defined as sets of regions that share temporally coincident BOLD signal fluctuations, the topography of which closely correspond to responses elicited by a variety of tasks such as sensory, motor or cognitive tasks (Fox and Raichle, 2007; Smith et al., 2009). These resting-state networks can be extracted through data-driven approaches such as independent component analysis (ICA) that clusters voxels into networks that are spatially independent but share fMRI time-course (Lv et al., 2018).

In this thesis, fMRI was used in all studies due to the advantages outlined above (non-invasiveness, high spatial resolution, and whole-brain converge). Furthermore, fMRI was the method of choice because of its availability within the established research infrastructure at Umeå Center for Functional Brain Imaging. Task-based fMRI was used in studies I, II and III. In studies I and II, somatosensory stimulation was applied in patients with clinically complete SCI. Trials with stimulation were compared with trials without stimulation. In study III, ET patients treated with DBS performed different motor tasks. In study IV, DBS effects on resting-state functional connectivity were investigated by means of rs-fMRI.

2 Aims

Overall aim for part 1

To investigate potentially preserved somatosensory conduction from below-injury body parts in clinically complete SCI (AIS grade A), while controlling for top-down cortico-cortical effects.

Study I

- Investigate whether somatosensory stimulation below the injury level of a clinically complete SCI (thus in an anaesthetic skin area) can activate the corresponding somatosensory cortex.
- Examine whether the activity of the somatosensory cortex can be driven by top-down mechanisms such as vision despite long-standing sensorimotor loss after clinically complete SCI.

Study II

- Verify the concept of sensory discomplete SCI in a larger group of participants with clinically complete SCI.
- Get an indication of how common sensory discomplete SCI is, and whether it is associated with specific clinical outcomes.

Overall aim for part 2

To clarify the mechanisms of cZi-DBS in ET by using fMRI during motor tasks and resting state.

Study III:

Explore DBS effects on the functional activity within the cerebello-thalamo-cerebral circuit during motor tasks, with and without tremor, in order to investigate:

- Task-dependent DBS modulation (whether DBS effects vary depending on the motor task at hand).
- Task-independent DBS modulation (DBS effects regardless of the tasks).

Study IV:

Explore DBS effects on resting-state functional connectivity in ET.

3 Methods and Results

BOLD fMRI was used in all studies; task-based fMRI in studies I-III and rs-fMRI in study IV. In studies I and II, somatosensory stimulation was used to investigate residual somatosensory function after clinically complete SCI. In study III and IV, ET patients treated with DBS in the cZi/PSA were studied to elucidate DBS mechanisms during different motor tasks (study III), and resting-state (study IV).

MRI data were obtained by a 3.0 Tesla MRI scanner with a 32-channel head coil in studies I and II. Due to safety concerns regarding DBS-MRI interactions, a 1.5 Tesla MR scanner with a transmit-receive (T/R) head coil was used in studies III and IV. DBS-MRI interactions are elaborated on in detail in the section "*Combining DBS and fMRI: safety concerns and technical challenges*" below.

3.1 Residual somatosensory function in complete SCI (Part 1)

3.1.1 Study I

Study I included 3 experiments on a 59-year-old male participant with clinically complete traumatic cervical SCI, AIS grade A, at the C6-C7 level for 29 years due to a diving accident (included in experiments 1, 2, and 3). No zones of partial preservation were present below the neurological level of lesion. A 24-year-old, right-handed, neurologically healthy male participant was included to verify the experimental protocol and expected outcomes (included in experiment 1).

The somatosensory apparatus and procedure of study I

The experimental setup and results of study I are shown in **Figure 11**. The somatosensory stimulation paradigm was adapted from a previous study in our lab (Lindgren et al., 2012).

Experiment 1 was constructed as a 2×2 factorial design, with somatosensory

stimulation (touch or no touch) and vision (presence or absence of visual feedback) as factors. The inclusion of "vision" was aimed to investigate potentially residual cortico-cortically driven responses in the somatosensory cortex (Dionne et al., 2010; Meyer et al., 2011; Kuehn et al., 2018), and to further explore possible touch-vision interaction effects.

Somatosensory stimulation was applied on the anterior surface of the left upper leg, with and without visual feedback through a tilted mirror attached to the head coil. During conditions with no visual feedback, a curtain was pulled in front of the scanner bore to prevent the participant from seeing his own legs. During the condition of no-touch but visual feedback, the experimenter moved the hand just above the skin surface of the leg at the same pace as during actual stimulation. The stimulation trials were repeated 10 times for each condition. Each stimulation trial was followed by a response period; a verbal evaluation of the subjective sensory experience related to the tactile stimulation, according to the Perceptual Awareness Scale (PAS). PAS is an introspective measure by which participants indicate the experienced intensity of a stimulus (Sandberg et al., 2010). Three grades were used: 1 = no experience, 2 = weak experience, and 3 = distinct experience.

In **experiment 2**, only somatosensory stimulation was applied (i.e. without visual feedback). The somatosensory paradigm was expanded to include stimulation of the right and left leg (i.e. well below the lesion level), on the right and left arm (i.e. above the lesion level), and also a no-stimulation condition that was used as a reference baseline. During the response period, two questions were asked: (i) Did you feel anything? (Graded according to PAS) and (ii) Which body part was stimulated? For the first question, the participant used the PAS. However, the subjective evaluation of somatosensory stimulation of the legs was this time not limited to somatic sensations in the legs, but included any sensation whatsoever that appeared to differ from the rest condition, including somatic sensations from other body parts, visual input, etc.

In **experiment 3**, the experimental design was identical to experiment 2 but with an expanded stimulation paradigm to include the feet.

Data analysis in study I

For details regarding the data acquisition, pre-processing and analysis, see the methods section in paper I. Briefly, fMRI data were pre-processed, and then analysed voxel-by-voxel by applying a general linear model (GLM) on the pre-processed data, at whole-brain level. Somatosensory stimulation trials were then contrasted with no-stimulation trials for each condition. A

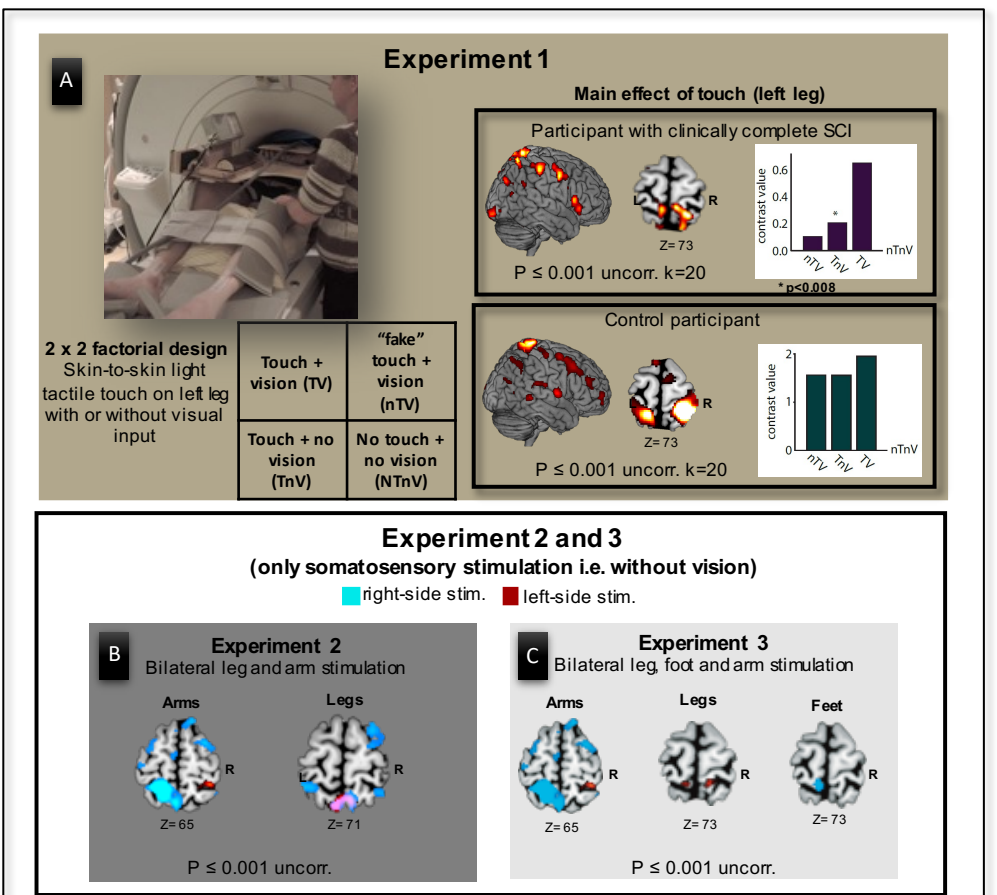


Figure 11. Experimental design and fMRI results from study I: (A) Stimulation paradigm and results from study I. A touch device was used to guide the experimenter to the required pressure, velocity and onset/offset of the stimulation conditions. During application of skin-to-skin stimulation, the experimenter also applied mirrored stimulations with the contralateral hand to a dummy arm at which forces and movements were measured. The results (right) show comparable activation pattern for the control and SCI participant. (B) fMRI results from experiment 2, and (C) fMRI results from experiment 3.

statistical threshold of $p < 0.001$, cluster size $k \geq 20$ was considered significant.

Results of study I

The SCI participant did not report any somatosensory perception due to stimulation on the legs, and could not perform better than chance when guessing which body part, if any, was stimulated. Perception from arm stimulation was nearly normal. In experiment 1, despite the lack of any conscious sensations, the main effect of touch did elicit BOLD signal change in bilateral S1 and BA5, left S2, bilateral anterior insula, and anterior cingulate gyrus. The main effect of vision overlapped with the effect of touch in bilateral S1, left S2, and right anterior insula. Moreover, there was a significant touch-by-vision interaction in bilateral S1. Critically, touch in the absence of visual input produced BOLD signal change in S1 within the areas displaying the main effect of touch, but at a more liberal statistical threshold (**Figure 11 A**).

Two additional experiments were conducted on the participant with SCI and a similar activation pattern was obtained due to below-level (leg) stimulation while controlling for top-down effects like vision and attention. In experiment 2, somatosensory stimulation of the left and right arm produced expected BOLD signal change in right and left S1, respectively. Stimulation of the left upper leg again produced a significant BOLD signal change in BA5 bilaterally (**Figure 11 B**). In experiment 3, the protocol was further extended to also include stimulation of the feet. When the left leg was stimulated, there was a significant BOLD signal change in bilateral S1 (**Figure 11 C)**. Right leg stimulation gave rise to a less significant BOLD signal change in left S1, though it was consistent with expected topology ($t = 2.36$, $p = 0.01$). Stimulation of the right foot produced a significant BOLD signal change in the left S1.

3.1.2 Study II

Participants, interview and clinical examination

Eleven participants with clinically complete traumatic SCI (AIS grade A) were

included in study II. The recruitment was based on patients in Västerbotten County with regular follow-ups at the Department of Rehabilitation medicine, Umeå University Hospital. For details on the recruitment process, inclusion/exclusion criteria, see the methods section of paper II).

In the first part of study II, I interviewed the participants via a semi-structured interview to assess SCI-related complications and consequences. The interview was constructed to address pain, spasticity, bladder and bowel function, autonomic dysreflexia, propensity for below-level injuries including pressure ulcers, sensation from sacral regions, body image, current medications and MRI contraindications. Interviews were conducted in Swedish (see the English translation of the interview template in the appendix). Secondly, I conducted a clinical examination of the participants according to the ISNCSCI protocol (revised 2011 and updated 2015, see the ISNCSCI worksheet in the appendix) to ensure the SCI was complete (i.e. absent sacral sparing), establish the neurological level of injury and ensure that a possible zone of partial preservation (ZPP) would not include the area for subsequent somatosensory stimulation during fMRI (Kirshblum et al., 2011). **Table 2** shows the participant demographics. In summary, all participants had complete traumatic SCI (AIS A) with neurological lesion levels ranging from C4 to L1. None of the participants had a ZPP that included the area for somatosensory stimulation during the fMRI. Six participants suffered from below-level neuropathic pain, and ten participants had symptomatic spasticity on a daily basis.

Participant	Sex	Age	Years since Injury	NLI	AIS	Sensory level R/L	Motor level R/L	ZPP	Below-level neuropathic pain	Spasticity (major impact)
1	M	38	27	C6	A	C6/C6	C6/C6	T1	Yes	Yes (No)
2	M	47	29	T1	A	T2/T1	T1/T1	T4	No	Yes (No)
3	M	62	25	C8	A	C8/C8	T1/T1	T5	No	Yes (No)
4	F	46	25	L1	A	L1/L1	L1/L1	L2	No	Yes (No)
5	F	51	36	T9	A	T9/T9	T9/T9	T12	Yes	No
6	M	72	12	T10	A	T10/T10	T10/T10	T11	Yes	Yes (Yes)
7	M	40	19	C4	A	C4/C4	C5/C5	T3	No	Yes (No)
8	M	66	41	C4	A	C5/C4	C5/C5	T3	Yes	Yes (No)
9	F	63	42	C6	A	C6/C6	C6/C7	T2	No	Yes (No)
10	M	57	21	T3	A	T3/T3	T3/T3	T9	No	Yes (No)
11	M	37	10	T8	A	T8/T8	T8/T8	T9	Yes	Yes (Yes)

Table 2. participant demographics. NLI = neurologic level of injury; AIS = ASIA Impairment Scale (A denotes complete injury); R/L = right/left; ZPP = zone of partial preservation; "Major

impact" indicates impact on quality of life. Rows coloured in dark grey indicate participants with discomplete SCI (evidence grade 1), the row coloured in light grey indicates a participant with discomplete SCI (evidence grade 2), and rows coloured in white indicate participants with no evidence for discomplete SCI.

fMRI experimental design study II

The experimental setup is shown in **Figure 12**. To assess the functional integrity of the dorsal column-medial lemniscus tract and the anterolateral spinothalamic tract, we applied light innocuous tactile touch as well as sharp

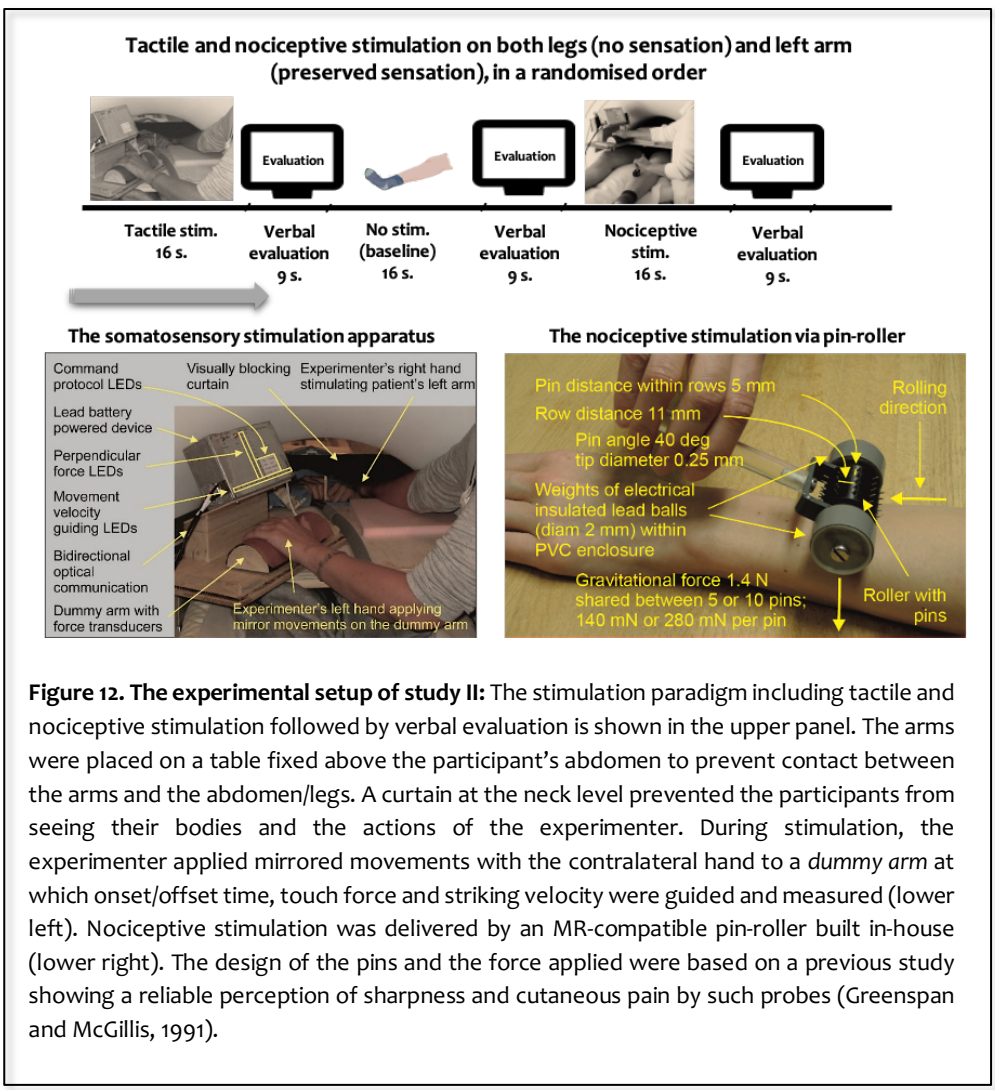


Figure 12. The experimental setup of study II: The stimulation paradigm including tactile and nociceptive stimulation followed by verbal evaluation is shown in the upper panel. The arms were placed on a table fixed above the participant's abdomen to prevent contact between the arms and the abdomen/legs. A curtain at the neck level prevented the participants from seeing their bodies and the actions of the experimenter. During stimulation, the experimenter applied mirrored movements with the contralateral hand to a *dummy arm* at which onset/offset time, touch force and striking velocity were guided and measured (lower left). Nociceptive stimulation was delivered by an MR-compatible pin-roller built in-house (lower right). The design of the pins and the force applied were based on a previous study showing a reliable perception of sharpness and cutaneous pain by such probes (Greenspan and McGillis, 1991).

nociceptive stimulation, respectively. The stimulation conditions were applied on one arm (above the level of injury) and on both legs (well below the level of injury), in a randomised order. The inclusion of above-level arm stimulation, where our participants had normal sensation, functioned as a control condition where we could confirm that expected brain activity pattern was captured for each participant. For leg stimulation conditions, several insensate dermatomes were stimulated (range L2-S1) depending on the level of injury and ZPP. The somatosensory stimulation was applied on insensate skin regions well below the level of ZPP in all participants (see table 2).

Each stimulation was followed by an oral report during which the participants gave a verbal response to these four questions:
1) Did you feel anything? According to PAS (see study I)
2) Did you perceive the stimulation as sharp? (Yes or No)
3) Did you perceive the stimulation as painful? Grade according to the Numeric Rating Scale: 0 indicates "no pain", 10 indicates "the worst possible pain"
4) Which body part was stimulated? Arm, right leg, or left leg. Guess if you do not know.

The answers to the first question were used to exclude blocks with possible top-down effects during leg stimulation (would be reported as PAS= 2 or 3). The participants were asked to report PAS 2 on liberal grounds. A vague experience could include vision of stimulation, any vague sensation from the legs, sensation of the mechanical stimuli through the transmission to sensate regions, and attention to leg stimulation, spasticity etc. To qualitatively distinguish between tactile and nociceptive stimulation, the participants were asked to report sharpness of stimulation (question 2).

Data analysis in study II

Details on fMRI data acquisition and pre-processing are found in the methods section of paper II. Briefly, fMRI data were pre-processed, and then analysed voxel-by-voxel by applying a GLM to the pre-processed data. Analyses were set up by including stimulation conditions as regressors of interest in the GLM, convolved with the canonical haemodynamic response

function. A stimulation regressor started at the first and ended after the last movement. A stimulation event was defined as a perpendicular force > 0.5 N. In order to minimize the confounding impact of top-down effects during leg stimulation, we only analysed stimulation blocks without any conscious experience or visual or attentional confounds (i.e. PAS = 1).

Since we had a strong *a priori* hypothesis regarding activation locations, the analyses were restricted to brain regions concerned with somatosensory processing; S1, S2, BA 5, anterior cingulate gyrus, and insula (**Figure 13**). The motivation for using a ROI approach was to optimize sensitivity to detect presumably weak preserved somatosensory signalling. Sensitivity was increased by reducing the number of multiple-comparison corrections at the statistical evaluation stage. We, thus, focused on brain regions considered as primary recipients of somatosensory stimuli (both tactile and nociceptive).

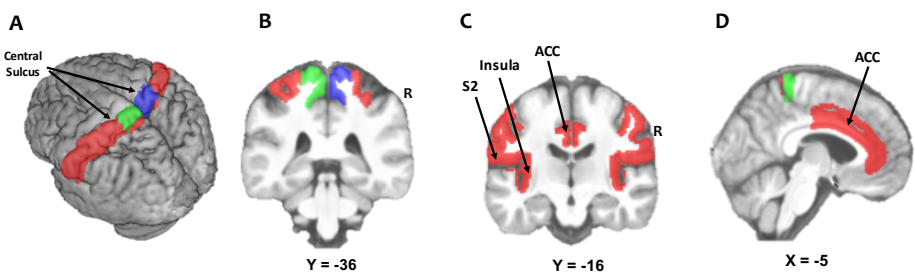


Figure 13. Somatosensory regions of interest (ROI): ROIs were used to restrict fMRI analysis to brain regions concerned with somatosensory processing according to our *a priori* prediction. (**A**-**D**) show a somatosensory mask (coloured in red) consisting of the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2), Brodmann area 5 (BA 5), the insulae and anterior cingulate cortex (ACC). Somatotopically specific S1-ROIs (leg's representation) within the somatosensory mask are shown in (**A** and **B**); right ROI in blue and left ROI in green. The insulae and ACC are considered only for the nociceptive trials. The ROIs are visualized on a group-specific anatomical image. Coordinates (Y and X) are in Montreal Neurological Institute (MNI) standard space; R = right hemisphere.

Criteria for discomplete SCI

As S1 is the primary cortical site to receive somatosensory input and is organized in a somatotopic fashion, somatosensory stimulation of the legs

was expected to primarily activate the somatotopically specific part of the contralateral S1. Accordingly, we adopted a criterion that a SCI must fulfil in order to be determined discomplete: activation of the somatotopically appropriate part of the contralateral S1 due to tactile or nociceptive stimulation on one or both leg(s). Such response is here referred to as **evidence grade 1 for discomplete SCI**. This was explored by analysing leg stimulation conditions (right/left) within their corresponding contralateral S1-ROI, p≤ 0.05 FWE-corrected at the voxel level within the S1-ROI (**Figure 13 A and B**). As somatosensory input also is conveyed to other cortical regions beyond S1 (Qi et al., 2008), activation in these regions was also investigated. Potentialyl significant responses in such regions are here referred to as **evidence grade 2 for discomplete SCI**, and defined as activation of S2, somatotopically unspecific part of S1 (ipsilateral or more lateral than "leg area") or BA 5 due to leg stimulation. For the nociceptive trials, the insulae and the anterior cingulate cortex were also considered, in addition to the abovementioned regions (Apkarian and Shi, 1998; Treede and Apkarian, 2008). Accordingly, the tactile trials were analysed within the somatosensory mask consisting of bilateral S1, S2 and BA 5, and the nociceptive trials were analysed within the somatosensory mask consisting of bilateral S1, S2, BA 5, insula and anterior cingulate cortex. Results were considered statistically significant at a threshold of p≤ 0.05 FWE-corrected at the voxel level within the somatosensory mask.

Results of study II

All participants showed a reliable signal change in the contralateral S1, S2 and BA 5 due to arm stimulation (**Figure 14**). We found that six out of 11 patients had evidence for discomplete SCI as determined by a somatotopically appropriate response in the contralateral S1 due to tactile or nociceptive stimulation on one or both legs, p ≤ 0.05, FWE-corrected. One patient had an indication for a discomplete SCI as determined by activation of somatosensory regions other than S1 due to tactile or nociceptive stimulation, p≤ 0.05 FWE-corrected. Four patients had no evidence for discomplete SCI (**Figure 15**).

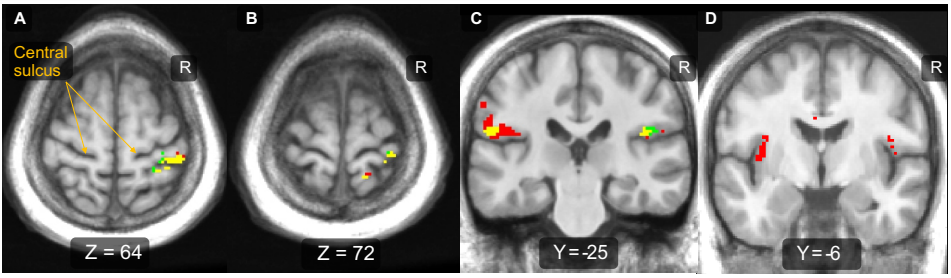


Figure 14. Tactile and nociceptive arm stimulation: Activation pattern due to above-level somatosensory stimulation on the left arm as compared to the no-stimulation condition from a representative participant. BOLD responses are visualized on a group-specific anatomical image; tactile stimulation in green, nociceptive stimulation in red and the overlap in yellow. Tactile and nociceptive stimulation activated the contralateral primary somatosensory cortex (A), contralateral Brodmann area 5 (B), and the secondary somatosensory cortex bilaterally (C). Moreover, the nociceptive stimulation activated the insula and the anterior cingulate cortex (D). P≤ 0.05 FWE voxel-corrected within the somatosensory mask. Coordinates (Y and Z) in Montreal Neurological Institute (MNI) standard space. R = right hemisphere.

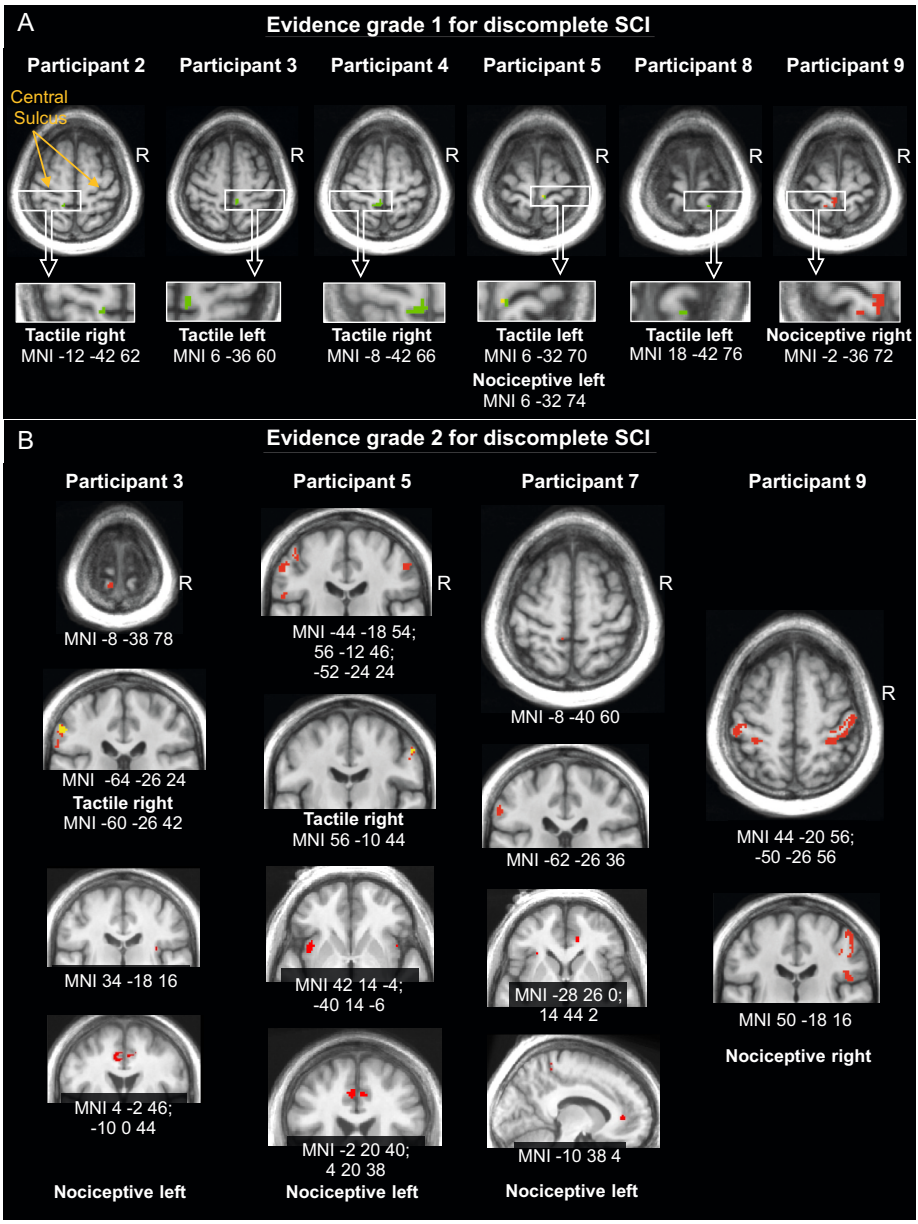


Figure 15. Results from leg stimulation conditions: Brain activation due to below-level (leg) somatosensory stimulation as compared to the no-stimulation condition for individual participants, p≤ 0.05 FWE voxel-corrected. BOLD responses are visualized on a group-specific anatomical image; tactile stimulation in green, nociceptive stimulation in red and the overlap in yellow. *Evidence grade 1 for discomplete SCI* (A) denotes contralateral and somatotopically appropriate activation of S1 due to tactile or nociceptive stimulation on one or both legs, and *Evidence grade 2 for discomplete SCI* (B) denotes activation of somatosensory regions other than somatotopic contralateral S1 due to leg stimulation; R = right hemisphere; MNI = Montreal Neurological Institute standard space.

3.2 DBS modulation of the sensorimotor circuit in ET (Part 2)

In part 2 of the thesis (studies III and IV), fMRI was used to explore the mechanisms of action of chronic DBS in the cZi/PSA in 16 ET patients. The patients had fully-implanted DBS systems with stable clinical effect for at least one year. BOLD fMRI was used during On and Off *therapeutic* stimulation to investigate DBS effects via within-subject design. DBS effects were explored during different motor tasks (study III) and resting-state (study IV). In study III, we applied a task-based design during which the patients performed motor tasks, with and without tremor (postural holding, pointing and rest). The study aimed to explore whether DBS modulated the activity of the sensorimotor circuit during tasks with and without tremor. In study IV, resting-state runs were obtained during On and Off stimulation to investigate DBS effects on resting-state functional connectivity. The two studies would provide insights on whether DBS acted upon modulating the cerebello-thalamo-cerebral circuit during motor tasks, resting state, or both.

3.2.1 Combining DBS and fMRI: safety concerns and technical challenges

DBS has rarely been examined with fMRI due to 1) safety concerns and 2) experimental feasibility challenges, preventing the combination of DBS and MRI. The safety issues associated with examining DBS patients with MRI include heating and induction of current in the DBS system. Although MRI can be conducted safely in DBS patients if adhered to strict safety protocols, deviations from safety guidelines have been reported to result in serious adverse events and even permanent brain injury as shown in two unfortunate case reports (Spiegel et al., 2003; Henderson et al., 2005).

Experimental feasibility challenges caused by MR-signal loss due to hardware-related artefact, and the potential MR-IPG interaction which may cause instability in the DBS system´s functionality. Phantom studies, in which a clinical DBS system is implanted in phantoms that simulate the thermal and electrical properties of the body, have been very useful in evaluating the safety risks (e.g. heating) and the experimental feasibility (device function)

of combining DBS with MRI (Carmichael et al., 2007; Kahan et al., 2015; Boutet et al., 2020b).

Safety issues

The major safety risk of combining DBS with MRI concerns *heating* at the tip of the electrode caused by the rapidly changing magnetic fields during RF excitation which induces heating in the DBS device (i.e. the "resonant coupling" or "antenna effect") (Georgi et al., 2004; Carmichael et al., 2007). Such rapid temperature increases may reach potentially dangerous levels and cause brain damage. There have been general guidelines, partly imposed by the DBS companies, proposing that MRI-induced temperature increase should not exceed 1°C (Rezai et al., 2005; Carmichael et al., 2007). Heating in DBS electrodes depends on several factors including MRI-sequence specific absorption rate (SAR), DBS-device model and brand, DBS-system configuration and geometry in relation to the magnetic field, magnetic field strength and type of the MR-coil (Boutet et al., 2020a). The most important source of tissue heating is SAR, which is a measure of the amount of power deposited by an RF field in a certain mass of tissue, expressed as watts per kg (W/kg). As indicated by phantom studies, there is a linear relationship between SAR and induced heating at the electrode tip (Georgi et al., 2004). To prevent higher SAR values, the MRI acquisition needs to be adjusted by adopting lower magnetic field strengths, reducing the number of slices and flip angles, and using RF transmit/receive head coil (Allison and Yanasak, 2015). Such adjustments may compromise image quality by reducing the signal-to-noise ratio.

However, several phantom studies reported that SAR values below 0.4 W/kg induced negligible DBS lead heating during fMRI at 1.5 Tesla and using RF transmit/receive head coil, regardless of the stimulation setting (On or Off) (Georgi et al., 2004; Carmichael et al., 2007; Kahan et al., 2015). The findings from these experiments have guided our experiment design in part II of the thesis where ET patients with fully-implanted DBS systems when examined with fMRI during On and Off DBS.

Another safety concern is the *potential induction of currents*. MRI may induce inappropriate and potentially harmful currents in the DBS system.

This may be due to the gradient switching resulting in varying magnetic fields, or due to the antenna effect induced by RF excitation pulses (Carmichael et al., 2007; Kahan et al., 2015; Boutet et al., 2020a). The currents induced by RF excitation pulses should not trigger neuronal activity as they have a high frequency (MHz range). However, the induced signals due to gradient-switching are lower in frequency (about 1 kHz) which is far above therapeutic stimulation frequencies. Still, currents induced by gradient-switching can measure up to 1.5 V, and thus, theoretically cause paraesthesia or muscle spasms (Georgi et al., 2004; Carmichael et al., 2007; Kahan et al., 2015).

Experimental feasibility challenges

Comparisons of On and Off DBS offer fascinating opportunities to shed some light on the mechanisms of actions of DBS, as well as enrich our understanding of the underlying disease itself. Such experimentation requisites that MR-DBS interactions do not cause instability in the DBS output (such as uncontrolled switching between On and Off), or substantial MR-signal drop-out due to hardware artefacts. Dysfunction of the DBS system has also been addressed by means of phantom studies. While old DBS systems could switch between On and Off, modern models showed stable IPG output during MRI with multiple sequences (Carmichael et al., 2007; Kahan et al., 2015; Boutet et al., 2020b).

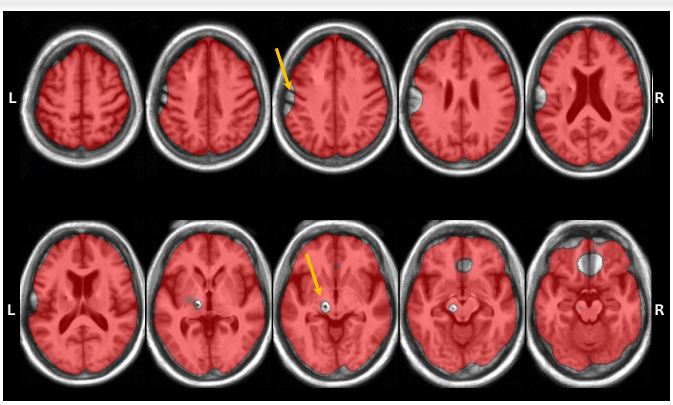


Figure 16. MR-signal loss due to DBS-hardware: group-averaged EPI images from our DBS patients overlaid on a group T1-image in MNI space. Yellow arrows highlight the regions lost to the DBS artefacts (typically in left parietal region and around the electrode tip).

Moreover, susceptibility artefacts created by the metallic objects in the DBS leads and extension cables cause signal loss around the electrode tip and

over the left parietal cortex adjacent to the connection cables (**Figure 16**). The signal loss prevents the acquisition of useful image data from these regions but does not affect other brain regions. This issue has been proven hard to solve (Kahan et al., 2012; Gibson et al., 2016; Boutet et al., 2020b).

Recent developments (after the conduction of the current studies): recent phantom studies with modern DBS devices and MRI hardware have shown that image acquisition, including fMRI sequences, in DBS patients at 3.0 Tesla by using body-transmit coils is safe (Sammartino et al., 2017; Boutet et al., 2020b). These studies found that the difference in temperature between 3.0 Tesla and 1.5 Tesla was less than 1°C. However, hardware-related artefacts are larger at 3.0 Tesla compared to 1.5 Tesla (Boutet et al., 2019).

3.2.2 Study III and IV (patients and surgical procedure)

Study III and IV included the same cohort of patients; 16 ET patients (9 male; average age 70 years, range 52-80 years) chronically treated with DBS in the

Table 3. Patient demographics and DBS parameters

Patient	Sex	Age	Handed-ness	Months since surgery	Family history	Active DBS lead during fMRI	Stimulation parameters (amplitude, pulse width, frequency)
1	M	75	L	27	Yes	Right	2.3 V, 60 µs, 130 Hz
2	F	78	R	70	No	Left	2.7 V, 60 µs, 150Hz
3	F	78	R	36	Yes	Left	1.2 V, 60 µs, 160 Hz
4	F	80	R	54	Yes	Left	1.3 V, 60 µs, 140 Hz
5	F	59	R	43	Yes	Right	1.5 V, 60 µs, 130 Hz
6	M	67	R	17	Yes	Left	1.8 V, 60 µs, 160 Hz
7	M	78	R	34	Yes	Left	1.6 V, 60 µs, 140 Hz
8	F	75	R	37	Yes	Left	2.3 V, 60 µs, 140 Hz
9	M	67	R	36	No	Left	1.8 V, 60 µs, 160 Hz
10	F	69	R	11	Uncertain	Left	1.5 V, 60 µs, 140 Hz
11	M	68	R	44	Yes	Left	1.6 V, 60 µs, 140 Hz
12	F	70	R	59	Yes	Left	1.8 V, 60 µs, 150 Hz
13	M	75	R	59	No	Left	2.2 V, 60 µs, 160 Hz
14	M	57	R	26	Yes	Left	2.3 V, 60 µs, 160 Hz
15	M	52	R	50	Yes	Left	2.5 V, 60 µs, 140 Hz
16	M	77	R	17	No	Left	1.7 V, 60 µs, 140 Hz

cZi (**Table 3**).

The stereotactic neurosurgical technique used in Umeå to implant DBS is based on visual anatomical targeting where the whole procedure is conducted under general anaesthesia and without microelectrode recording or intraoperative test-stimulation. The target in the cZi/PSA was visually identified on stereotactic MRI slightly posteromedial to the posterior tip of the subthalamic nucleus at the level of the maximal diameter of the red nucleus (**Figure 9** in background section "DBS as a treatment for ET: where is the optimal target?"). The location of the electrodes was verified using an intraoperative, or postoperative, CT fused with the preoperative MRI. The patients were implanted with electrode model 3389 Medtronic and a single "implanted pulse generator" (Activa, Medtronic).

fMRI experimental design of study III

Details regarding image acquisition parameters are found in the method section of paper III. The experimental design of study III is depicted in **Figure 17** below. During scanning, the patients performed unilateral tremor-inducing postural holding and pointing tasks as well as rest (right-sided tasks in all but 2 patients), with the stimulation contralateral to the motor tasks turned on and off in two subsequent sessions.

Data analysis of study III

Details on the pre-processing of accelerometer and fMRI data are found in the method section of paper III. Briefly, fMRI data were pre-processed and analysed by using SPM12. Pre-processed fMRI data were analysed voxel-by-voxel by using a GLM, where the experimental conditions for each task during DBS On as well as during DBS Off (postural, pointing and rest) were included as boxcar regressors of interest, convolved with the canonical haemodynamic response function.

At the group-level, we applied repeated-measures DBS-by-motor task 2 x 2 ANOVAs to explore DBS x task interactions (task-dependent modulation), and main effects of DBS (task-independent modulation) within the cerebello-thalamo-cerebral circuit (a binary mask that included all regions

involved in active motor tasks vs. rest, both during On and Off DBS) separately in the case of postural holding and pointing. Regions were considered significant at the threshold of $p \leq 0.05$, FWE cluster-corrected for multiple comparisons within the circuit mask (cluster-defining threshold was set to an uncorrected voxel-based threshold of $p \leq 0.001$).

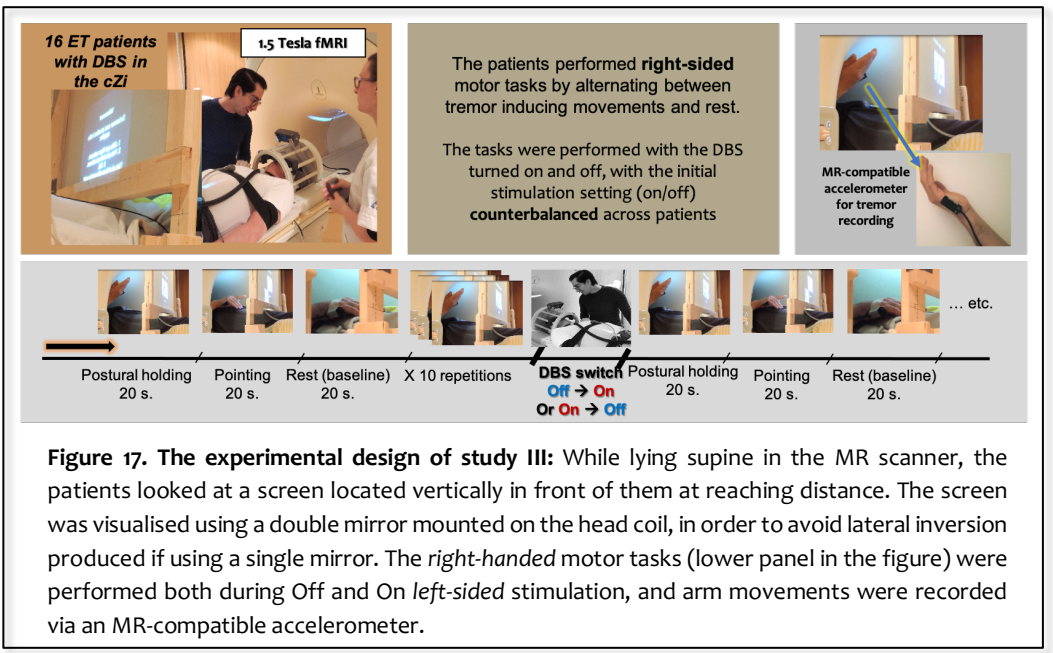


Figure 17. The experimental design of study III: While lying supine in the MR scanner, the patients looked at a screen located vertically in front of them at reaching distance. The screen was visualised using a double mirror mounted on the head coil, in order to avoid lateral inversion produced if using a single mirror. The *right-handed* motor tasks (lower panel in the figure) were performed both during Off and On *left-sided* stimulation, and arm movements were recorded via an MR-compatible accelerometer.

Results of study III

Task-dependent DBS modulation (DBS x task interaction)

In the case of postural holding, task-dependent modulation was evident in four regions: left primary sensorimotor cortex, SMA, right anterior cerebellum (lobule IV and V) and posterior cerebellum (lobule VIII), ($p \leq 0.05$, FWE cluster-corrected). The cerebral effects were located contralateral, whereas cerebellar effects were ipsilateral, to arm movements (**Figure 18**). *Post hoc* t-tests ($p \leq 0.05$, uncorrected) revealed differential DBS effects depending on whether the patients performed postural holding or rest. Specifically, BOLD signal in the primary sensorimotor cortex and cerebellar lobule VIII decreased when performing postural holding while DBS was turned on. In contrast, BOLD signal in the SMA proper and cerebellar lobule V increased during the resting condition when DBS was turned on. There were no statistically significant DBS x task

interaction effects during the pointing task.

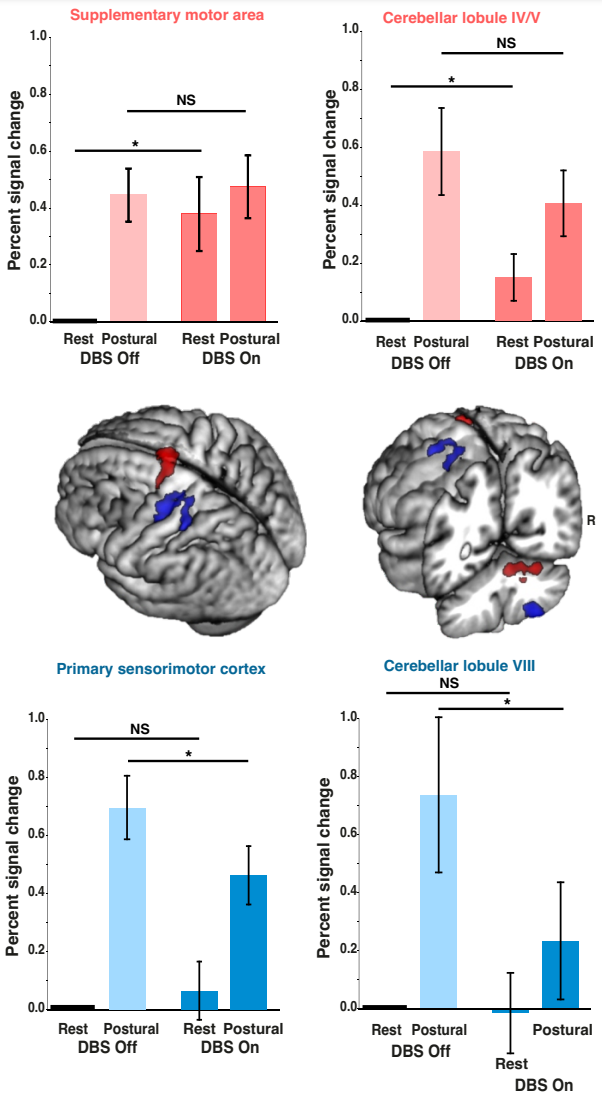


Figure 18. DBS and task interaction effects in the case of postural holding (task-dependent DBS modulation): Brain regions with significant interaction effects (DBS x motor task) on a group-specific rendered anatomical image ($p \leq 0.05$, FWE-corrected), and bar plots with percent signal changes as benchmarked to the rest condition Off stimulation in each region. Brain regions and bar plots showing increased BOLD signal due to DBS are red-coloured, whereas regions and plots with decreased BOLD signal due to DBS are blue-coloured. R = right hemisphere; * = $p \leq 0.05$; NS = not significant ($p > 0.05$). Error bars represent SEM.

Task-independent DBS modulation (main effects of DBS)

Task-independent DBS modulation, calculated as main effects of DBS, was observed in the left premotor cortex as increased BOLD due to DBS in all motor tasks, both in the case of postural holding ($p \leq 0.05$ FWE voxel-

corrected) and pointing ($p \leq 0.05$, FWE cluster-corrected) (**Figure 19**). The main effect of DBS in the case of postural holding did not survive correcting for multiple comparisons at the cluster level, but was statistically significant when correcting for multiple comparisons at the voxel level. There were no significant DBS-related effects in the thalamus.

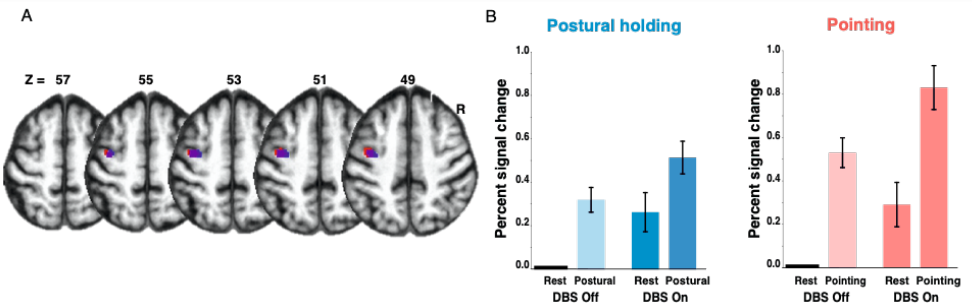


Figure 19. Main effects of DBS (task-independent DBS modulation): (A) Task-independent DBS modulation, calculated as main effect of DBS, in the left premotor cortex (ipsilateral to DBS) in the case of postural holding in blue and pointing in red ($p \leq 0.05$ FWE-corrected) and the anatomical overlap is in purple. For illustrative purposes, the main effect for postural holding is presented at $p \leq 0.001$ uncorrected to more easily compare with effects from the pointing task. Percent signal change as benchmarked to the rest condition Off stimulation in the case of postural holding and pointing in (B). Coordinates (z) are in the MNI space; R = right hemisphere. Error bars represent SEM.

Study design and data analysis of study IV

In study IV, we investigated the effects of therapeutic unilateral (left-sided in all except two patients) cZi-DBS on the resting-state functional connectivity in ET patients by comparing the correlation in BOLD fluctuations in multiple regions between On and Off DBS. Thus, two (~8 minutes) rs-fMRI time-series were collected per patient, one for each stimulation condition (unilateral On and Off cZi-DBS). Details on the pre-processing of fMRI data are found in the method section of paper IV. Briefly, fMRI data were pre-processed using the CONN toolbox, where images were realigned, unwarped and slice-time corrected. Outlier volumes were detected. fMRI data were further denoised by component-based noise correction method where realignment parameters and their quadratic

effects, potential outlier scans, and signal from white matter and cerebrospinal fluid masks were used as confounds. Further, the data were bandpass-filtered (0.008-0.09 Hz). Global signal regression was not applied.

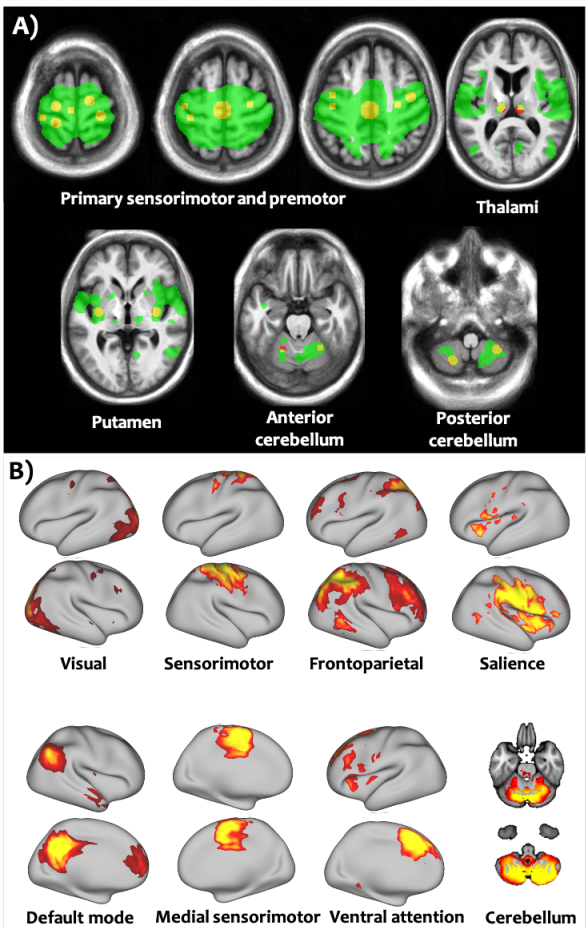


Figure 20. The sensorimotor and other canonical resting-state networks: (A) Sensorimotor network and region of interests (ROIs). The sensorimotor functional connectivity map as extracted from voxel-wise correlation to Yeo-17 left-motor-cortex ROI (green), and the created sensorimotor ROIs (red/yellow), (B) Eight resting-state networks as identified by independent component analysis (ICA)

The sensorimotor circuit was defined based on voxel-based functional connectivity with the Yeo-17 left-motor-cortex ROI (Yeo et al., 2011), and sensorimotor ROIs were created as spheres around relevant peak coordinates from the abovementioned seed-based analysis. Further, dual-regression was conducted to investigate DBS effects on resting-state networks identified through independent component analysis (ICA) (**Figure 20**)

Results of study IV

We found no significant modulation of resting-state functional connectivity from cZi-DBS. This was the case when examining DBS effects on i) widespread functional connectivity between averaged sensorimotor ROIs in the cerebral cortex, thalamus, putamen, and cerebellum (**Figure 21**); ii) hemisphere-specific functional connectivity in ROIs within the aforementioned regions; iii) amplitude of low-frequency fluctuations within sensorimotor ROIs; and iv) multiple well-known resting-state networks as identified with ICA, sensorimotor as well as non-sensorimotor.

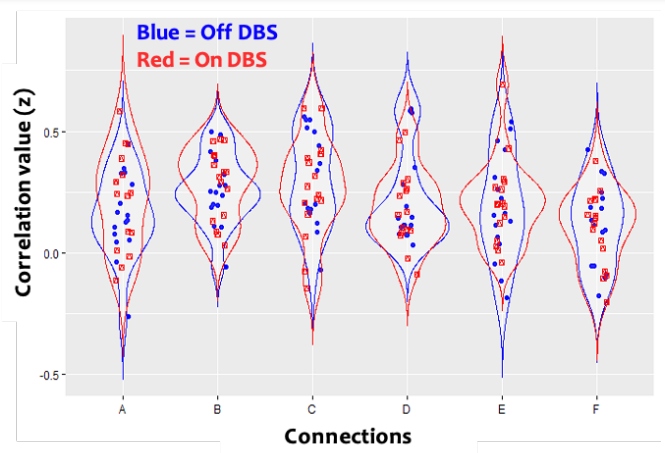


Figure 21. Functional connectivity between averaged sensorimotor ROIs. The diagram illustrated the relatively similar distributions in correlational values between On and Off DBS. Correlation values (z) are shown on the y-axis, and connections on the x-axis: A) thalamus-cerebral cortex, B) putamen-cerebral cortex, C) thalamus-putamen, D) cerebellum-cerebral cortex, E) cerebellum-thalamus, and F) cerebellum-putamen.

4 Discussion

The purpose of this thesis was to probe the sensorimotor system by means of BOLD fMRI to investigate 1) residual somatosensory function in patients with complete SCI, i.e. sensory discomplete SCI as a distinct injury phenotype; and 2) DBS mechanisms of restoring sensorimotor function in ET patients during motor tasks and resting-state.

4.1 Evidence for sensory discomplete SCI

In part 1 of the thesis (studies I and II), we showed somatosensory cortical responses due to blinded somatosensory stimulation well below the injury level in a subset of patients with clinically complete SCI (AIS grade A). We argue that these responses indicate preserved somatosensory conduction across the spinal lesion despite being classified as clinically complete, i.e. *sensory discomplete* SCI. By accounting for potential confounding top-down effects, our results most likely reflect residual afferent-driven cortical activation and, thus, strongly support the presence of discomplete SCI among a subgroup of persons with clinically complete SCI. The studies add to the growing evidence for the existence of discomplete SCIs representing an intermediate degree of injury severity between complete and incomplete SCI (Sherwood et al., 1992; Finnerup et al., 2004; Wrigley et al., 2018). Furthermore, objective assessment of residual function following severe SCI might have a potential explanatory value to the hitherto unexplained variation in complication patterns, such as neuropathic pain and spasticity in patients with clinically complete SCI.

4.1.1 The discomplete phenotype: A new (and old) syndrome

The discomplete syndrome is a SCI phenotype in a subset of patients currently classified as having complete SCIs (AIS grade A). Despite complete sensory and motor loss based on routine clinical examination and according to the well-adopted classification system for SCI (Kirshblum et al., 2011, 2020), this injury phenotype exhibits evidence for preserved motor and/or sensory-signal conduction across the injury. Such preserved signal

conduction can be detected by means of electrophysiological measures such as EEG and EMG, functional brain imaging methods such as fMRI and MEG, or through detailed quantitative sensory testing.

Motor discomplete SCI as evidenced by electrophysiological measures: The term *discomplete* was first coined by Dimitrijević et al. to denote preserved supraspinal (brain) control of below-level reflex activity in complete SCI (Dimitrijević, 1988). This injury entity, together with post-mortem evidence for preserved white matter tracts in complete SCI, was described in the introduction (section "The spinal cord is rarely severed in SCI").

Sensory discomplete SCI as evidenced by fMRI (the findings in this thesis): In this thesis, I have described how task-based fMRI with a strict experimental paradigm can be used to probe residual somatosensory signals from the body parts innervated from below-injury spinal segments in SCI. By adopting this methodology, we provided a proof of concept for the existence of a sensory equivalent to motor discomplete SCI in study I (Awad et al., 2015). We further developed the method to include bilateral, tactile as well as nociceptive stimulation while simultaneously controlling and monitoring mechanical and top-down cortico-cortical confounding effects such as vision and attention. We showed that below-level somatosensory stimulation activated the somatosensory cortex in half of the participants with clinically complete SCI, i.e. representing sensory discomplete SCI (Awad et al., 2020b).

Importantly, in study I, we demonstrated preserved top-down modulation effects on the somatosensory activity, as activation of S1 merely by the visual appearance of touch, as well as the interaction between touch proper and vision. Those results were also intriguing *per se* as they demonstrated residual somatosensory-cortex reactivity as driven by cortico-cortical connections (in that case visual cortex) despite long-standing sensory loss. While such top-down effects are well-known phenomena in the normal sensory system (Mima et al., 1998; Hopfinger et al., 2000; Dionne et al., 2010; Langner et al., 2011; Meyer et al., 2011; Ruff, 2013; Kuehn et al., 2018), it has been unknown whether SCI affects these mechanisms. Stated simply, how does the brain react to seeing the legs being touched after nearly 30 years

of complete sensory loss from the neck level and below? However, demonstrating the preservation of such effects, despite long-standing sensory loss due to clinically complete SCI, was not investigated further beyond the first experiment in study I. We became intrigued by the finding that even touch without vision activated the somatosensory cortex, which we focused on in the subsequent experiments and also in study II.

We were pleased to notice that our description of sensory discomplete SCI (Awad et al., 2015) stimulated further investigations of this notion by other groups (Wrigley et al., 2018). Unfortunately, and similar to previous reports (Ioannides et al., 2002; Sabbah et al., 2002), Wrigley et al. did not properly account for possible top-down confounding effects, such as the attention to, and the expectation of the stimulation. In that study, a group of persons with clinically complete SCI received unilateral somatosensory foot stimulation (repeated right-sided big toe stimulation) and found evidence for sensory discomplete SCI in about half of the participants. The repeated stimulation on the same location (big toe) potentially made the participants attentive specifically to the right big toe as they knew that they would receive such stimulation in the experiment. Furthermore, the authors did not explicitly measure stimulation awareness and it is, therefore, unclear whether some stimulation trials were contaminated by stimulation awareness due to attention, expectation, vision, pain or spasticity etc. (Wrigley et al., 2018).

Thus, when evaluating afferent-driven, bottom-up, somatosensory activation to investigate sensory discomplete SCI, it is of paramount importance to use an experimental design which eliminates or minimises mechanical and top-down cortico-cortical confounding effects such as vision and attention.

Vague perceptions during quantitative sensory testing: With quantitative sensory testing, the somatosensory function is evaluated in response to mechanical and/or thermal stimuli that can activate both large (A-beta) and small (A-delta and C) nerve fibres and their central pathways in the spinal cord and brain. Quantifying the perceptual responses to these stimuli can give an indication of the functional integrity of the dorsal column-medial

lemniscus tract or the spinothalamic tract. Finnerup et al. found that in half of the patients with clinically complete SCI, nociceptive (pressure, pinch, repetitive pinprick, heat or cold) stimuli were accompanied by vague localised sensations (Finnerup et al., 2004). Notably, in that study, SSEPs were absent in all patients including those who reported vague sensations, probably indicating low sensitivity of SSEPs to detect weak residual activations (Finnerup et al., 2004). Another study, specifically testing c-fibre function, found heat- and capsaicin-evoked sensations in 8 out of 24 patients with clinically complete injury, indicating a discomplete lesion of the spinothalamic tract (Wasner et al., 2008).

4.1.2 So what? On the potential clinical relevance of discomplete SCI

The variation in the prevalence of SCI-related conditions and complications among persons with similar injury severity (AIS grade) is only poorly explained. The presence or absence of residual subclinical communication across clinically complete SCIs might add explanatory power regarding these variations in the prevalence of e.g. neuropathic pain, excessive spasticity or the propensity to below-level injuries such as pressure ulcers. One of the initial aims of study II was to investigate whether discomplete injuries were associated with specific clinical and behavioural outcomes. Due to the small sample size, however, such analysis was considered unfeasible. Thus, such putative correlations remain to be assessed. Nevertheless, below I give a brief overview of the hypothetical clinical impact of discomplete SCI regarding the relationship with below-level neuropathic pain, and the restoration of sensorimotor function in SCI.

Below-level neuropathic pain

Pain in SCI can be classified based on its subtype (nociceptive or neuropathic) and its location in relation to the injury level (above-level, at-level, or below-level) (Bryce et al., 2012). While nociceptive pain is a "physiological" pain arising from activation of nociceptors due to actual or potential tissue damage, neuropathic pain is a "pathological" pain caused by a lesion in the somatosensory system (Jensen et al., 2011; Bryce et al., 2012). Neuropathic pain as a result of SCI can be at-level or below-level in relation

to the neurological level of injury. Here, I hypothesise how discomplete SCI might be related to below-level neuropathic pain. About one-third of patients with SCI are unfortunate to develop below-level neuropathic pain (Burke et al., 2017) which is one of the most excruciating and therapeutically refractory pain conditions (Burke et al., 2018). There is a myriad of proposed mechanisms for below-level neuropathic pain which, in general, are related to spinal-tract damage that is followed by spinal grey-matter or supraspinal (brain) maladaptive plasticity (Vierck, 2020).

Spinothalamic tract injury has been proposed to be of particular importance in generating neuropathic pain. While below-level pain is rare following complete spinal transection, a partially injured spinothalamic tract may be a source for pain generation through partially remaining input (Nees et al., 2017; Vierck, 2020). Indeed, 8 of 12 patients with below-level pain following clinically complete SCI had evoked vague pain-related sensation due to below-level c-fibre thermal or Capsaicin-stimulation (Wasner et al., 2008). Along similar lines, spontaneous recovery of spinothalamic tract function (as measured through improved pinprick sensation) was predictive of the development of neuropathic pain and correlated with larger ventral tissue bridges visible on structural MRI (Hari et al., 2009; Pfyffer et al., 2020). However, the degree of injury to the spinothalamic tract alone cannot predict the development of pain, suggesting that injury to the spinothalamic tract is necessary but not sufficient for the development of pain (Finnerup et al., 2007). One interesting theory to reconcile these findings proposes a contributory role of the dorsal column-medial lemniscus tract. This "imbalance hypothesis" suggests that spinothalamic tract lesions in combination with relative preservation of dorsal-column function might play a role in generating below-level pain (Berić et al., 1988; Cruz-Almeida et al., 2012). While this hypothesis still awaits further verification, it is tenable to test especially by means of our experimental design in study II, which provides an objective assessment of the functional integrity of both spinothalamic and dorsal column tracts (Awad et al., 2020b). Finding an anatomical correlate for neuropathic pain is important since it may constitute a therapeutic avenue via functional neurosurgical means such as dorsal root entry zone microcoagulation (Falci et al., 2002) or electrical spinal cord stimulation (Huang et al., 2019)

In the study by Wrigley et al., 2018, however, no statistically significant association was found between below-level neuropathic pain and the existence of *discomplete* SCI. The lack of a statistically significant correlation might very well be rooted in the fact that they did not account for important confounding factors such as expectation, attention and vision (as described above). Those limitations might have impacted the specificity of that study in detecting true discomplete lesions, and subsequently, rendering a correlational analysis unreliable. Hopefully, prospective well-conducted studies will continue to explore the relationship between the discomplete-phenotype and pain as well as other SCI-related conditions.

Restoring the sense of touch and the ability to move in SCI

The demonstration of discomplete SCI has generated interest in restoring the sense of touch by augmenting residual somatosensory connections via a brain-computer interface. In a pioneering study, Ganzer et al. decoded residual somatosensory signals through intracortical electrodes in a patient with sensory discomplete SCI (AIS A) and transformed these signals into conscious perception through intracortically-controlled closed-loop sensory feedback (Ganzer et al., 2020). Furthermore, by means of spinal cord epidural stimulation, the restoration of the ability to walk was demonstrated in some SCI patients (Angeli et al., 2014, 2018; Wagner et al., 2018). Restoring sensorimotor function was enabled by stimulating "functionally silent" but anatomically preserved connections.

4.1.3 Does the existence of discomplete SCI justify a revision of the current classification system?

I argue that the presence of discomplete SCI, as an intermediate degree of injury severity between complete and incomplete SCI, advocates a revision of the current classification system, ISNCSCI (Kirshblum et al., 2014, 2020), by including a sensory and/or motor discomplete subgroup. Dichotomising SCIs into complete and incomplete seems to be relatively crude and insufficient to account for the neurobiological complexity of spinal lesions. One counter-argument against a revision of SCI classification could be "*Beyond scientific objectives, the only reason to consider the concept of discomplete injury as it pertains to classification is that it somehow improves*

either diagnosis or prognosis". That was actually one of the critiques we received from one of the reviewers from a previous submission. Nonetheless, if an injury entity lacks recognition by the scientific community, it will subsequently be neglected and rarely explored for its importance. This can result in a catch-22 situation that seldom brings about scientific or clinical advancement.

First, I believe the ISNCSCI system is good and has, legitimately, merited international endorsement and implementation as a tool routinely used in both clinical management and in research. Further, it has been shown to have a high interrater and intrarater reliability (Savic et al., 2007; Marino et al., 2008). However, there are limits to the explanatory power of the current classification system that crudely dichotomises the lesions into complete and incomplete. For example, as outlined above, it is not known why some patients with clinically complete SCI suffer severe below-level neuropathic pain while others do not (Levi et al., 1995; Burke et al., 2017). Further, the classification system provides limited information about the potential recovery in patients with the same injury severity. About 20 to 30 % of patients with initially complete SCI (AIS grade A) convert to an incomplete SCI, but the current classification system does not provide data to prognosticate which patients are likely or unlikely to recover (beyond the level of injury indicating worse prognosis for thoracic compared to cervical and lumbar injuries) (Chay and Kirshblum, 2020; Kirshblum et al., 2021).

Quantitative methods to evaluate residual tissue sparing after severe SCI have been requested also by the scientific community to better inform the inclusion and evaluation of clinical trials in SCI (Krishna et al., 2014). The heterogeneity of the included SCI patients in clinical trials, e.g. regeneration-promoting interventions, might explain why many trials have "failed" because of the dilution of the therapeutic effect. Residual sensory and motor fibres are of particular importance since many experimental therapies either try to preserve or augment residual axons and their repair (Krishna et al., 2014). The assessment of residual axons after complete SCI would inform therapies seeking to preserve or enhance the function of residual connections, which otherwise would be futile if no remaining viable fibres exist. Accordingly, including discomplete SCI as a distinct entity would guide

the inclusion/exclusion criteria of eligible patients for trials regarding regeneration-promoting interventions (Cadotte and Fehlings, 2013; Ahuja and Fehlings, 2016). Further, it may also guide studies on neuromodulatory treatments, for example, spinal electrical stimulation to restore sensorimotor function in "functionally silent" but anatomically preserved connections (Angeli et al., 2014, 2018; Wagner et al., 2018).

While the current classification is very useful for clinical practice, it is important to note that in many neurological conditions, clinical practice has been influenced and improved by technical advances in diagnostics. There is no reason to believe that SCI should be exceptional in this regard. For example, histopathological methods have been the foundations of the diagnosis and classification of brain tumours for decades. However, recent molecular analyses and genetic sequencing made it possible to disentangle numerous tumours based on the genetic signatures that distinguished them as distinct clusters (Louis et al., 2021a). A previously well-known tumour entity was proved to consist of several distinct diseases, which resulted in immense changes in the classification of these tumours. It is noteworthy that these significant changes in the classification of brain tumours are, for now, hardly met by the clinical care of these patients in terms of therapy and prognosis. In other words, it is still largely unknown whether the new entities generated by the new classification have different prognoses, or should receive different treatment strategies. Nonetheless, the adoption of the new classification and diagnosing criteria were motivated by the fact that upgraded stratification based on biological grounds is necessary to develop new treatments such as molecular-targeted therapies and improve the understanding of the nature of these diseases.

4.1.4 Sensory-driven brain activation without perception

The findings of studies I and II intrigued me into thinking "How can a sensory stimulus reach the brain and *not* produce a conscious experience?!". This question has been proven difficult to tackle since the question "How can a sensory stimulus reach the brain and produce a conscious experience?" is still begging for an answer. Diving into deep waters of consciousness problems was (fortunately) not the aim of my studies. It is nonetheless appealing to briefly reflect upon what is required for stimulus

awareness (or to be conscious of a stimulus). I will try to adhere to the term awareness (stimulus awareness), which perhaps is more accurate to describe the conscious experience of a stimulus. The term consciousness is rather loaded and subject to misinterpretations; it may refer to the level of wakefulness/arousal (as we use in everyday neurological/neurosurgical practice), the experience of stimulus, self-consciousness etc. (Zeman, 2001).

So, what does it take in terms of neuronal activation/engagement in the brain to be aware of a stimulus, in our case a somatosensory stimulus? While no clear answer for this big question exists yet, substantial progress has been made in the field regarding the neural correlates of consciousness (Koch et al., 2016; Mashour et al., 2020; Melloni et al., 2021). However, it is still debated whether awareness emerges from the engagement of localised neural populations related to particular perceptual modality such as S2 for somatosensory perception (Schröder et al., 2019), a parietal hot zone regardless of modality (Koch et al., 2016), or a wide-spread engagement of frontoparietal networks (Naghavi and Nyberg, 2005; Mashour et al., 2020).

In a series of experiments, Romo and colleagues obtained invasive single-unit recordings from multiple sensorimotor regions in monkeys during somatosensory detection tasks and related these recordings to the detection of the stimulus. By applying near-threshold vibrotactile stimuli, sensory perception and subsequently reporting may or may not be produced (Romo and Rossi-Pool, 2020; Romo et al., 2020). To detect a stimulus can be considered as the simplest perceptual experience, and may reasonably constitute a prerequisite for any further conscious sensory processing. Romo et al. recorded from the thalamus (more specifically in VPL), S1, S2, premotor cortices and M1 (Romo and Rossi-Pool, 2020). They showed that subjective sensory experience gradually builds up across cortical areas as signals travel across the somatosensory/sensorimotor hierarchy (de Lafuente and Romo, 2006).

While S1 neurons were found to code the physical presence, or absence, of the stimulus, activity in S1 did not inform whether the subject perceived and reported the stimulation or not (de Lafuente and Romo, 2005). These findings were in accordance with Libet´s early observation where subdural

recordings over S1 during awake neurosurgery showed that the S1-evoked responses to tactile stimulation were present even when the stimulus intensity was below the threshold of stimulus awareness (Libet et al., 1967). The VPL responses behaved similarly to S1, i.e. did not seem to be involved in perceptual coding. However, the thalamic spontaneous firing rate was higher than in S1 and the responses did not represent the sensory input as robustly as S1 (Vázquez et al., 2013). This may partly explain the weak (statistically non-significant) thalamic responses in our studies even during perceived arm stimulations applied above the SCI level. Interestingly, de Lafuente and Romo showed that activity in premotor areas (both medial and lateral premotor cortices) was more correlated with stimulus perception, and thus, highlighted the importance of motor cortex in perceptual judgments (note that M1 neurons did not predict the subjects´ perceptual responses). S2 neurons exhibited an intermediate level as the first site to be predictive of perceptual reports (de Lafuente and Romo, 2006).

The studies described above in monkeys and humans (Romo and Rossi-Pool, 2020) are in agreement with the Global Neuronal Workspace theory, according to which awareness arises when a sensory input reaches a certain activity threshold that leads to ignition of a global network of higher-order sensory and frontoparietal areas. Thanks to this network broadcasting, the sensory input can be made accessible for integrative and executive functions (Mashour et al., 2020)

As stated before, exploring the neural correlates of awareness was not the aim of our studies. Nonetheless, we report afferent-driven somatosensory cortex activation without concurrent awareness in persons with clinically complete SCI. Our findings are in agreement with the previous studies demonstrating that S1 activity does not reflect stimulus awareness. Few SCI participants (with evidence grade 2 for discomplete SCI) showed responses due to nociceptive stimulation in S2, insula, cingulate cortex or ipsilateral S1, without concomitant contralateral S1 activation (**Figure 15**). These responses are probably driven by C-fibre activation with direct thalamo-cortical projections (Stevens et al., 1993; Craig, 2004; Dostrovsky and Craig, 2020).

Based on these findings, it may be concluded that S1 activation perhaps is important but not sufficient for somatosensory awareness. S1 does process and convey the signal to other "higher-order" cortical regions where further processing of "S1-processed" signals generates awareness. Perhaps, a stimulus is accompanied by awareness when the brain has the possibility to act upon it for generating adaptive (motor) behaviour, directly or later.

4.1.5 Limitations and methodological considerations (study I & II)

In study I, responses due to touch were not only limited to S1 but also S2, BA 5, insula and anterior cingulate cortex (experiment 1), S1 and BA 5 (experiment 2), and in S1 (experiment 3). Overall, these effects were weak and not consistent across the 3 experiments. This might be due to the experimental differences between the experiments, which evolved from examining the effects of touch as well as its interaction with vision (experiment 1) to only examining the effects of touch with a focus on excluding vision and other confounding factors such as attention. Further, the main effect of touch across all conditions (including touch + vision tasks) was calculated in experiment 1. Thus, the possibility of contamination of visually-driven responses within "main effect of touch" cannot be confidently excluded. In retrospect, I am also self-critical about the analytical/statistical approach we adopted in this study. Given the specific question regarding somatosensory activation, a restricted analysis with focus on somatosensory brain regions should be more appropriate than whole-brain analyses that we adopted instead.

The experiments in this study are perhaps best to be considered as pilot trials to provide a proof that discomplete SCI at least could be a possibility within clinically complete SCI. Further, it provided a description of an experimental paradigm to test the concept of discomplete SCI. While it could be argued that pilot studies do not need to get published, this particular pilot study was intended to encourage larger-scale studies and raise awareness of the critical issue regarding controlling top-down modulation effects that otherwise could contaminate somatosensory cortex activity when pure afferent-driven (bottom-up) activation was being

investigated. Indeed, the study encouraged us and other groups (Wrigley et al., 2018; Awad et al., 2020b; Wahlgren et al., 2021) to further investigate the existence of discomplete SCI, a concept that was more or less forgotten for more than 20 years.

In the subsequent study (II), we adopted an experimental design to increase both sensitivity and specificity regarding the detection of discomplete SCI. To increase the sensitivity, we used a somatosensory stimulation paradigm that included bilateral stimulation on multiple dermatomes. Further, both tactile (touch) and nociceptive stimulation were used to assess the functional integrity of two different spinal tracts (dorsal column-medial lemniscus tract and the anterolateral spinothalamic tract). To increase the specificity for detecting discomplete SCI due to below-level afferent-driven stimulation, we used an experimental setup to 1) prevent the potential transmission of stimulation movement from insensate to sensate regions, 2) prevent the participants from seeing their body or the action of the experimenter, and 3) exclude top-down effects. The order of the stimulation trials was random so that the participants could not predict what stimulation condition was used (for the legs) or coming next. Thus, we minimized the preparatory and attention bias to the stimulation in our study. We further monitored the stimulation awareness (by PAS) on a trial-by-trial basis on liberal grounds. Restricting the analysis to ROIs specifically associated with somatosensory processing increased both the sensitivity through improving statistical power (by reducing the number the multiple comparisons), and also the specificity by focusing on regions specifically involved in the task at hand (for example, right-leg area of S1 due left-leg stimulation).

Despite that, both false negative and false positive findings could have contaminated some of the results. For example, instructing the participants to report whatever vague sensations they experience (as PAS =2) on liberal grounds decreased the statistical power of the study as trials with PAS > 1 were excluded from the analysis. In most cases, the participants could not explain why they reported vague sensations. Future studies may include more specific instructions about the PAS. However, monitoring stimulation awareness is important to detect potentially false positive results driven by

vision, attention, mechanical stimulation from sensate regions, spasticity, or autonomic reactions. For example, participant 9 reported spasticity in the hands due to a few trials of below-level nociceptive stimulations. These trials were reported as PAS = 2 (weak experience) and were excluded subsequently. However, the results based on the trials with PAS = 1 (no experience) showed S1 activation in the leg area, but also bilaterally in hand areas of S1 which might have resulted from spasticity from the hands (**Figure 15**). This case illustrates the risk of potentially false positive results, and the importance of closely monitoring the participants´ stimulation awareness during fMRI.

Both studies I and II are small studies with limited sample sizes. Study I is to be considered a case report demonstrating that sensory discomplete SCI at least is a possibility in a subset of patients with clinically complete SCI. Study II also was small (N =11) which precluded further investigation of potential correlation between discomplete SCI and SCI-related conditions such as pain.

Clinical utility of fMRI to diagnose sensory discomplete SCI:

The clinical utility of a diagnostic or prognostic method depends on its ability to provide clinically useful information on a patient-by-patient basis. Obviously, CT is a gold standard method to diagnose intracerebral haemorrhage not because of its ability to detect bleedings at the group level. When it comes to everyday practice, the clinical applications of fMRI are still limited to presurgical sensorimotor and language mapping despite nearly 30 years of investigations in neurological and psychiatric disorders (Bullmore, 2012; Stippich, 2015). This is mostly because fMRI historically has been used to describe group, rather than individual, differences between patients and controls. What makes fMRI an invaluable, and currently a standard, method for presurgical mapping is its reliability to map brain sensorimotor and language functions in the individual patient. In analogy to that, the method described in this thesis to investigate SCI discompleteness is objective and based on a patient-by-patient basis highlighting its clinical feasibility in that respect.

4.2 Cerebello-cerebral modulation by DBS

In study III (Awad et al., 2020a), we used task-based fMRI to explore DBS effects in ET patients while they performed right-handed motor tasks with and without tremor, during On and Off cZi/PSA DBS with therapeutic stimulation parameters. DBS was demonstrated to exert both task-dependent as well as task-independent effects on the sensorimotor circuit in ET. Task-dependent (DBS x task interaction) effects were seen in sensorimotor cerebello-cerebral regions: the primary sensorimotor cortex, SMA proper and cerebellum. Differential DBS effects were found depending on whether the patients performed tremor-inducing postural holding or rest. Specifically, BOLD signal in the primary sensorimotor cortex and cerebellar lobule VIII decreased when performing postural holding while DBS was turned on. In contrast, BOLD signal in the SMA proper and cerebellar lobule V increased during the resting condition when DBS was turned on. Task-independent effect was observed as activity increase in the lateral premotor cortex during all motor tasks including rest. There were no DBS x task interaction effects during pointing tasks.

In study IV, rs-fMRI was used during On and Off stimulation in the same group of ET patients with the aim to investigate DBS effects on resting-state function connectivity. We show that DBS does not modulate functional connectivity of the sensorimotor circuit or other resting-state networks.

4.2.1 What is being stimulated, really?

The DBS electrodes are placed in the PSA, slightly posteromedial to the posterior tip of the subthalamic nucleus at the level of the maximal diameter of the red nucleus (Blomstedt et al., 2009a). The PSA (sometimes also called the field of Forel) contains several structures including the cZi, the cerebello-thalamic fibres and prelemniscal radiation (Gallay et al., 2008; Blomstedt et al., 2009b; Guridi and Gonzalez-Quarante, 2021). Here, the cZi is the target that we aim for during surgery. However, the effects of DBS in alleviating tremor are proposed to be mediated through modulation of the cerebello-thalamic fibres in the PSA (Fytagoridis et al., 2016; Nowacki et al., 2022). Further, there are indications for a correlation between tremor control and nearness to the cerebello-thalamic tract as shown by MRI tractography

(Klein et al., 2012; Coenen et al., 2014, 2020; Groppa et al., 2014; Nowacki et al., 2022). Nonetheless, DBS exerts its effect through volumetric electric modulation that includes several millimetres around the active contact(s), and that volume depends on the stimulation parameters and tissue properties. It is not entirely clear how the electric field is spreading within the tissue, and currently, we only have estimations about the "volume of tissue activated" based on computational modelling (McIntyre et al., 2004; Astrom et al., 2015). It is, thus, likely that the electrical currents also reach the cZi.

The Zi is a diencephalic nucleus that has extensive connections with the thalamus, cerebral cortex, basal ganglia, brainstem and spinal cord in rodents. In rats, it has been shown to be involved in multisensory integration, visceral functions, attention, arousal, postural control and locomotion (Mitrofanis, 2005; Wang et al., 2020). If the Zi provides the same functions in humans as in rats, then modulating its activity by means of DBS would result in terrible stimulation-related side effects, but this does not seem to be the case. Actually, the target has a very favourable clinical profile regarding excellent tremor control without side effects on e.g. cognitive function or speech intelligibility (Fytagoridis et al., 2012; Philipson et al., 2019; Sandström et al., 2020). Thus, the DBS currents are probably only reaching the caudal subsection, cZi, which (in rats) has been assigned motor functions (Mitrofanis, 2005). The projections from Zi are mainly GABAergic (inhibitory) (Lin et al., 1990; Mitrofanis, 2005), and it has been speculated that DBS might stimulate these GABA-ergic connections to the cerebello-cerebral circuit and basal ganglia to alleviate tremor and parkinsonism (Plaha et al., 2008). While these speculations await further empirical support, there is a growing body of evidence for the involvement of the cerebello-thalamo-cerebral circuit in tremor generation and relief due to DBS, as has been outlined above.

4.2.2 How does DBS modulate the activity in the cerebello-cerebral circuit?

DBS effects on functional brain activity during different motor tasks (study III)

The **main effect of DBS was detected as increased BOLD in the left lateral premotor cortex** (same side as active DBS) during all motor tasks. While the role of the premotor cortex is not well understood in the pathophysiology of ET, it has been considered to be part of the dysfunctional synchronised circuit involved in tremor generation. Indeed, EEG/MEG studies reported coherence between central oscillations over the premotor cortex and peripheral tremor oscillations (Schnitzler et al., 2009; Muthuraman et al., 2012). In functional neuroimaging studies, the premotor cortex has been shown to exhibit abnormalities in blood flow and BOLD signal during rest and motor tasks (Buijink et al., 2015a; Colebatch et al., 1990; Jenkins et al., 1993), and decreased functional connectivity with the cerebellum (Neely et al., 2015; Lenka et al., 2017). Moreover, dysfunctional GABAergic neurotransmission, as shown by increased ^{11}C-flumazenil binding to GABA-receptors, has been observed in the premotor cortex, along with the dentate and the ventrolateral thalamus (Boecker et al., 2010).

However, it is debated in the MRI tractography literature whether tremor relief is achieved via modulating cerebello-cerebral fibres terminating in M1 or premotor cortices (Akram et al., 2019). Some studies claim that tremor relief is best achieved by targeting cerebellar fibres connecting the dentate nucleus to M1 (Akram et al., 2018; Riskin-Jones et al., 2021), while others claim connections to premotor cortices to be a better predictor for tremor relief (Middlebrooks et al., 2018). This issue cannot be resolved by the available tractography studies as they seem to confuse M1 with premotor cortices since they use anatomical, rather than functional, segmentation of the cerebral cortex. For example, M1 is assumed to equate the whole precentral gyrus, which is not accurate (see section "Motor cortex" in the introduction). Anatomical tracing studies in monkeys do not provide evidence in favour or against either argument. Indeed, both M1 (Kelly and Strick, 2003) and premotor cortices (Akkal et al., 2007; Hashimoto et al., 2010) are targets of cerebellar fibres through the ventrolateral thalamus (Schell and Strick, 1984). Interestingly, evidence derived from tremor alleviation due to various lesions may support the involvement of the premotor cortex in tremor generation. Certainly, a small stroke limited to the premotor cortex resulted in tremor disappearance in an ET patient (Kim et al., 2006). Furthermore, reports on motor-cortex resections to treat

tremor during the pre-stereotactic era included BA 6 in the resection for better tremor control (Bucy and Case, 1939; Klemme, 1940)

The primary sensorimotor cortex and cerebellar lobule VIII exhibited decreased BOLD due to DBS during the postural holding task, which might reflect tremor reduction *per se*. Indeed, both cerebellum (Bucher et al., 1997; Broersma et al., 2016) and the primary sensorimotor cortex (Neely et al., 2015; Broersma et al., 2016) have been shown to exhibit increased activity during tremor-inducing motor tasks in ET patients as compared to controls. Increased activity that accompanies conditions with tremor, and similarly decreased activity in conditions with less tremor, may be discarded as merely reflecting differences in proprioceptive input to the brain. However, functional imaging studies in ET showed abnormal tremor-related activity in primary sensorimotor and cerebellar regions even when compared with passive tremor (passive wrist oscillations induced by an experimenter) in patients as well as with passive tremor and "mimicked" tremor in controls (Bucher et al., 1997; Boecker and Brooks, 2008; Broersma et al., 2016). Such control tasks were designed to reproduce the proprioceptive input resulting from involuntary tremor. Thus, increased motor task-related activation in ET patients is not only due to different proprioceptive tremor-input but also represents underlying functional abnormality, and it seems that DBS normalises this overactivity in the primary sensorimotor cortex and cerebellar lobule VIII.

Furthermore, considering the motor and sensory circuits as separate systems is an obvious oversimplification as sensory input is known to be crucial for optimal motor output (Johansson and Westling, 1987). The importance of sensorimotor integration in tremor generation is evident from neurosurgical observations during thalamotomy where the effective target (VLp/Vim) for tremor elimination represented the part of the thalamus receiving proprioceptive input (Tasker et al., 1987). Indeed, the VLp receives both sensory and cerebellar inputs, and therefore, may represent one of the locations for sensorimotor integration (Stepniewska et al., 2003). Thus, afferent inputs might be as important as the efferent driving output in tremor generation.

The BOLD signal in **the SMA and cerebellar lobule V** increased during the resting task, but not active motor tasks, due to DBS. These effects are somewhat difficult to interpret but are partially consistent with two previous studies. A previous PET study demonstrated increased blood flow in the SMA (Perlmutter et al., 2002), and the intraoperative fMRI study by Gibson et al. showed increased BOLD signal in all cerebello-thalamo-cerebral regions (including cerebellar lobule V and the SMA) due to DBS (Gibson et al., 2016). This DBS-induced activation in the SMA and cerebellar lobule V might also be perceived as reflecting reduced motor task-related activation but through increasing the baseline activity-level during rest. The SMA has been hypothesised to be involved in a compensatory mechanism that mitigates tremor oscillations originating from the cerebellum. This notion has been claimed in one study based on the findings of grey matter increase in the SMA as opposed to decrease in cerebellar grey matter (Gallea et al., 2015). Our finding of DBS-associated BOLD signal increase in the SMA during rest cannot corroborate a compensatory function of the SMA. Furthermore, grey matter changes in the SMA (and other regions) have not been replicated in subsequent larger studies or metanalyses (Luo et al., 2019).

Differential DBS modulation of the anterior (lobule V) and posterior (lobule VIII) is intriguing. The cerebellum has double representations of sensorimotor functions in each hemisphere; lobules I-VI in the anterior cerebellum, and lobule VIII in the posterior cerebellum (Grodd et al., 2001; Habas et al., 2004; King et al., 2019). It has been difficult to disentangle the functions of these sensorimotor representations. However, it has been suggested that the anterior cerebellum (lobule V) is engaged in both simple and complex arm movements, but exhibits increased recruitment with increased complexity (Manto et al., 2012). On the other hand, the posterior sensorimotor cerebellum (lobule VIII) was shown to be involved in the coordination of more complex movements such as out-of-phase movements (Habas et al., 2004).

Our task-dependent effects (**Figure 18**) indicate that cerebellar lobule V is part of the sensorimotor network during On DBS (as shown by a relative increase in postural holding vs. rest). On the other hand, cerebellar lobule VIII does not seem to be part of the network during On DBS (non-significant

difference between postural holding and rest). I speculate that ET, perhaps, is specifically associated with dysfunction in the posterior cerebellum. This speculation is supported by two studies. The posterior cerebellum exhibited increased tremor-related activity during tremor-inducing tasks (Broersma et al., 2016). Further, the posterior cerebellum showed decreased functional connectivity with M1, which also correlated with tremor severity during motor tasks (Buijink et al., 2015b).

DBS effects during resting state (study IV)

Study IV is the first rs-fMRI study examining the effects of DBS on resting-state functional connectivity in ET. We showed that cZi-DBS does not modulate resting-state functional connectivity in ET. This was demonstrated when examining DBS effects on i) widespread functional connectivity between averaged sensorimotor ROIs within the cerebral cortex, thalamus, putamen, and cerebellum; ii) hemisphere-specific functional connectivity in ROIs within the aforementioned regions; iii) amplitude of low frequency fluctuations within sensorimotor ROIs; and iv) multiple well-known resting-state networks, sensorimotor as well as non-sensorimotor. In summary, DBS did not modulate resting-state functional connectivity in ET. The lack of previous resting-state functional imaging studies (fMRI or PET) that assess DBS effects in ET imposes some difficulties when relating to other studies. However, the conduction of this study was motivated by other rs-fMRI studies in ET that, despite their heterogeneity, have demonstrated altered resting-state functional connectivity within the cerebello-thalamo-cerebral circuit in ET as compared to controls (Fang et al., 2015, 2016; Gallea et al., 2015; Pietracupa et al., 2021). ET has, further, been shown to be associated with altered functional connectivity outside the sensorimotor circuit, e.g. the default mode and frontoparietal network (Benito-León et al., 2015; Fang et al., 2015).

DBS modulation is action-dependent

The lack of DBS modulation during resting-state (study IV), in combination with demonstrated effects on the cerebello-thalamo-cerebral circuit during motor tasks (study III), suggest an action-dependent modulation of DBS. In study III, differences in BOLD-signal amplitude during DBS On versus Off

were assessed for a postural holding task, a pointing task, and a resting control task. DBS led to reduced activity in primary sensorimotor cortex and cerebellar lobule VIII during postural holding but not during rest. These results are in agreement with the findings in study VI of no DBS effects during resting state. However, in study III we found DBS-related activity increase in left premotor cortex during all tasks (including rest), and also selective activity increase during the rest condition in the SMA and cerebellar lobule IV/V.

Still, functional brain activity at rest (study III) and resting-state functional connectivity (study IV) are distinct from each other. Task effects capture transient modulation of BOLD signal, whereas functional connectivity might reflect stable functional networks of regions that typically are co-activated and minimally influenced by brief interventions. Therefore, DBS-induced modulation of the BOLD-signal amplitude during rest could reflect elements of motor preparedness/planning and task-set switching (i.e., getting prepared for the upcoming postural holding task and task set switching from the pointing task to rest) (Sakai, 2008; Baker et al., 2011) that are not taxed during a long period of rest in resting-state fMRI. Thus, DBS modulation during rest as well as motor tasks in study III might reflect multiple aspects of action, and we therefore propose that DBS modulation of the sensorimotor circuit in ET is action-dependent. This notion is coherent with the fact that DBS alleviates tremor, which in ET is action tremor that is present during action and rarely during rest (Cohen et al., 2003; Bhatia et al., 2018).

Null findings

Here, I elaborate on potential reasons behind null findings in studies III and IV. There were **no DBS-related effects in the thalamus** in study III, which was partly unexpected given the central role of the thalamus in ET pathophysiology and presumed DBS mechanisms. Further, two previous smaller functional imaging studies showed increase in blood flow and BOLD signal due to DBS (Perlmutter et al., 2002; Gibson et al., 2016). There are important differences between those two previous reports and study III. While our DBS patients were awake and performing different motor tasks, the previous studies were conducted during rest (Perlmutter et al., 2002) or

general anaesthesia (Gibson et al., 2016). Moreover, the surgical targets (and subsequently the stimulated structure) were slightly different: cZi/PSA here and thalamic Vim in the previous studies. In study III, the activity in a significant thalamic cluster was still possible to detect and, did indeed exhibit increased BOLD signal due to active motor tasks (postural holding/pointing vs. rest) but no DBS-related effects. However, potential DBS-effects might be located within a region where we had MR signal loss around the DBS lead while passing through the ventrolateral thalamus.

While the main DBS effect was evident, there were **no significant DBS-by-task interaction effects during the pointing condition**. The pointing tasks were included to assess potential intention tremor if present in some patients. However, the experimental design of this task was probably suboptimal with too many pointing trials within each block, not allowing sufficient time for intention tremor to develop. Another, perhaps speculative, reason for the lack of interaction effects might be related to a balance between the complexity of the task and the ability to detect effects related to an experimental manipulation. Pointing toward a target maybe engaged sensorimotor regions to a similar extent during On and Off DBS, and thus, rendered the possibility to measure, presumably subtle, DBS effects on the activity of these regions.

Study IV, on the whole, represented a null-finding study, showing that DBS did not modulate resting-state functional connectivity in ET. The null findings could of course be a result of the small sample size, and the study might simply have been underpowered to detect potential effects of interest. However, the distributions of ROI-ROI correlation values were relatively similar during On and Off DBS, which implied that a potential modest effect would require a much larger sample size to be detected. Moreover, negative findings were demonstrated despite (deliberately) liberal statistical testing, and thus, unlikely to represent false negative findings. Moreover, the negative findings were demonstrated even with different constellations of connections, from averaged-ROI-connections to capture potential widespread changes, to individual ROI-connections to capture potential specific changes between ROIs. Also, no statistically significant effects were detected in the dual-regression analysis which was

based on ICA, a data-driven method for identifying networks independent on the choice of ROIs (Stone, 2002; Nickerson et al., 2017).

4.2.3 Hypothetical architecture for tremor generation and suppression

DBS was found to modulate the activity of several regions within the cerebello-cerebral circuit in a rather complicated manner with increased and decreased activity (as measured by BOLD fMRI), both dependent and independent on the motor task at hand. Here, I will attempt to describe these effects based on an integrated view that considers the function and anatomy of the cerebello-cerebral circuit in normal and pathological action generation.

As described in the introduction, the cerebello-cerebral circuit, consisting of reciprocal connections between the cerebellum and cerebral cortex, is thought to be dysfunctional in ET (Schnitzler et al., 2009; Raethjen and Deuschl, 2012; Helmich et al., 2013) but it is also involved in normal sensorimotor control (Gross et al., 2002; Schnitzler and Gross, 2005; Raethjen and Deuschl, 2012). Movements, although perceived as smooth, consist of smaller movement discontinuities (micro-movements) at a frequency of 6–12 Hz (Vallbo and Wessberg, 1993; Kakuda et al., 1999). By means of MEG with concomitant EMG, movement discontinuities have been shown to originate from the primary sensorimotor cortex but are sustained by a cerebellar drive through the thalamus to the premotor cortex (Gross et al., 2002). Motor output discontinuities represent alternating agonist and antagonist bursts, the timing and the amplitude of which are controlled by the cerebellum to produce smooth and coordinated movements (Schnitzler and Gross, 2005; Filip et al., 2016). Fractionating the movement in the brain perhaps is a convenient way to control and correct ongoing motor output as the bursts of agonist/antagonist muscles are continuously evaluated and corrected (Gross et al., 2002). What drives this circuit into pathological tremor oscillations is yet unknown. Below, I argue that a subcircuit, engaging the posterior cerebellum and motor cortex, might be involved in redundant movement bursts, when they are in fact no longer needed.

Postural tremor, a hallmark of ET, was probed in study III by instructing the

patients to hold a steady posture both during On and Off DBS. If we, for argument's sake, dichotomise movements into simple and complex[7] a postural holding is to be considered relatively simple; basically maintaining postural holding of the arms "motionless" against gravity. Once a certain posture is reached, there is no further need for adjustments such as correcting the position or trajectory according to incoming sensory signals. This notion is particularly plausible regarding the function of the cerebellum, which seems to be engaged in providing the motor cortex with corrective signals if the sensory feedback from a movement does not match the predicted sensory state (that the cerebellum already has generated based on the efference copy of the motor command) (Wolpert et al., 1998; D'Angelo, 2018; Kandel et al., 2021). When maintaining a posture, the sensory input matches the predicted "desired" sensory state, and thus, the cerebellum does not need to be engaged during the maintenance of posture. Indeed, disrupting cerebellar function with transcranial magnetic stimulation induced errors during goal-directed movements, but not when the arm was held in a stable position, i.e. when updating the sensory state was not required (Miall et al., 2007; Therrien and Bastian, 2019). Thus, the engagement of the cerebellum in postural holding is perhaps abnormal *per se* and may explain the increased activity in ET patients while holding a posture (Bucher et al., 1997; Broersma et al., 2016). The involvement of the posterior cerebellum is particularly suspicious for being pathological. Indeed, while the anterior cerebellum (lobule V) is engaged in both simple and complex arm movements, the posterior cerebellum is only recruited with increased movement complexity in terms of higher demands on coordination (Habas et al., 2004; Manto et al., 2012).

Postural holding is arguably a function of the motor cortex, both in terms of reaching a posture (which initially also involves the cerebellum) and maintaining it by sustaining the desired posture and inhibiting unwanted potentially perturbing movements. Indeed, cortical stimulation of the precentral gyrus (including premotor and M1) not only moves the limb, but also produces specific postures (Graziano et al., 2002a). Further, much of

[7] which is not uncommon in neuroscience literature

the activity of motor cortex (mostly premotor cortex) is devoted to inhibit actions, which may include signals perturbing a posture while trying to hold still (Ebbesen and Brecht, 2017). It can thus be speculated that postural tremor is generated by a combination of inappropriate tremor bursts from the posterior cerebellum, as well as suboptimal premotor control permitting such signals to perturb ongoing postural holding.

Perhaps, DBS is specifically modulating cerebello-thalamic fibres originating from the posterior cerebellum to premotor and primary sensorimotor cortex. The hypothesis that DBS is modulating this specific "posterior cerebellum - ventrolateral thalamus - motor cortex" subcircuit may explain why DBS, and thalamotomy/subthalamotomy, are well-tolerated and do not regularly cause ataxia (Groppa et al., 2014). Indeed, strokes of the sensorimotor part of posterior cerebellum only cause minor or no motor deficits (Stoodley et al., 2016).

Accordingly, DBS is alleviating tremor partly by potentiating (restoring?) premotor control over the sensorimotor circuit, making it less susceptible to tremor entrainment. This was demonstrated by task-independent DBS-induced BOLD-signal increase in the left premotor cortex (main effect of DBS) in study III. This effect is consistent with the direction of the signals responsible for intermittent motor output, and pathological tremor oscillations, i.e. signals originating from the cerebellum and reaching the primary sensorimotor cortex after passing through the thalamus and the premotor cortex (Gross et al., 2002; Schnitzler et al., 2009). However, DBS also seems to downregulate the tremor-generation *per se* through task-dependent modulation of the cerebello-cerebral circuit, especially decreasing the BOLD signal in posterior cerebellum (lobule VIII) and primary sensorimotor cortex. The results illustrate the complexity of DBS mechanisms by demonstrating distant changes in the cerebello-cerebral circuit that partly reflect potentiating the circuit´s control mechanisms, and also downregulating tremor-generation mechanisms.

4.2.4 Limitations and methodological considerations (study III & IV)

Study III and IV are the first to use fMRI to investigate DBS effects in awake

ET patients with fully-implanted DBS-systems and by using therapeutic stimulation parameters. Despite the novelty of these studies, the combination of DBS and fMRI was technically challenging and accompanied by limitations that need to be addressed. Elaboration on specific negative findings was handled previously (section "Null findings" above). Here, I focus on general technical limitations.

Although studies III and IV are among the largest cohorts with such a unique combination of DBS and fMRI, the sample sizes are still small. The studies might have been underpowered to detect effects of interest such as DBS x task interaction during the pointing task, DBS-related effects in the thalamus, or DBS-effects on resting-state functional connectivity. Beyond null-findings, underpowered studies might also overestimate detected effect sizes (Button et al., 2013). To partly tackle this issue, we restricted our primary analyses to brain regions known a priori to be relevant for ET (sensorimotor cerebello-thalamo-cerebral regions). This approach aimed to increase the sensitivity of the analysis by reducing the numbers of multiple comparisons when compared to whole-brain analysis.

Due to the safety concerns that were addressed previously, we adhered to strict MR imaging protocol that included lower magnetic field strength (1.5 Tesla), use of RF transmit/receive head coil, big voxels (3.44 x 3.49 x 4.4 mm), and adjusted imaging parameters to keep the SAR values below 0.1 W/kg. Such adjustments came at the cost of compromised image quality with lower signal-to-noise ratio as a result. The protocol we used was based on knowledge about DBS-MRI interactions at the time of data collection (Georgi et al., 2004; Carmichael et al., 2007; Kahan et al., 2015). However, recent studies have informed us that improved image acquisition, such as using 3.0 Tesla scanners and body-transmit coils, is feasible and safe in DBS patients (Sammartino et al., 2017; Boutet et al., 2020b).

Another important (general) limitation in DBS-fMRI studies is the signal loss adjacent to DBS-hardware. Susceptibility artefacts due to metallic components in the DBS electrodes and extension cables result in fMRI signal loss, most prominent at the electrode tip and over the connection between the electrode and extension cables (often left parietal region).

Unfortunately, this issue is common in DBS-fMRI studies and it has been challenging to overcome (Kahan et al., 2012, 2019; Gibson et al., 2016; Boutet et al., 2020b). As a result, it was not possible to collect data from the DBS target itself (cZi) and the left parietal cortex in my studies. Signal loss in the left parietal cortex was particularly unfortunate since it impacted relevant parts of the left sensorimotor cortex during right-sided arm movements (study III) and resting-state sensorimotor network (study IV). Further, since we only used left-sided DBS, signal loss specifically impacted the "stimulated" cerebral hemisphere. Other studies focused on collecting data from the right-hemisphere (less affected by hardware-related artefacts) by adopting left-sided motor tasks when patients are bilaterally stimulated (Kahan et al., 2012, 2019), or only used right-sided DBS (Gibson et al., 2016). We did not make use of such solution because the majority of our patients (10 out of 16) had only unilateral left-sided DBS. Future studies should address this issue by optimising the imaging parameters to minimise the artefacts, but there will likely always be some signal loss due to DBS-hardware.

For the time being, the research questions or hypotheses need to be carefully proposed in relation to what is feasible to obtain with DBS-fMRI. For example, questions regarding how DBS modulates the activity of the stimulated target cannot be addressed with fMRI due to signal loss. Further, the low temporal resolution of fMRI signal precludes the detection of fast effects, such as tremor-oscillations. Most importantly, fMRI is an indirect proxy for neural activation, and also a relative measure by which we cannot fully disentangle excitatory and inhibitory processes (Logothetis, 2008). With fMRI, however, global (whole-brain) changes at the network-level due to DBS are possible to assess with relatively good spatiotemporal resolution.

To conclude, it should be pointed out that the limitations and challenges - outlined above do not make DBS-fMRI unfeasible. On the contrary and as study III and IV illustrate, fMRI in combination with DBS can provide a unique imaging opportunity of functional brain activity during disease-relevant tasks (tremor-provoking tasks), On and Off DBS, with high spatial resolution and whole-brain coverage.

4.3 Separating sensory and motor systems: An artificial divorce

In this thesis, and as often done in neuroscience, the sensory and the motor system are handled rather separately. Regardless of the (sometimes necessary) separation for pragmatic reasons, it should be underscored that it represents an over-simplification. The sensory and motor systems are fundamentally intertwined at the anatomical, functional and subsequently the conceptual level. Our actions i.e. movements are guided by our sensorium, and vice versa. Without sensation, our movements are severely disabled, and without movement, we can hardly collect useful sensory input (Johansson and Westling, 1987). Although partially detached at some levels along their pathways, the communication between the motor and sensory systems is widespread and takes place at multiple levels along their hierarchies. This sensorimotor crosstalk spans from the spinal level where sensory input can generate motor reflexes, to complex sensory-guided movements at the cortical levels as a result of heavy communications between sensory association areas and premotor cortices (Haaland et al., 2017).

The conditions that were handled in this thesis are no exception regarding the tangled nature of sensory and motor systems. Indeed, clinically complete SCI results in equal sensory and motor disruption. Conceptually, residual somatosensory input, as described in sensory discomplete SCI, is only relevant when proved to be of value for modulating behaviour in an adaptive manner such as predicting sensorimotor recovery, elucidating pain mechanisms that can be targeted, or restoring sensorimotor function by neuromodulation. Along similar lines, sensory input must be crucial for tremor generation in ET. Indeed, sensorimotor integration is the functional foundation of the cerebello-cerebral circuit that is responsible for tremor generation. Sensory input from movements sets the circuit into tremor oscillations, and modulating sensorimotor nodes along the circuit by DBS alleviates that tremor.

4.4 Future prospects

In research, new questions tend to arise from obtained answers, and this thesis is no exception in this regard.

* The description of a distinct injury phenotype, i.e. sensory discomplete SCI, naturally leads to the questions such as "So what? Or what does it mean?" I tackled several questions on the potential relevance of discomplete SCI in the discussion above. Those hypotheses are scientifically tenable for future research to answer. For example, it should be possible to investigate the relationship between sensory discomplete SCI and the presence of neuropathic pain according to the imbalance hypothesis, which states that spinothalamic tract lesions in combination with relative preservation of dorsal column function are important for pain generation (Berić et al., 1988).
* In part 1 of the thesis, we have provided evidence for sensory discomplete SCI a group of patients with chronic SCI. Our protocol perhaps can be used during the subacute phase of the injury to predict recovery of somatosensory function.
* Looking back at my early research thoughts about SCI, I still think it is interesting to investigate the consequences of long-standing sensorimotor deprivation on top-down mechanisms. Does SCI alter visually-driven somatosensory representations? Beyond demonstrating that vision could drive somatosensory cortex activity in a SCI participant (in study I), this question was not further investigated because we got hooked on sensory discomplete SCI.

* Regarding fMRI investigation of DBS mechanisms, the most obvious step forward is to use an optimised imaging protocol to obtain better data. The limitations in data quality of study III and IV were largely enforced by compromised imaging parameters due to safety concerns about MRI-DBS interactions, which were based on the available knowledge at the time of data collection. Future fMRI studies should obtain images with higher signal-to-noise ratio as it recently has been shown that improved image acquisition, such as using 3.0 Tesla scanners and body-transmit coils, is feasible and safe in DBS patients (Sammartino et al., 2017; Boutet et al., 2020b).
* The fMRI signal loss due to DBS-hardware is still a limiting issue for fMRI-

DBS studies, and should be addressed in the future by means of phantom studies with variable MR-sequence acquisitions to find a potential imaging protocol that is less affected by signal loss.

* Along similar lines, fMRI can be integrated with direct recordings from the stimulated brain target, which is especially critical since the fMRI signal loss is mostly prominent at the electrode tips in the target. For example, modern DBS-systems with the possibility to record LFPs can provide insights about DBS actions in the ventrolateral thalamus (specifically VLp) during different motor tasks (as investigated in study III). According to my hypothetical architecture on tremor generation and suppression, the VLp should exhibit a response pattern similar to the posterior cerebellum and primary sensorimotor cortex (i.e. decreased LFPs due to DBS during postural holding).

4.5 Conclusions

* fMRI is a valuable tool to investigate sensorimotor dysfunction and restoration in SCI and DBS-treated ET.
* There is evidence for sensory discomplete SCI in about half of the patients with clinically complete SCI.
* To investigate sensory discomplete SCI, experimentation must be rigorous to exclude confounding mechanical and cortico-cortical top-down effects (e.g. attention/expectation and vision).
* Exploring DBS mechanisms by fMRI in patients with fully implanted DBS-systems is feasible and safe.
* DBS in the cZi for ET modulates the sensorimotor cerebello-cerebral circuit in a motor task-dependent as well as task-independent manner.
* DBS does not modulate resting-state functional connectivity in ET.
* DBS effects, as evident during motor tasks and not during resting-state, suggest an action-dependent modulation of DBS on the cerebello-cerebral circuit.

Acknowledgements

I have been fortunate to get the opportunity to meet and interact with so many inspiring people throughout my PhD studies.

First and foremost, I want to express my sincere gratitude to my supervisors Johan Eriksson, Patric Blomstedt, Richard Levi and Lars Nyberg for their superb guidance throughout these years and for believing in me. **Johan Eriksson**, my main supervisor, for his kindness, patience and never-ending support. You have always been considerate of my scientific development throughout the 10 years (!) of being my supervisor for summer scholarships, my master's project, and ultimately PhD studies. **Patric Blomstedt**, for introducing me to the world of stereotactic neurosurgery and for providing me with wise and oftentimes reassuring perspectives both on the professional and personal level. **Richard Levi**, for educating me about spinal cord injury and widening my views about philosophy and neuroscience through stimulating conversations and books. **Lars Nyberg**, for being a scientific role model and for always encouraging me towards better scientific performance.

My collaborators and friends. **Göran Westling**, for endless and contagious enthusiasm, technical excellence and for building any MR-compatible device I could think of. **Lenita Lindgren**, for inspiring scientific curiosity and all the fun we had during the experiments. **Filip Grill** for enjoyable collaboration in study IV and for our illuminating discussions/debates about motor and predictive processing.

My former/current fellow PhD students and friends for sharing the occasionally frustrating and oftentimes rewarding existence of being a PhD student: **Fredrik B, Lars S**, **Sara S**, **Per N** and **Robin P**.

Umeå center for Functional Brain Imaging (UFBI) for being an excellent scientific and friendly environment. **Micael A** for data analysis support, DataZ and for coordinating the eminent lunch train. **Anders B** and **Mikael S** for technical support. **Anders L** for significant statistical support (corrected for multiple comparisons). All other bright and valuable people at UFBI and IMB.

Roland and **Ben** for inspiring and educational conversations on sensorimotor control.

Claes H and **Mikael W** for fruitful collaboration and for widening my perspective on spinal cord injury.

My colleagues at the **unit for deep brain stimulation (DBS)**. **Marwan H** for being a role model in the field of stereotactic neurosurgery. Thank you for your kindness, insightful comments on my texts and for educating me about the history of neurosurgery. **AnnaKarin** for recruitment of DBS patients and assistance during the DBS experiments. **Rasmus** (my DBS brother), **Johanna**, **Linda S**, **Matilda**, and **Anne-Louice** for stimulating conversations and teamwork.

All my colleagues at the **department of neurosurgery** for their encouragement and for facilitating this work.

Sara P, **David** and **Staffan** for valuable comments on the thesis. Also, thank you, **Sara H** for excellent proofreading of the thesis. You will most likely remain the only family member who actually has read the whole thesis.

I must also express my genuine gratitude to all the patients who selflessly and patiently participated in my studies. Thank you!

My dear friends **Björn**, **Sofie**, and **Per Ö** for cheerful moments, needed distraction, and laughter.

My family for boundless support and love: **Nouri**, **Bushra**, **Nooriya**, **Rasha**, **Samar**, **Haidar**, **Stefan**, and **Malin**.

Last but not least, I would like to thank my beloved wife **Emy** for her support, patience, the beautiful cover image and for reminding me about the (other) important things in life. My daughter **Asta** for providing the most wonderful distraction.

Amar Awad
Umeå, 2022

References

Ågren R, Awad A, Blomstedt P, Fytagoridis A (2021) Voxel-Based Morphometry of Cerebellar Lobules in Essential Tremor. *Front Aging Neurosci* 13:1–6.

Ahuja CS, Fehlings M (2016) Concise Review: Bridging the Gap: Novel Neuroregenerative and Neuroprotective Strategies in Spinal Cord Injury. *Stem Cells Transl Med* 5:914–924.

Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, Fehlings MG (2017) Traumatic spinal cord injury. *Nat Rev Dis Prim* 3:17018.

Akkal D, Dum RP, Strick PL (2007) Supplementary Motor Area and Presupplementary Motor Area: Targets of Basal Ganglia and Cerebellar Output. *J Neurosci* 27:10659–10673.

Akram H, Dayal V, Mahlknecht P, Georgiev D, Hyam J, Foltynie T, Limousin P, De Vita E, Jahanshahi M, Ashburner J, Behrens T, Hariz M, Zrinzo L (2018) Connectivity derived thalamic segmentation in deep brain stimulation for tremor. *NeuroImage Clin* 18:130–142.

Akram H, Hariz M, Zrinzo L (2019) Connectivity derived thalamic segmentation: Separating myth from reality. *NeuroImage Clin* 22:101758.

Akselrod M, Martuzzi R, Serino A, van der Zwaag W, Gassert R, Blanke O (2017) Anatomical and functional properties of the foot and leg representation in areas 3b, 1 and 2 of primary somatosensory cortex in humans: A 7T fMRI study. *Neuroimage* 159:473–487.

Allison J, Yanasak N (2015) What MRI Sequences Produce the Highest Specific Absorption Rate (SAR), and Is There Something We Should Be Doing to Reduce the SAR During Standard Examinations? *Am J Roentgenol* 205:W140–W140.

American Spinal Association (2019) ISNCSCI worksheet. ASIA.

Amiez C, Petrides M (2014) Neuroimaging Evidence of the Anatomo-Functional Organization of the Human Cingulate Motor Areas. *Cereb Cortex* 24:563–578.

Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, Ferreira CK, Harkema SJ (2018) Recovery of Over-Ground Walking after Chronic Motor Complete Spinal Cord Injury. *N Engl J Med* 379:1244–1250.

Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ (2014) Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain* 137:1394–1409.

Apkarian A, Shi T (1998) Thalamocortical connections of the cingulate and insula in relation to nociceptive inputs to the cortex. In: Pain Mechanisms and Management (Ayrapetyan S, Apkarian A, eds), pp 212–220. IOS Press, Amsterdam.

Apkarian AV, Hodge CJ (1989) Primate spinothalamic pathways: II. The cells of origin of the dorsolateral and ventral spinothalamic pathways. *J Comp Neurol* 288:474–492.

Astrom M, Diczfalusy E, Martens H, Wardell K (2015) Relationship between Neural Activation and Electric Field Distribution during Deep Brain Stimulation. *IEEE Trans Biomed Eng* 62:664–672.

Attwell D, Iadecola C (2002) The neural basis of functional brain imaging signals. *Trends Neurosci* 25:621–625.

Awad A, Blomstedt P, Westling G, Eriksson J (2020a) Deep brain stimulation in the caudal zona incerta modulates the sensorimotor cerebello-cerebral circuit in essential tremor. *Neuroimage* 209:116511.

Awad A, Levi R, Lindgren L, Hultling C, Westling G, Nyberg L, Eriksson J (2015) Preserved somatosensory conduction in a patient with complete cervical spinal cord injury. *J Rehabil Med* 47:426–431.

Awad A, Levi R, Waller M, Westling G, Lindgren L, Eriksson J (2020b) Preserved somatosensory conduction in complete spinal cord injury: Discomplete SCI. *Clin Neurophysiol* 131:1059–1067.

Baker KS, Mattingley JB, Chambers CD, Cunnington R (2011) Attention and the readiness for action. *Neuropsychologia* 49:3303–3313.

Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS (1992) Time course EPI of human brain function during task activation. *Magn Reson Med* 25:390–397.

Barbe MT, Reker P, Hamacher S, Franklin J, Kraus D, Dembek TA, Becker J, Steffen JK, Allert N, Wirths J, Dafsari HS, Voges J, Fink GR, Visser-Vandewalle V, Timmermann L (2018) DBS of the PSA and the VIM in essential tremor. *Neurology* 91:e543–e550.

Bastian AJ (2006) Learning to predict the future: the cerebellum adapts feedforward movement control. *Curr Opin Neurobiol* 16:645–649.

Battaglia-Mayer A, Buiatti T, Caminiti R, Ferraina S, Lacquaniti F, Shallice T (2014) Correction and suppression of reaching movements in the cerebral cortex: Physiological and neuropsychological aspects. *Neurosci Biobehav Rev* 42:232–251.

Behrens TEJ, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CAM, Boulby PA, Barker GJ, Sillery EL, Sheehan K, Ciccarelli O, Thompson AJ, Brady JM, Matthews PM (2003) Non-invasive mapping of connections between human

thalamus and cortex using diffusion imaging. *Nat Neurosci* 6:750–757.

Belliveau JW, Kennedy DN, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, Vevea JM, Brady TJ, Rosen BR (1991) Functional Mapping of the Human Visual Cortex by Magnetic Resonance Imaging. *Science (80-)* 254:716–719.

Bellows ST, Jankovic J (2021) Phenotypic Features of Isolated Essential Tremor, Essential Tremor Plus, and Essential Tremor-Parkinson's Disease in a Movement Disorders Clinic. *Tremor and Other Hyperkinetic Movements* 11:1–11.

Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J (1987) Combined (Thalamotomy and Stimulation) Stereotactic Surgery of the VIM Thalamic Nucleus for Bilateral Parkinson Disease. *Stereotact Funct Neurosurg* 50:344–346.

Benagiano V, Rizzi A, Lorusso L, Flace P, Saccia M, Cagiano R, Ribatti D, Roncali L, Ambrosi G (2018) The functional anatomy of the cerebrocerebellar circuit: A review and new concepts. *J Comp Neurol* 526:769–789.

Benito-León J, Labiano-Fontcuberta A (2016) Linking Essential Tremor to the Cerebellum: Clinical Evidence. *The Cerebellum* 15:253–262.

Benito-León J, Louis ED, Romero JP, Hernández-Tamames JA, Manzanedo E, Álvarez-Linera J, Bermejo-Pareja F, Posada I, Rocon E (2015) Altered Functional Connectivity in Essential Tremor. *Medicine (Baltimore)* 94:e1936.

Berardelli A, Hallett M, Rothwell JC, Agostino R, Manfredi M, Thompson PD, Marsden CD (1996) Single–joint rapid arm movements in normal subjects and in patients with motor disorders. *Brain* 119:661–674.

Berić A, Dimitrijević MR, Lindblom U (1988) Central dysesthesia syndrome in spinal cord injury patients. *Pain* 34:109–116.

Bhalsing KS, Saini J, Pal PK (2013) Understanding the pathophysiology of essential tremor through advanced neuroimaging: A review. *J Neurol Sci* 335:9–13.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G (2018) Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord* 33:75–87.

Biswal B, Zerrin Yetkin F, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magn Reson Med* 34:537–541.

Blomstedt P, Fytagoridis A, Tisch S (2009a) Deep brain stimulation of the posterior subthalamic area in the treatment of tremor. *Acta Neurochir (Wien)* 151:31–36.

Blomstedt P, Hariz G-M, Hariz MI, Koskinen L-OD (2007) Thalamic deep brain stimulation in the treatment of essential tremor: a long-term follow-up. *Br J Neurosurg* 21:504–509.

Blomstedt P, Hariz MI (2010) Deep brain stimulation for movement disorders before DBS for movement disorders. *Parkinsonism Relat Disord* 16:429–433.

Blomstedt P, Sandvik U, Fytagoridis A, Tisch S (2009b) The posterior subthalamic area in the treatment of movement disorders: past, present, and future. *Neurosurgery* 64:1029–1038.

Blomstedt P, Sandvik U, Tisch S (2010) Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. *Mov Disord* 25:1350–1356.

Boecker H, Brooks DJ (2008) Functional Imaging of Tremor. *Mov Disord* 13:64–72.

Boecker H, Weindl A, Brooks DJ, Ceballos-Baumann AO, Liedtke C, Miederer M, Sprenger T, Wagner KJ, Miederer I (2010) GABAergic Dysfunction in Essential Tremor: An 11C-Flumazenil PET Study. *J Nucl Med* 51:1030–1035.

Boecker H, Wills AJ, Ceballos-Baumann A, Samuel M, Thompson PD, Findley LJ, Brooks DJ (1996) The effect of ethanol on alcohol-responsive essential tremor: A positron emission tomography study. *Ann Neurol* 39:650–658.

Bostan AC, Dum RP, Strick PL (2013) Cerebellar networks with the cerebral cortex and basal ganglia. *Trends Cogn Sci* 17:241–254.

Boutet A et al. (2019) Functional MRI Safety and Artifacts during Deep Brain Stimulation: Experience in 102 Patients. *Radiology* 293:174–183.

Boutet A, Chow CT, Narang K, Elias GJB, Neudorfer C, Germann J, Ranjan M, Loh A, Martin AJ, Kucharczyk W, Steele CJ, Hancu I, Rezai AR, Lozano AM (2020a) Improving Safety of MRI in Patients with Deep Brain Stimulation Devices. *Radiology* 296:250–262.

Boutet A, Hancu I, Saha U, Crawley A, Xu DS, Ranjan M, Hlasny E, Chen R, Foltz W, Sammartino F, Coblentz A, Kucharczyk W, Lozano AM (2020b) 3-Tesla MRI of deep brain stimulation patients: safety assessment of coils and pulse sequences. *J Neurosurg* 132:586–594.

Brodmann K (1909) Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Barth.

Broersma M, van der Stouwe AMM, Buijink AWG, de Jong BM, Groot PFC, Speelman JD, Tijssen MAJ, van Rootselaar A-F, Maurits NM (2016) Bilateral cerebellar activation in unilaterally challenged essential tremor. *NeuroImage Clin* 11:1–9.

Brown JM, Kakulas BA (2012) Restorative neurology: Past, present, and future. *Clin Neurol Neurosurg* 114:524–527.

Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, Defrin R, Lundeberg T, Norrbrink C, Richards JS, Siddall P, Stripling T, Treede R-D, Waxman SG, Widerström-Noga E, Yezierski RP, Dijkers M (2012) International Spinal Cord Injury Pain Classification: part I. Background and description. *Spinal Cord* 50:413–417.

Bucher SF, Seelos KC, Dodel RC, Reiser M, Oertel WH (1997) Activation mapping in essential tremor with functional magnetic resonance imaging. *Ann Neurol* 41:32–40.

Bucy P, Case J (1939) Tremor: physiologic mechanism and abolition by surgical means. *Arch Neurol Psychiatry* 41:721.

Bucy PC (1948) Cortical extirpation in the treatment of involuntary movements. *Am J Surg* 75:257–263.

Buijink AWG, Broersma M, van der Stouwe AMM, van Wingen GA, Groot PFC, Speelman JD, Maurits NM, van Rootselaar AF (2015a) Rhythmic finger tapping reveals cerebellar dysfunction in essential tremor. *Parkinsonism Relat Disord* 21:383–388.

Buijink AWG, van der Stouwe AMM, Broersma M, Sharifi S, Groot PFC, Speelman JD, Maurits NM, van Rootselaar A-F (2015b) Motor network disruption in essential tremor: a functional and effective connectivity study. *Brain* 138:2934–2947.

Bullmore E (2012) The future of functional MRI in clinical medicine. *Neuroimage* 62:1267–1271.

Burke D, Fullen BM, Stokes D, Lennon O (2017) Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis. *Eur J Pain* 21:29–44.

Burke D, Lennon O, Fullen BM (2018) Quality of life after spinal cord injury: The impact of pain. *Eur J Pain* 22:1662–1672.

Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, Munafò MR (2013) Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci* 14:365–376.

Cadotte DW, Fehlings MG (2013) Will imaging biomarkers transform spinal cord injury trials? *Lancet Neurol* 12:843–844.

Carmichael DW, Pinto S, Limousin-Dowsey P, Thobois S, Allen PJ, Lemieux L, Yousry T, Thornton JS (2007) Functional MRI with active, fully implanted, deep brain stimulation systems: Safety and experimental confounds. *Neuroimage* 37:508–517.

Catani M (2017) A little man of some importance. *Brain* 140:3055–3061.

Ceballos-Baumann A., Boecker H, Fogel W, Alesch F, Bartenstein P, Conrad B, Diederich N, von Falkenhayn I, Moringlane JR, Schwaiger M, Tronnier VM (2001) Thalamic stimulation for essential tremor activates motor and deactivates vestibular cortex. *Neurology* 56:1347–1354.

Chay W, Kirshblum S (2020) Predicting Outcomes After Spinal Cord Injury. *Phys Med Rehabil Clin N Am* 31:331–343.

Chouinard PA, Paus T (2006) The Primary Motor and Premotor Areas of the Human Cerebral Cortex. *Neurosci* 12:143–152.

Coenen VA, Allert N, Paus S, Kronenbürger M, Urbach H, Mädler B (2014) Modulation of the Cerebello-Thalamo-Cortical Network in Thalamic Deep Brain Stimulation for Tremor. *Neurosurgery* 75:657–670.

Coenen VA, Sajonz B, Prokop T, Reisert M, Piroth T, Urbach H, Jenkner C, Reinacher PC (2020) The dentato-rubro-thalamic tract as the potential common deep brain stimulation target for tremor of various origin: an observational case series. *Acta Neurochir (Wien)*.

Cohen O, Pullman S, Jurewicz E, Watner D, Louis ED (2003) Rest Tremor in Patients With Essential Tremor. *Arch Neurol* 60:405.

Colebatch JG, Findley LJ, Frackowiak RS, Marsden CD, Brooks DJ (1990) Preliminary report: activation of the cerebellum in essential tremor. *Lancet* 336:1028–1030.

Craig AD (Bud) (2004) Distribution of trigeminothalamic and spinothalamic lamina I terminations in the macaque monkey. *J Comp Neurol* 477:119–148.

Cruz-Almeida Y, Felix ER, Martinez-Arizala A, Widerström-Noga EG (2012) Decreased Spinothalamic and Dorsal Column Medial Lemniscus-Mediated Function Is Associated with Neuropathic Pain after Spinal Cord Injury. *J Neurotrauma* 29:2706–2715.

D'Angelo E (2018) Physiology of the cerebellum. In: Handbook of Clinical Neurology, 1st ed., pp 85–108. Elsevier.

Dallapiazza RF, Lee DJ, De Vloo P, Fomenko A, Hamani C, Hodaie M, Kalia SK, Fasano A, Lozano AM (2019) Outcomes from stereotactic surgery for essential tremor. *J Neurol Neurosurg Psychiatry* 90:474–482.

de Haan EHF, Dijkerman HC (2020) Somatosensation in the Brain: A Theoretical Re-evaluation and a New Model. *Trends Cogn Sci* 24:529–541.

de Lafuente V, Romo R (2005) Neuronal correlates of subjective sensory experience. *Nat Neurosci* 8:1698–1703.

de Lafuente V, Romo R (2006) Neural correlate of subjective sensory experience gradually builds up across cortical areas. *Proc Natl Acad Sci* 103:14266–14271.

Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP (2003) Internal vs external generation of movements: Differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. *Neuroimage* 19:764–776.

Delhaye BP, Long KH, Bensmaia SJ (2018) Neural Basis of Touch and Proprioception in Primate Cortex. *Compr Physiol* 8:1575–1602.

Deuschl G, Bain P, Brin M (2008) Consensus Statement of the Movement Disorder Society on Tremor. *Mov Disord* 13:2–23.

Deuschl G, Bhatia KP, Elble R, Hallett M (2018) Understanding the new tremor classification. *Mov Disord* 33:1267–1268.

Deuschl G, Raethjen J, Hellriegel H, Elble R (2011) Treatment of patients with essential tremor. *Lancet Neurol* 10:148–161.

Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H (2000) Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. *Brain* 123:1568–1580.

Dijkerman HC, de Haan EHF (2007) Somatosensory processes subserving perception and action. *Behav Brain Sci* 30:189–201.

Dimitrijevic MR (1987) Neurophysiology in spinal cord injury. *Spinal Cord* 25:205–208.

Dimitrijević MR (1988) Residual motor functions in spinal cord injury. *Adv Neurol* 47:138–155.

Dimitrijevic MR, Kakulas BA (2020) Spinal cord injuries, human neuropathology and neurophysiology. *Acta Myol* 39:353–358.

Dimitrijevic MR, Prevec TS, Sherwood AM (1983) Somatosensory perception and cortical evoked potentials in established paraplegia. *J Neurol Sci* 60:253–265.

Dionne JK, Meehan SK, Legon W, Staines WR (2010) Crossmodal influences in somatosensory cortex: Interaction of vision and touch. *Hum Brain Mapp* 31:14–25.

Disbrow E, Litinas E, Recanzone G, Slutsky D, Krubitzer L (2002) Thalamocortical connections of the parietal ventral area (PV) and the second somatosensory area

(S2) in macaque monkeys. *Thalamus Relat Syst* 1:289.

Disbrow E, Litinas E, Recanzone GH, Padberg J, Krubitzer L (2003) Cortical connections of the second somatosensory area and the parietal ventral area in macaque monkeys. *J Comp Neurol* 462:382–399.

Dostrovsky JO, Craig AD (2020) The Thalamus and Nociceptive Processing, Second Edi. Elsevier.

Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM (2000) Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *J Neurophysiol* 84:570–574.

Dum R, Strick P (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* 11:667–689.

Dum RP, Strick PL (2002) Motor areas in the frontal lobe of the primate. *Physiol Behav* 77:677–682.

Dum RP, Strick PL (2003) An Unfolded Map of the Cerebellar Dentate Nucleus and its Projections to the Cerebral Cortex. *J Neurophysiol* 89:634–639.

Dum RP, Strick PL (2004) Motor Areas in the Frontal Lobe: The Anatomical Substrate for the Central Control of Movement. In: Motor Cortex in Voluntary Movements: A Distributed System for Distributed Functions, pp 1–46. CRC Press.

Dupuis MJM, Delwaide PJ, Boucquey D, Gonsette RE (1989) Homolateral disappearance of essential tremor after cerebellar stroke. *Mov Disord* 4:183–187.

Ebbesen CL, Brecht M (2017) Motor cortex — to act or not to act? *Nat Rev Neurosci* 18:694–705.

Eickhoff SB, Amunts K, Mohlberg H, Zilles K (2006a) The Human Parietal Operculum. II. Stereotaxic Maps and Correlation with Functional Imaging Results. *Cereb Cortex* 16:268–279.

Eickhoff SB, Grefkes C, Fink GR, Zilles K (2008) Functional lateralization of face, hand, and trunk representation in anatomically defined human somatosensory areas. *Cereb Cortex* 18:2820–2830.

Eickhoff SB, Schleicher A, Zilles K, Amunts K (2006b) The Human Parietal Operculum. I. Cytoarchitectonic Mapping of Subdivisions. *Cereb Cortex* 16:254–267.

Falci S, Best L, Bayles R, Lammertse D, Starnes C (2002) Dorsal root entry zone microcoagulation for spinal cord injury—related central pain: operative intramedullary electrophysiological guidance and clinical outcome. *J Neurosurg*

Spine 97:193–200.

Fang PC, Stepniewska I, Kaas JH (2006) The thalamic connections of motor, premotor, and prefrontal areas of cortex in a prosimian primate (Otolemur garnetti). *Neuroscience* 143:987–1020.

Fang W, Chen H, Wang H, Zhang H, Liu M, Puneet M, Lv F, Cheng O, Wang X, Lu X, Luo T (2015) Multiple Resting-State Networks Are Associated With Tremors and Cognitive Features in Essential Tremor. *Mov Disord* 30:1926–1936.

Fang W, Chen H, Wang H, Zhang H, Puneet M, Liu M, Lv F, Luo T, Cheng O, Wang X, Lu X (2016) Essential tremor is associated with disruption of functional connectivity in the ventral intermediate Nucleus-Motor Cortex-Cerebellum circuit. *Hum Brain Mapp* 37:165–178.

Fasano A, Herzog J, Raethjen J, Rose FEM, Muthuraman M, Volkmann J, Falk D, Elble R, Deuschl G (2010) Gait ataxia in essential tremor is differentially modulated by thalamic stimulation. *Brain* 133:3635–3648.

Fasano A, Lang AE, Espay AJ (2018) What is "essential" about essential tremor? A diagnostic placeholder. *Mov Disord* 33:58–61.

Ferreira JJ, Mestre TA, Lyons KE, Benito-León J, Tan E, Abbruzzese G, Hallett M, Haubenberger D, Elble R, Deuschl G (2019) MDS evidence-based review of treatments for essential tremor. *Mov Disord* 34:950–958.

Filip P, Lungu O V., Manto M-U, Bareš M (2016) Linking Essential Tremor to the Cerebellum: Physiological Evidence. *The Cerebellum* 15:774–780.

Fine JM, Hayden BY (2022) The whole prefrontal cortex is premotor cortex. *Philos Trans R Soc B Biol Sci* 377:20200524.

Finnerup NB, Gyldensted C, Fuglsang-Frederiksen A, Bach FW, Jensen TS (2004) Sensory perception in complete spinal cord injury. *Acta Neurol Scand* 109:194–199.

Finnerup NB, Sørensen L, Biering-Sørensen F, Johannesen IL, Jensen TS (2007) Segmental hypersensitivity and spinothalamic function in spinal cord injury pain. *Exp Neurol* 207:139–149.

Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8:700–711.

Fox PT, Raichle ME (1986) Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci* 83:1140–1144.

Fox PT, Raichle ME, Mintun MA, Dence C (1988) Nonoxidative glucose consumption during focal physiologic neural activity. *Science (80-)* 241:462–464.

Freund P, Seif M, Weiskopf N, Friston K, Fehlings MG, Thompson AJ, Curt A (2019) MRI in traumatic spinal cord injury: from clinical assessment to neuroimaging biomarkers. *Lancet Neurol* 18:1123–1135.

Frot M, Mauguière F (2003) Dual representation of pain in the operculo-insular cortex in humans. *Brain* 126:438–450.

Fulton JF (1928) Observations upon the Vascularity of the Human Occipital Lobe during Visual Activity. *Brain* 51:310–320.

Fulton JF (1935) A note on the definition of the "motor" and "premotor" areas. *Brain* 58:311–316.

Fuster JM (2000) Executive frontal functions. *Exp Brain Res* 133:66–70.

Fytagoridis A, Åström M, Samuelsson J, Blomstedt P (2016) Deep Brain Stimulation of the Caudal Zona Incerta: Tremor Control in Relation to the Location of Stimulation Fields. *Stereotact Funct Neurosurg* 94:363–370.

Fytagoridis A, Sandvik U, Åström M, Bergenheim T, Blomstedt P (2012) Long term follow-up of deep brain stimulation of the caudal zona incerta for essential tremor. *J Neurol Neurosurg Psychiatry* 83:258–262.

Gallay MN, Jeanmonod D, Liu J, Morel A (2008) Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery. *Brain Struct Funct* 212:443–463.

Gallea C, Popa T, García-Lorenzo D, Valabregue R, Legrand A-P, Marais L, Degos B, Hubsch C, Fernández-Vidal S, Bardinet E, Roze E, Lehéricy S, Vidailhet M, Meunier S (2015) Intrinsic signature of essential tremor in the cerebello-frontal network. *Brain* 138:2920–2933.

Ganzer PD, Colachis SC, Schwemmer MA, Friedenberg DA, Dunlap CF, Swiftney CE, Jacobowitz AF, Weber DJ, Bockbrader MA, Sharma G (2020) Restoring the Sense of Touch Using a Sensorimotor Demultiplexing Neural Interface. *Cell* 181:763-773.e12.

Gardner EP (2020) Dorsal and Ventral Streams in the Sense of Touch. In: The Senses: A Comprehensive Reference, Second Edi., pp 302–323. Elsevier.

Georgi J-C, Stippich C, Tronnier VM, Heiland S (2004) Active deep brain stimulation during MRI: A feasibility study. *Magn Reson Med* 51:380–388.

Geyer S, Luppino G, Rozzi S (2012) Motor Cortex. In: The Human Nervous System, Third Edit., pp 1012–1035. Elsevier.

Geyer S, Matelli M, Luppino G, Zilles K (2000) Functional neuroanatomy of the primate isocortical motor system. *Anat Embryol (Berl)* 202:443–474.

Gibson WS, Jo HJ, Testini P, Cho S, Felmlee JP, Welker KM, Klassen BT, Min H-K, Lee KH (2016) Functional correlates of the therapeutic and adverse effects evoked by thalamic stimulation for essential tremor. *Brain* 27:aww145.

Gildenberg PL (2003) History Repeats Itself. *Stereotact Funct Neurosurg* 80:61–75.

Goense JBM, Logothetis NK (2008) Neurophysiology of the BOLD fMRI Signal in Awake Monkeys. *Curr Biol* 18:631–640.

Graziano MSA (2016) Ethological Action Maps: A Paradigm Shift for the Motor Cortex. *Trends Cogn Sci* 20:121–132.

Graziano MSA, Taylor CSR, Moore T (2002a) Complex Movements Evoked by Microstimulation of Precentral Cortex. *Neuron* 34:841–851.

Graziano MSA, Taylor CSR, Moore T, Cooke DF (2002b) The cortical control of movement revisited. *Neuron* 36:349–362.

Greenspan JD, McGillis SLB (1991) Stimulus Features Relevant to the Perception of Sharpness and Mechanically Evoked Cutaneous Pain. *Somatosens Mot Res* 8:137–147.

Grill WM, Snyder AN, Miocinovic S (2004) Deep brain stimulation creates an informational lesion of the stimulated nucleus. *Neuroreport* 15:1137–1140.

Grodd W, Hülsmann E, Lotze M, Wildgruber D, Erb M (2001) Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. *Hum Brain Mapp* 13:55–73.

Groppa S, Herzog J, Falk D, Riedel C, Deuschl G, Volkmann J (2014) Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. *Brain* 137:109–121.

Gross CG (2007) The Discovery of Motor Cortex and its Background. *J Hist Neurosci* 16:320–331.

Gross J, Timmermann L, Kujala J, Dirks M, Schmitz F, Salmelin R, Schnitzler A (2002) The neural basis of intermittent motor control in humans. *Proc Natl Acad Sci* 99:2299–2302.

Guridi J, Gonzalez-Quarante LH (2021) Revisiting Forel Field Surgery. *World Neurosurg* 147:11–22.

Haaland KY, Dum RP, Mutha PK, Strick PL, Tröster AI (2017) The Neuropsychology of Movement and Movement Disorders: Neuroanatomical and Cognitive Considerations. *J Int Neuropsychol Soc* 23:768–777.

Habas C, Axelrad H, Nguyen TH, Cabanis E-A (2004) Specific neocerebellar activation during out-of-phase bimanual movements. *Neuroreport* 15:595–599.

Hachem LD, Fehlings MG (2021) Pathophysiology of Spinal Cord Injury. *Neurosurg Clin N Am* 32:305–313.

Hallett M, Dubinsky RM (1993) Glucose metabolism in the brain of patients with essential tremor. *J Neurol Sci* 114:45–48.

Halsband U, Ito N, Tanji J, Freund HJ (1993) The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain* 116:243–266.

Hamani C, Dostrovsky JO, Lozano AM (2006) The Motor Thalamus in Neurosurgery. *Neurosurgery* 58:146–158.

Handforth A (2016) Linking Essential Tremor to the Cerebellum—Animal Model Evidence. *The Cerebellum* 15:285–298.

Hari AR, Wydenkeller S, Dokladal P, Halder P (2009) Enhanced recovery of human spinothalamic function is associated with central neuropathic pain after SCI. *Exp Neurol* 216:428–430.

Hariz MI, Blomstedt P, Zrinzo L (2010) Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurg Focus* 29:E1.

Hashimoto M, Takahara D, Hirata Y, Inoue K, Miyachi S, Nambu A, Tanji J, Takada M, Hoshi E (2010) Motor and non-motor projections from the cerebellum to rostrocaudally distinct sectors of the dorsal premotor cortex in macaques. *Eur J Neurosci* 31:1402–1413.

Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL (2003) Stimulation of the Subthalamic Nucleus Changes the Firing Pattern of Pallidal Neurons. *J Neurosci* 23:1916–1923.

Haslinger B, Boecker H, Büchel C, Vesper J, Tronnier V., Pfister R, Alesch F, Moringlane J., Krauss J., Conrad B, Schwaiger M, Ceballos-Baumann A. (2003) Differential modulation of subcortical target and cortex during deep brain stimulation. *Neuroimage* 18:517–524.

Hassler R, Riechert T, Mundinger F, Umbach W, Ganglberger JA (1960) Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. *Brain* 83:337–350.

Heald E, Hart R, Kilgore K, Peckham PH (2017) Characterization of Volitional Electromyographic Signals in the Lower Extremity After Motor Complete Spinal Cord Injury. *Neurorehabil Neural Repair* 31:583–591.

Heeger DJ, Ress D (2002) What does fMRI tell us about neuronal activity? *Nat Rev Neurosci* 3:142–151.

Helmich RC, Toni I, Deuschl G, Bloem BR (2013) The pathophysiology of essential tremor and parkinson's tremor. *Curr Neurol Neurosci Rep* 13:378.

Henderson JM, Tkach J, Phillips M, Baker K, Shellock FG, Rezai AR (2005) Permanent Neurological Deficit Related to Magnetic Resonance Imaging in a Patient with Implanted Deep Brain Stimulation Electrodes for Parkinson's Disease: Case Report. *Neurosurgery* 57:E1063–E1063.

Herculano-Houzel S (2012) The remarkable, yet not extraordinary, human brain as a scaled-up primate brain and its associated cost. *Proc Natl Acad Sci* 109:10661–10668.

Herrup K, Kuemerle B (1997) The compartmentalization of the cerebellum. *Annu Rev Neurosci* 20:61–90.

Herzog J, Hamel W, Wenzelburger R, Pötter M, Pinsker MO, Bartussek J, Morsnowski A, Steigerwald F, Deuschl G, Volkmann J (2007) Kinematic analysis of thalamic versus subthalamic neurostimulation in postural and intention tremor. *Brain* 130:1608–1625.

Holsapple JW, Preston JB, Strick PL (1991) The origin of thalamic inputs to the "hand" representation in the primary motor cortex. *J Neurosci* 11:2644–2654.

Holtbernd F, Shah NJ (2021) Imaging the Pathophysiology of Essential Tremor—A Systematic Review. *Front Neurol* 12:1–17.

Hopfinger JB, Buonocore MH, Mangun GR (2000) The neural mechanisms of top-down attentional control. *Nat Neurosci* 3:284–291.

Hopfner F, Ahlf A, Lorenz D, Klebe S, Zeuner KE, Kuhlenbäumer G, Deuschl G (2016) Early- and late-onset essential tremor patients represent clinically distinct subgroups. *Mov Disord* 31:1560–1566.

Hopfner F, Deuschl G (2018) Is essential tremor a single entity? *Eur J Neurol* 25:71–82.

Hopfner F, Deuschl G (2020) Managing Essential Tremor. *Neurotherapeutics* 17:1603–1621.

Hopfner F, Helmich RC (2018) The etiology of essential tremor: Genes versus environment. *Parkinsonism Relat Disord* 46:S92–S96.

Horsley V (1909) The function of so-called motor area of the brain. *BMJ* 2:121–132.

Horsley V, Clarke RH (1908) The structure and functions of the cerebellum examined by a new method. *Brain* 31:45–124.

Hoshi E, Tanji J (2007) Distinctions between dorsal and ventral premotor areas: anatomical connectivity and functional properties. *Curr Opin Neurobiol* 17:234–242.

Hua SE, Lenz FA (2005) Posture-related oscillations in human cerebellar thalamus in essential tremor are enabled by voluntary motor circuits. *J Neurophysiol* 93:117–127.

Huang Q, Duan W, Sivanesan E, Liu S, Yang F, Chen Z, Ford NC, Chen X, Guan Y (2019) Spinal Cord Stimulation for Pain Treatment After Spinal Cord Injury. *Neurosci Bull* 35:527–539.

Huettel SA, Song AW, McCarthy G (2009) Functional magnetic resonance imaging, 2nd editio. Sunderland, MA: Sinauer Associates.

Iadecola C (2017) The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron* 96:17–42.

Ioannides A a, Liu L, Khurshudyan A, Bodley R, Poghosyan V, Shibata T, Dammers J, Jamous A (2002) Brain Activation Sequences Following Electrical Limb Stimulation of Normal and Paraplegic Subjects. *Neuroimage* 16:115–129.

Ishikawa T, Tomatsu S, Izawa J, Kakei S (2016) The cerebro-cerebellum: Could it be loci of forward models? *Neurosci Res* 104:72–79.

Iwamura Y, Tanaka M, Iriki A, Taoka M, Toda T (2002) Processing of tactile and kinesthetic signals from bilateral sides of the body in the postcentral gyrus of awake monkeys. *Behav Brain Res* 135:185–190.

Iwamura Y, Tanaka M, Sakamoto M, Hikosaka O (1993) Rostrocaudal gradients in the neuronal receptive field complexity in the finger region of the alert monkey's postcentral gyrus. *Exp Brain Res* 92:360–368.

Jackson AB, Dijkers M, DeVivo MJ, Poczatek RB (2004) A demographic profile of new traumatic spinal cord injuries: Change and stability over 30 years. *Arch Phys Med Rehabil* 85:1740–1748.

Jenkins IH, Bain PG, Colebatch JG, Thompson PD, Findley LJ, Frackowiak RSJ, Marsden CD, Brooks DJ (1993) A positron emission tomography study of essential tremor: Evidence for overactivity of cerebellar connections. *Ann Neurol* 34:82–90.

Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, Treede RD (2011) A new definition of neuropathic pain. *Pain* 152:2204–2205.

Johansson RS, Flanagan JR (2009) Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nat Rev Neurosci* 10:345–359.

Johansson RS, Westling G (1987) Tactile Afferent Input Influencing Motor Coordination During Precision Grip. In: Clinical Aspects of Sensory Motor Integration, pp 3–13.

Joseph C, Andersson N, Bjelak S, Giesecke K, Hultling C, Wikmar L, Phillips J, Seiger Ã, Stenimahitis V, Trok K, Ã…kesson E, Wahman K (2017) Incidence, aetiology and injury characteristics of traumatic spinal cord injury in Stockholm, Sweden: A prospective, population-based update. *J Rehabil Med* 49:431–436.

Kaas JH (2008) The Somatosensory Thalamus and Associated Pathways. In: The Senses: A Comprehensive Reference, pp 117–141. Elsevier.

Kaas JH (2012) Somatosensory System. In: The Human Nervous System, pp 1074–1109. Elsevier.

Kaas JH, Nelson RJ, Sur M, Lin CS, Merzenich MM (1979) Multiple representations of the body within the primary somatosensory cortex of primates. *Science (80-)* 204:521–523.

Kahan J, Mancini L, Flandin G, White M, Papadaki A, Thornton J, Yousry T, Zrinzo L, Hariz M, Limousin P, Friston K, Foltynie T (2019) Deep brain stimulation has state-dependent effects on motor connectivity in Parkinson's disease. *Brain* 142:2417–2431.

Kahan J, Mancini L, Urner M, Friston K, Hariz M, Holl E, White M, Ruge D, Jahanshahi M, Boertien T, Yousry T, Thornton JS, Limousin P, Zrinzo L, Foltynie T (2012) Therapeutic Subthalamic Nucleus Deep Brain Stimulation Reverses Cortico-Thalamic Coupling during Voluntary Movements in Parkinson's Disease. *PLoS One* 7:e50270.

Kahan J, Papadaki A, White M, Mancini L, Yousry T, Zrinzo L, Limousin P, Hariz M, Foltynie T, Thornton J (2015) The safety of using body-transmit MRI in patients with implanted deep brain stimulation devices. *PLoS One* 10:1–21.

Kahan J, Urner M, Moran R, Flandin G, Marreiros A, Mancini L, White M, Thornton J, Yousry T, Zrinzo L, Hariz M, Limousin P, Friston K, Foltynie T (2014) Resting state functional MRI in Parkinson's disease: the impact of deep brain stimulation on 'effective' connectivity. *Brain* 137:1130–1144.

Kakei S, Hoffman DS, Strick PL (1999) Muscle and Movement Representations in the Primary Motor Cortex. *Science (80-)* 285:2136–2139.

Kakei S, Manto M, Tanaka H, Mitoma H (2021) Pathophysiology of Cerebellar Tremor: The Forward Model-Related Tremor and the Inferior Olive Oscillation-Related Tremor. *Front Neurol* 12:1–14.

Kakuda N, Nagaoka M, Wessberg J (1999) Common modulation of motor unit pairs during slow wrist movement in man. *J Physiol* 520:929–940.

Kakulas B (1999) The applied neuropathology of human spinal cord injury. *Spinal Cord* 37:79–88.

Kakulas B (2004) Neuropathology: the foundation for new treatments in spinal cord injury. *Spinal Cord* 42:549–563.

Kandel ER, Koester JD, Mack SH, Siegelbaum SA (2021) The Cerebellum. In: Principles of Neural Science, 6e. New York, NY: McGraw Hill.

Kayser C, Logothetis NK (2013) The Electrophysiological Background of the fMRI Signal. In: fMRI, pp 25–36. Berlin, Heidelberg: Springer Berlin Heidelberg.

Kelly RM, Strick PL (2003) Cerebellar Loops with Motor Cortex and Prefrontal Cortex of a Nonhuman Primate. *J Neurosci* 23:8432–8444.

Kim J-S, Park J-W, Kim W-J, Kim H-T, Kim Y-I, Lee K-S (2006) Disappearance of essential tremor after frontal cortical infarct. *Mov Disord* 21:1284–1285.

King M, Hernandez-Castillo CR, Poldrack RA, Ivry R, Diedrichsen J (2019) Functional Boundaries in the Human Cerebellum revealed by a Multi-Domain Task Battery. *Nat Neurosci* 22.

Kirshblum S, Snider B, Eren F, Guest J (2021) Characterizing Natural Recovery after Traumatic Spinal Cord Injury. *J Neurotrauma* 38:1267–1284.

Kirshblum S, Snider B, Rupp R, Read MS (2020) Updates of the International Standards for Neurologic Classification of Spinal Cord Injury. *Phys Med Rehabil Clin N Am* 31:319–330.

Kirshblum SC, Biering-s FØ, Betz R, Burns S, Donovan W, Graves DE (2014) International Standards for Neurological Classification of Spinal Cord Injury : Cases With Classification Challenges. *J Spinal Cord Med* 20:81–89.

Kirshblum SC, Botticello AL, Dyson-Hudson TA, Byrne R, Marino RJ, Lammertse DP (2016) Patterns of Sacral Sparing Components on Neurologic Recovery in Newly Injured Persons With Traumatic Spinal Cord Injury. *Arch Phys Med Rehabil* 97:1647–

1655.

Kirshblum SC, Waring W, Biering-Sorensen F, Burns SP, Johansen M, Schmidt-Read M, Donovan W, Graves DE, Jha A, Jones L, Mulcahey MJ, Krassioukov A (2011) Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. *J Spinal Cord Med* 34:547–554.

Klein JC, Barbe MT, Seifried C, Baudrexel S, Runge M, Maarouf M, Gasser T, Hattingen E, Liebig T, Deichmann R, Timmermann L, Weise L, Hilker R (2012) The tremor network targeted by successful VIM deep brain stimulation in humans. *Neurology* 78:787–795.

Klemme R (1940) Surgical treatment of dystonia, paralysis agitans and athetosis. *Arch Neurol Psychiatry* 44.

Koch C, Massimini M, Boly M, Tononi G (2016) Neural correlates of consciousness: progress and problems. *Nat Rev Neurosci* 17:307–321.

Kringelbach ML, Jenkinson N, Owen SLF, Aziz TZ (2007) Translational principles of deep brain stimulation. *Nat Rev Neurosci* 8:623–635.

Krishna V, Andrews H, Varma A, Mintzer J, Kindy MS, Guest J (2014) Spinal cord injury: how can we improve the classification and quantification of its severity and prognosis? *J Neurotrauma* 31:215–227.

Kuehn E, Haggard P, Villringer A, Pleger B, Sereno MI (2018) Visually-driven maps in area 3b. *J Neurosci* 38:0491–17.

Kvernmo N, Konglund AE, Reich MM, Roothans J, Pripp AH, Dietrichs E, Volkmann J, Skogseid IM (2022) Deep Brain Stimulation for Arm Tremor: A Randomized Trial Comparing Two Targets. *Ann Neurol* 91:585–601.

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci* 89:5675–5679.

Langner R, Kellermann T, Boers F, Sturm W, Willmes K, Eickhoff SB (2011) Modality-Specific Perceptual Expectations Selectively Modulate Baseline Activity in Auditory, Somatosensory, and Visual Cortices. *Cereb Cortex* 21:2850–2862.

Lassen NA, Ingvar DH, Skinhøj E (1978) Brain Function and Blood Flow. *Sci Am* 239:62–71.

Lenka A, Bhalsing KS, Panda R, Jhunjhunwala K, Naduthota RM, Saini J, Bharath RD, Yadav R, Pal PK (2017) Role of altered cerebello-thalamo-cortical network in the neurobiology of essential tremor. *Neuroradiology* 59:157–168.

Lenz FA, Rios M, Chau D, Krauss GL, Zirh TA, Lesser RP (1998) Painful Stimuli Evoke Potentials Recorded From the Parasylvian Cortex in Humans. *J Neurophysiol* 80:2077–2088.

Levi R, Hultling C, Seiger Å (1995) The Stockholm Spinal Cord Injury Study: 2. Associations between clinical patient characteristics and post-acute medical problems. *Paraplegia* 33:585–594.

Libet B, Alberts WW, Wright EW, Feinstein B (1967) Responses of human somatosensory cortex to stimuli below threshold for conscious sensation. *Science (80-)* 158:1597–1600.

Lin C, Nicolelis M, Schneider J, Chapin J (1990) A major direct GABAergic pathway from zona incerta to neocortex. *Science (80-)* 248:1553–1556.

Lindgren L, Westling G, Brulin C, Lehtipalo S, Andersson M, Nyberg L (2012) Pleasant human touch is represented in pregenual anterior cingulate cortex. *Neuroimage* 59:3427–3432.

Llinás R, Volkind RA (1973) The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. *Exp brain Res* 18:69–87.

Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc B Biol Sci* 357:1003–1037.

Logothetis NK (2008) What we can do and what we cannot do with fMRI. *Nature* 453:869–878.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150–157.

Loh KK, Hadj-Bouziane F, Petrides M, Procyk E, Amiez C (2018) Rostro-Caudal Organization of Connectivity between Cingulate Motor Areas and Lateral Frontal Regions. *Front Neurosci* 11:1–17.

Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW (2021a) The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 23:1231–1251.

Louis ED (2010) Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. *Lancet Neurol* 9:613–622.

Louis ED (2016a) Non-motor symptoms in essential tremor: A review of the current data and state of the field. *Park Relat Disord* 22:S115–S118.

Louis ED (2016b) Linking Essential Tremor to the Cerebellum: Neuropathological Evidence. *The Cerebellum* 15:235–242.

Louis ED (2021) The Essential Tremors: Evolving Concepts of a Family of Diseases. *Front Neurol* 12:1–7.

Louis ED, Bares M, Benito-Leon J, Fahn S, Frucht SJ, Jankovic J, Ondo WG, Pal PK, Tan E-K (2019) Essential tremor-plus: a controversial new concept. *Lancet Neurol* 4422.

Louis ED, Faust PL (2020) Essential tremor pathology: neurodegeneration and reorganization of neuronal connections. *Nat Rev Neurol* 16:69–83.

Louis ED, Faust PL, Vonsattel J-PG, Honig LS, Rajput A, Robinson C a., Rajput A, Pahwa R, Lyons KE, Ross GW, Borden S, Moskowitz CB, Lawton A, Hernandez N (2007) Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain* 130:3297–3307.

Louis ED, Ferreira JJ (2010) How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord* 25:534–541.

Louis ED, Huey ED, Cosentino S (2021b) Features of "ET plus" correlate with age and tremor duration: "ET plus" may be a disease stage rather than a subtype of essential tremor. *Parkinsonism Relat Disord* 91:42–47.

Louis ED, Lenka A (2017) The Olivary Hypothesis of Essential Tremor: Time to Lay this Model to Rest? *Tremor and other hyperkinetic movements* 7:473.

Louis ED, McCreary M (2021) How Common is Essential Tremor? Update on the Worldwide Prevalence of Essential Tremor. *Tremor and Other Hyperkinetic Movements* 11:1–14.

Louis ED, Okun MS (2011) It is time to remove the 'benign' from the essential tremor label. *Parkinsonism Relat Disord* 17:516–520.

Louis RJ, Lin C-Y, Faust PL, Koeppen AH, Kuo S-H (2015) Climbing fiber synaptic changes correlate with clinical features in essential tremor. *Neurology* 84:2284–2286.

Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, Matthews K, McIntyre CC, Schlaepfer TE, Schulder M, Temel Y, Volkmann J, Krauss JK (2019) Deep brain stimulation: current challenges and future directions. *Nat Rev Neurol* 15:148–160.

Luo R, Pan PL, Xu Y, Chen L (2019) No reliable gray matter changes in essential tremor. *Neurol Sci* 40:2051–2063.

Lv H, Wang Z, Tong E, Williams LM, Zaharchuk G, Zeineh M, Goldstein-Piekarski AN, Ball TM, Liao C, Wintermark M (2018) Resting-state functional MRI: Everything that nonexperts have always wanted to know. *Am J Neuroradiol* 39:1390–1399.

Macaluso E, Eimer M, Frith CD, Driver J (2003) Preparatory states in crossmodal spatial attention: spatial specificity and possible control mechanisms. *Exp Brain Res* 149:62–74.

Macchi G, Jones EG (1997) Toward an agreement on terminology of nuclear and subnuclear divisions of the motor thalamus. *J Neurosurg* 86:77–92.

Madelein van der Stouwe AM, Nieuwhof F, Helmich RC (2020) Tremor pathophysiology: lessons from neuroimaging. *Curr Opin Neurol* 33:474–481.

Mai JK, Majtanik M (2019) Toward a Common Terminology for the Thalamus. *Front Neuroanat* 12:1–23.

Manto M, Bower JM, Conforto AB, Delgado-García JM, da Guarda SNF, Gerwig M, Habas C, Hagura N, Ivry RB, Mariën P, Molinari M, Naito E, Nowak DA, Oulad Ben Taib N, Pelisson D, Tesche CD, Tilikete C, Timmann D (2012) Consensus Paper: Roles of the Cerebellum in Motor Control—The Diversity of Ideas on Cerebellar Involvement in Movement. *The Cerebellum* 11:457–487.

Marino RJ, Jones L, Kirshblum S, Tal J, Dasgupta A (2008) Reliability and Repeatability of the Motor and Sensory Examination of the International Standards for Neurological Classification of Spinal Cord Injury. *J Spinal Cord Med* 31:166–170.

Mashour GA, Roelfsema P, Changeux J-P, Dehaene S (2020) Conscious Processing and the Global Neuronal Workspace Hypothesis. *Neuron* 105:776–798.

Matthews PB (1966) The reflex excitation of the soleus muscle of the decerebrate cat caused by vibbration applied to its tendon. *J Physiol* 184:450–472.

McIntyre CC, Grill WM, Sherman DL, Thakor N V (2004) Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. *J Neurophysiol* 91:1457–1469.

McIntyre CC, Hahn PJ (2010) Network perspectives on the mechanisms of deep brain stimulation. *Neurobiol Dis* 38:329–337.

McKay WB, Lim HK, Priebe MM, Stokic DS, Sherwood AM (2004) Clinical Neurophysiological Assessment of Residual Motor Control in Post-Spinal Cord Injury Paralysis. *Neurorehabil Neural Repair* 18:144–153.

Meftah E-M, Shenasa J, Chapman CE (2002) Effects of a Cross-Modal Manipulation of Attention on Somatosensory Cortical Neuronal Responses to Tactile Stimuli in the

Monkey. *J Neurophysiol* 88:3133–3149.

Melloni L, Mudrik L, Pitts M, Koch C (2021) Making the hard problem of consciousness easier. *Science (80-)* 372:911–912.

Meoni S, Macerollo A, Moro E (2020) Sex differences in movement disorders. *Nat Rev Neurol* 16:84–96.

Meyer K (2011) Primary sensory cortices, top-down projections and conscious experience. *Prog Neurobiol* 94:408–417.

Meyer K, Kaplan JT, Essex R, Damasio H, Damasio A (2011) Seeing Touch Is Correlated with Content-Specific Activity in Primary Somatosensory Cortex. *Cereb Cortex* 21:2113–2121.

Miall RC, Christensen LOD, Cain O, Stanley J (2007) Disruption of state estimation in the human lateral cerebellum. *PLoS Biol* 5:2733–2744.

Middlebrooks EH, Tuna IS, Almeida L, Grewal SS, Wong J, Heckman MG, Lesser ER, Bredel M, Foote KD, Okun MS, Holanda VM (2018) Structural connectivity–based segmentation of the thalamus and prediction of tremor improvement following thalamic deep brain stimulation of the ventral intermediate nucleus. *NeuroImage Clin* 20:1266–1273.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD (2018) Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. *Brain* 141:2142–2155.

Mima T, Nagamine T, Nakamura K, Shibasaki H (1998) Attention Modulates Both Primary and Second Somatosensory Cortical Activities in Humans: A Magnetoencephalographic Study. *J Neurophysiol* 80:2215–2221.

Miocinovic S, Somayajula S, Chitnis S, Vitek JL (2013) History, Applications, and Mechanisms of Deep Brain Stimulation. *JAMA Neurol* 70:163.

Mitrofanis J (2005) Some certainty for the "zone of uncertainty"? Exploring the function of the zona incerta. *Neuroscience* 130:1–15.

Morel A (2007) Stereotactic Atlas of the Human Thalamus and Basal Ganglia. CRC Press.

Mundinger F (1965) Stereotaxic Interventions on the Zona Incerta Area for Treatment of Extrapyramidal Motor Disturbances and their Results. *Stereotact Funct Neurosurg* 26:222–230.

Muthuraman M, Heute U, Arning K, Anwar AR, Elble R, Deuschl G, Raethjen J (2012) Oscillating central motor networks in pathological tremors and voluntary

movements. What makes the difference? *Neuroimage* 60:1331–1339.

Muthuraman M, Raethjen J, Koirala N, Anwar AR, Mideksa KG, Elble R, Groppa S, Deuschl G (2018) Cerebello-cortical network fingerprints differ between essential, Parkinson's and mimicked tremors. *Brain* 141:1770–1781.

Nachev P, Kennard C, Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci* 9:856–869.

Naghavi HR, Nyberg L (2005) Common fronto-parietal activity in attention, memory, and consciousness: Shared demands on integration? *Conscious Cogn* 14:390–425.

Neely K a, Kurani AS, Shukla P, Planetta PJ, Wagle Shukla A, Goldman JG, Corcos DM, Okun MS, Vaillancourt DE (2015) Functional Brain Activity Relates to 0–3 and 3–8 Hz Force Oscillations in Essential Tremor. *Cereb Cortex* 25:4191–4202.

Nees TA, Finnerup NB, Blesch A, Weidner N (2017) Neuropathic pain after spinal cord injury. *Pain* 158:371–376.

Nickerson LD, Smith SM, Öngür D, Beckmann CF (2017) Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. *Front Neurosci* 11:1–18.

Nicoletti V, Cecchi P, Pesaresi I, Frosini D, Cosottini M, Ceravolo R (2020) Cerebello-thalamo-cortical network is intrinsically altered in essential tremor: evidence from a resting state functional MRI study. *Sci Rep* 10:16661.

Nowacki A, Barlatey S, Al-Fatly B, Dembek T, Bot M, Green AL, Kübler D, Lachenmayer ML, Debove I, Segura-Amil A, Horn A, Visser-Vandewalle V, Schuurman R, Barbe M, Aziz TZ, Kühn AA, Nguyen TAK, Pollo C (2022) Probabilistic Mapping Reveals Optimal Stimulation Site in Essential Tremor. *Ann Neurol* 91:602–612.

Ogawa S, Lee T -M, Nayak AS, Glynn P (1990a) Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med* 14:68–78.

Ogawa S, Lee TM, Kay AR, Tank DW (1990b) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci* 87:9868–9872.

Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci* 89:5951–5955.

Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G, Ekholm S, Strigo I, Worsley K, Vallbo ÅB, Bushnell MC (2002) Unmyelinated tactile afferents signal touch and project to insular cortex. *Nat Neurosci* 5:900–904.

Omori S, Isose S, Otsuru N, Nishihara M, Kuwabara S, Inui K, Kakigi R (2013) Somatotopic representation of pain in the primary somatosensory cortex (S1) in humans. *Clin Neurophysiol* 124:1422–1430.

Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguière F (2002) Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb cortex* 12:376–385.

Padberg J, Cerkevich C, Engle J, Rajan AT, Recanzone G, Kaas J, Krubitzer L (2009) Thalamocortical Connections of Parietal Somatosensory Cortical Fields in Macaque Monkeys are Highly Divergent and Convergent. *Cereb Cortex* 19:2038–2064.

Palesi F, Tournier J-D, Calamante F, Muhlert N, Castellazzi G, Chard D, D'Angelo E, Wheeler-Kingshott CAM (2015) Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo. *Brain Struct Funct* 220:3369–3384.

Pan M-K, Li Y-S, Wong S-B, Ni C-L, Wang Y-M, Liu W-C, Lu L-Y, Lee J-C, Cortes EP, Vonsattel J-PG, Sun Q, Louis ED, Faust PL, Kuo S-H (2020) Cerebellar oscillations driven by synaptic pruning deficits of cerebellar climbing fibers contribute to tremor pathophysiology. *Sci Transl Med* 12:1–15.

Paris-Robidas S, Brochu E, Sintes M, Emond V, Bousquet M, Vandal M, Pilote M, Tremblay C, Di Paolo T, Rajput AH, Rajput A, Calon F (2012) Defective dentate nucleus GABA receptors in essential tremor. *Brain* 135:105–116.

Passamonti L, Novellino F, Cerasa A, Chiriaco C, Rocca F, Matina MS, Fera F, Quattrone A (2011) Altered cortical-cerebellar circuits during verbal working memory in essential tremor. *Brain* 134:2274–2286.

Pauling L, Coryell CD (1936) The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. *Proc Natl Acad Sci* 22:210–216.

Pedrosa DJ, Brown P, Cagnan H, Visser-Vandewalle V, Wirths J, Timmermann L, Brittain J-S (2018) A functional micro-electrode mapping of ventral thalamus in essential tremor. *Brain* 141:2644–2654.

Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60:389–443.

Perlmutter JS, Mink JW, Bastian a J, Zackowski K, Hershey T, Miyawaki E, Koller W, Videen TO (2002) Blood flow responses to deep brain stimulation of thalamus. *Neurology* 58:1388–1394.

Pfyffer D, Huber E, Sutter R, Curt A, Freund P (2019) Tissue bridges predict recovery after traumatic and ischemic thoracic spinal cord injury. *Neurology* 93:e1550–e1560.

Pfyffer D, Vallotton K, Curt A, Freund P (2020) Tissue bridges predict neuropathic pain emergence after spinal cord injury. *J Neurol Neurosurg Psychiatry* 91:1111–1117.

Philipson J, Blomstedt P, Hariz M, Jahanshahi M (2019) Deep brain stimulation in the caudal zona incerta in patients with essential tremor: effects on cognition 1 year after surgery. *J Neurosurg* 136:1–8.

Picard N, Strick PL (1996) Motor Areas of the Medial Wall: A Review of Their Location and Functional Activation. *Cereb Cortex* 6:342–353.

Picard N, Strick PL (2001) Imaging the premotor areas. *Curr Opin Neurobiol* 11:663–672.

Pietracupa S, Bologna M, Tommasin S, Berardelli A, Pantano P (2021) The Contribution of Neuroimaging to the Understanding of Essential Tremor Pathophysiology: a Systematic Review. *The Cerebellum*.

Plaha P, Javed S, Agombar D, O' Farrell G, Khan S, Whone A, Gill S (2011) Bilateral caudal zona incerta nucleus stimulation for essential tremor: outcome and quality of life. *J Neurol Neurosurg Psychiatry* 82:899–904.

Plaha P, Khan S, Gill SS (2008) Bilateral stimulation of the caudal zona incerta nucleus for tremor control. *J Neurol Neurosurg Psychiatry* 79:504–513.

Pons TP, Garraghty PE, Friedman DP, Mishkin M (1987) Physiological Evidence for Serial Processing in Somatosensory Cortex. *Science (80-)* 237:417–420.

Putnam TJ (1940) Treatment of unilateral paralysis agitans by section of the lateral pyramidal tract. *Arch Neurol Psychiatry* 44:950–976.

Qi H-X, Preuss TM, Kaas JH (2008) Somatosensory Areas of the Cerebral Cortex: Architectonic Characteristics and Modular Organization. In: The Senses: A Comprehensive Reference, pp 143–169. Elsevier.

Raethjen J, Deuschl G (2012) The oscillating central network of Essential tremor. *Clin Neurophysiol* 123:61–64.

Raichle ME (2009) A brief history of human brain mapping. *Trends Neurosci* 32:118–126.

Rajput AH, Adler CH, Shill HA, Rajput A (2012) Essential tremor is not a neurodegenerative disease. *Neurodegener Dis Manag* 2:259–268.

Ramnani N (2006) The primate cortico-cerebellar system: anatomy and function. *Nat Rev Neurosci* 7:511–522.

Rezai AR, Baker KB, Tkach JA, Phillips M, Hrdlicka G, Sharan AD, Nyenhuis J, Ruggieri P, Shellock FG, Henderson J (2005) Is Magnetic Resonance Imaging Safe for Patients

with Neurostimulation Systems Used for Deep Brain Stimulation? *Neurosurgery* 57:1056–1062.

Rezai AR, Lozano AM, Crawley AP, Joy MLG, Davis KD, Kwan CL, Dostrovsky JO, Tasker RR, Mikulis DJ (1999) Thalamic stimulation and functional magnetic resonance imaging: localization of cortical and subcortical activation with implanted electrodes. *J Neurosurg* 90:583–590.

Riskin-Jones HH, Kashanian A, Sparks H, Tsolaki E, Pouratian N (2021) Increased structural connectivity of thalamic stimulation sites to motor cortex relates to tremor suppression. *NeuroImage Clin* 30:102628.

Rizzolatti G, Fogassi L (2014) The mirror mechanism: recent findings and perspectives. *Philos Trans R Soc B Biol Sci* 369:20130420.

Roland PE, Larsen B, Lassen NA, Skinhoj E (1980) Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J Neurophysiol* 43:118–136.

Romo R, Hernández A, de Lafuente V, Zainos A, Lemus L, Luna R, Nácher V, Alvarez M (2020) Role of Primary Somatosensory Cortex in Perceptual Touch Detection and Discrimination. In: The Senses: A Comprehensive Reference, pp 261–278. Elsevier.

Romo R, Rossi-Pool R (2020) Turning Touch into Perception. *Neuron* 105:16–33.

Roy CS, Sherrington CS (1890) On the Regulation of the Blood-supply of the Brain. *J Physiol* 11:85–158.

Ruff CC (2013) Sensory processing: who's in (top-down) control? *Ann N Y Acad Sci* 1296:88–107.

Sabbah P, de Schonen S, Leveque C, Gay S, Pfefer F, Nioche C, Sarrazin J-L, Barouti H, Tadie M, Cordoliani Y-S (2002) Sensorimotor Cortical Activity in Patients with Complete Spinal Cord Injury: A Functional Magnetic Resonance Imaging Study. *J Neurotrauma* 19:53–60.

Sakai K (2008) Task Set and Prefrontal Cortex. *Annu Rev Neurosci* 31:219–245.

Sakai ST, Stepniewska I, Qi HX, Kaas JH (2000) Pallidal and cerebellar afferents to pre-supplementary motor area thalamocortical neurons in the owl monkey: A multiple labeling study. *J Comp Neurol* 417:164–180.

Sammartino F, Krishna V, Sankar T, Fisico J, Kalia SK, Hodaie M, Kucharczyk W, Mikulis DJ, Crawley A, Lozano AM (2017) 3-Tesla MRI in patients with fully implanted deep brain stimulation devices: a preliminary study in 10 patients. *J Neurosurg* 127:892–898.

Sandberg K, Timmermans B, Overgaard M, Cleeremans A (2010) Measuring consciousness: is one measure better than the other? *Conscious Cogn* 19:1069–1078.

Sandrone S, Bacigaluppi M, Galloni MR, Cappa SF, Moro A, Catani M, Filippi M, Monti MM, Perani D, Martino G (2014) Weighing brain activity with the balance: Angelo Mosso's original manuscripts come to light. *Brain* 137:621–633.

Sandström L, Blomstedt P, Karlsson F, Hartelius L (2020) The Effects of Deep Brain Stimulation on Speech Intelligibility in Persons With Essential Tremor. *J Speech, Lang Hear Res* 63:456–471.

Sandvik U, Koskinen L-O, Lundquist A, Blomstedt P (2012) Thalamic and subthalamic deep brain stimulation for essential tremor: where is the optimal target? *Neurosurgery* 70:840–845.

Savic G, Bergström EMK, Frankel HL, Jamous MA, Jones PW (2007) Inter-rater reliability of motor and sensory examinations performed according to American Spinal Injury Association standards. *Spinal Cord* 45:444–451.

Schell G, Strick P (1984) The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. *J Neurosci* 4:539–560.

Schmahmann JD (1996) From movement to thought: Anatomic substrates of the cerebellar contribution to cognitive processing. *Hum Brain Mapp* 4:174–198.

Schmahmann JD, Guell X, Stoodley CJ, Halko MA (2019) The Theory and Neuroscience of Cerebellar Cognition. *Annu Rev Neurosci* 42.

Schmidt TT, Blankenburg F (2019) The Somatotopy of Mental Tactile Imagery. *Front Hum Neurosci* 13:1–10.

Schnitzler A, Gross J (2005) Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci* 6:285–296.

Schnitzler A, Münks C, Butz M, Timmermann L, Gross J (2009) Synchronized brain network associated with essential tremor as revealed by magnetoencephalography. *Mov Disord* 24:1629–1635.

Schröder P, Schmidt TT, Blankenburg F (2019) Neural basis of somatosensory target detection independent of uncertainty, relevance, and reports. *Elife* 8:1–19.

Schuurman PR, Bosch DA, Bossuyt PMM, Bonsel GJ, van Someren EJW, de Bie RMA, Merkus MP, Speelman JD (2000) A Comparison of Continuous Thalamic Stimulation and Thalamotomy for Suppression of Severe Tremor. *N Engl J Med* 342:461–468.

Sejnowski TJ, Churchland PS, Movshon JA (2014) Putting big data to good use in neuroscience. *Nat Neurosci* 17:1440–1441.

Sengul Y, Sengul HS, Yucekaya SK, Yucel S, Bakim B, Pazarcı NK, Özdemir G (2015) Cognitive functions, fatigue, depression, anxiety, and sleep disturbances: assessment of nonmotor features in young patients with essential tremor. *Acta Neurol Belg* 115:281–287.

Sharifi S, Nederveen AJ, Booij J, van Rootselaar A-F (2014) Neuroimaging essentials in essential tremor: A systematic review. *NeuroImage Clin* 5:217–231.

Sherwood AM, Dimitrijevic MR, Barry McKay W (1992) Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. *J Neurol Sci* 110:90–98.

Shill HA, Adler CH, Sabbagh MN, Connor DJ, Caviness JN, Hentz JG, Beach TG (2008) Pathologic findings in prospectively ascertained essential tremor subjects. *Neurology* 70:1452–1455.

Singh A, Tetreault L, Kalsi-Ryan S, Nouri A, Fehlings MG (2014) Global prevalence and incidence of traumatic spinal cord injury. *Clin Epidemiol* 6:309–331.

Sjöberg RL, Stålnacke M, Andersson M, Eriksson J (2019) The supplementary motor area syndrome and cognitive control. *Neuropsychologia* 129:141–145.

Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF (2009) Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A* 106:13040–13045.

Snyder AZ, Raichle ME (2012) A brief history of the resting state: The Washington University perspective. *Neuroimage* 62:902–910.

Spiegel EA, Wycis HT, Marks M, Lee AJ (1947) Stereotaxic apparatus for operations on the human brain. *Science (80-)* 106:349–350.

Spiegel EA, Wycis HT, Szekely EG, Adams J, Flanagan M, Baird HW (1963) Campotomy in Various Extrapyramidal Disorders. *J Neurosurg* 186:871–884.

Spiegel J, Fuss G, Backens M, Reith W, Magnus T, Becker G, Moringlane J-R, Dillmann U (2003) Transient dystonia following magnetic resonance imaging in a patient with deep brain stimulation electrodes for the treatment of Parkinson disease. *J Neurosurg* 99:772–774.

Stepniewska I, Preuss TM, Kaas JH (2007) Thalamic connections of the dorsal and ventral premotor areas in New World owl monkeys. *Neuroscience* 147:727–745.

Stepniewska I, Sakai ST, Qi H-X, Kaas JH (2003) Somatosensory input to the ventrolateral thalamic region in the macaque monkey: A potential substrate for parkinsonian tremor. *J Comp Neurol* 455:378–395.

Stevens RT, London SM, Vania Apkarian A (1993) Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey. *Brain Res* 631:241–246.

Stippich C (2015) Clinical Functional MRI (Stippich C, ed). Springer Berlin Heidelberg.

Stolze H, Petersen G, Raethjen J, Wenzelburger R, Deuschl G (2001) The gait disorder of advanced essential tremor. *Brain* 124:2278–2286.

Stone J V. (2002) Independent component analysis: an introduction. *Trends Cogn Sci* 6:59–64.

Stoodley CJ, MacMore JP, Makris N, Sherman JC, Schmahmann JD (2016) Location of lesion determines motor vs. cognitive consequences in patients with cerebellar stroke. *NeuroImage Clin* 12:765–775.

Strick PL, Dum RP, Rathelot J-A (2021) The Cortical Motor Areas and the Emergence of Motor Skills: A Neuroanatomical Perspective. *Annu Rev Neurosci* 44:425–447.

Sugiura Y, Lee CL, Perl ER (1986) Central Projections of Identified, Unmyelinated (C) Afferent Fibers Innervating Mammalian Skin. *Science (80-)* 234:358–361.

Tanaka Y, Fujimura N, Tsuji T, Maruishi M, Muranaka H, Kasai T (2009) Functional interactions between the cerebellum and the premotor cortex for error correction during the slow rate force production task: An fMRI study. *Exp Brain Res* 193:143–150.

Tasker RR, Lenz FA, Dostrovksy JO, Yamashiro K, Chodakiewitz J, Albe-Fessard DG (1987) The Physiological Basis of VIM Thalamotomy for Involuntary Movement Disorders. In: Clinical aspects of sensory motor integration, pp 265–276. Springer, Berlin.

Therrien AS, Bastian AJ (2019) The cerebellum as a movement sensor. *Neurosci Lett* 688:37–40.

Tikoo S, Pietracupa S, Tommasin S, Bologna M, Petsas N, Bharti K, Berardelli A, Pantano P (2020) Functional disconnection of the dentate nucleus in essential tremor. *J Neurol* 267:1358–1367.

Treede R-D (2020) Nociceptive Processing in the Cerebral Cortex. In: The Senses: A Comprehensive Reference, Second Edi., pp 47–57. Elsevier.

Treede RD, Apkarian AV (2008) Nociceptive Processing in the Cerebral Cortex. In: The

Senses: A Comprehensive Reference, pp 669–697. Elsevier.

Tröster AI, Woods SP, Fields J a., Lyons KE, Pahwa R, Higginson CI, Koller WC (2002) Neuropsychological deficits in essential tremor: an expression of cerebello-thalamo-cortical pathophysiology? *Eur J Neurol* 9:143–151.

Udupa K, Chen R (2015) The mechanisms of action of deep brain stimulation and ideas for the future development. *Prog Neurobiol* 133:27–49.

Vallbo ÅB, Wessberg J (1993) Organization of motor output in slow finger movements in man. *J Physiol* 469:673–691.

van den Berg KRE, Helmich RC (2021) The Role of the Cerebellum in Tremor – Evidence from Neuroimaging. *Tremor and Other Hyperkinetic Movements* 11:1–17.

Van Hees J, Gybels J (1981) C nociceptor activity in human nerve during painful and non painful skin stimulation. *J Neurol Neurosurg Psychiatry* 44:600–607.

Vázquez Y, Salinas E, Romo R (2013) Transformation of the neural code for tactile detection from thalamus to cortex. *Proc Natl Acad Sci* 110:E2635-44.

Velasco FC, Molina-Negro P, Bertrand C, Hardy J (1972) Further definition of the subthalamic target for arrest of tremor. *J Neurosurg* 36:184–191.

Vierck C (2020) Mechanisms of Below-Level Pain Following Spinal Cord Injury (SCI). *J Pain* 21:262–280.

Vierck CJ, Whitsel BL, Favorov O V., Brown AW, Tommerdahl M (2013) Role of primary somatosensory cortex in the coding of pain. *Pain* 154:334–344.

Vilis T, Hore J (1980) Central neural mechanisms contributing to cerebellar tremor produced by limb perturbations. *J Neurophysiol* 43:279–291.

Vogt B, Rosene D, Pandya D (1979) Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. *Science (80-)* 204:205–207.

Wagner FB et al. (2018) Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* 563:65–71.

Wahlgren C, Levi R, Amezcua S, Thorell O, Thordstein M (2021) Prevalence of discomplete sensorimotor spinal cord injury as evidenced by neurophysiological methods: A cross-sectional study. *J Rehabil Med* 53:jrm00156.

Walker AE (1949) Cerebral pedunculotomy for the relief of involuntary movements; hemiballismus. *Acta Psychiatr Neurol* 24:723–729.

Wang X, Chou X lin, Zhang LI, Tao HW (2020) Zona Incerta: An Integrative Node for Global Behavioral Modulation. *Trends Neurosci* 43:82–87.

Wasner G, Lee BB, Engel S, McLachlan E (2008) Residual spinothalamic tract pathways predict development of central pain after spinal cord injury. *Brain* 131:2387–2400.

Waters RL, Adkins RH, Yakura JS (1991) Definition of complete spinal cord injury. *Paraplegia* 29:573–581.

Welton T, Cardoso F, Carr JA, Chan L-L, Deuschl G, Jankovic J, Tan E-K (2021) Essential tremor. *Nat Rev Dis Prim* 7:83.

Wertheimer P, Bourret J, Lapras C (1960) Apropos of the treatment of a dyskinesia by stereotaxic leucotomy [in French]. *Rev Neurol (Paris)* 102:481–486.

White LE, Andrews TJ, Hulette C, Richards A, Groelle M, Paydarfar J, Purves D (1997) Structure of the human sensorimotor system. I: Morphology and cytoarchitecture of the central sulcus. *Cereb cortex* 7:18–30.

Wills AJ, Jenkins IH, Thompson PD, Findley LJ, Brooks DJ (1994) Red nuclear and cerebellar but no olivary activation associated with essential tremor: A positron emission tomoraphic study. *Ann Neurol* 36:636–642.

Wolpert DM, Ghahramani Z, Flanagan JR (2001) Perspectives and problems in motor learning. *Trends Cogn Sci* 5:487–494.

Wolpert DM, Miall RC, Kawato M (1998) Internal models in the cerebellum. *Trends Cogn Sci* 2:338–347.

Wrigley PJ, Siddall PJ, Gustin SM (2018) New evidence for preserved somatosensory pathways in complete spinal cord injury: A fMRI study. *Hum Brain Mapp* 39:588–598.

Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, Fischl B, Liu H, Buckner RL (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* 106:1125–1165.

Zeman A (2001) Consciousness. *Brain* 124:1263–1289.

Zilles K, Palomero-Gallagher N (2020) The Architecture of Somatosensory Cortex. In: The Senses: A Comprehensive Reference, Second Edi., pp 225–260. Elsevier.

Appendix

The semi-structured interview in study II (English translation)

Pain
Definition/inclusion of chronic pain: persistent/recurrent pain during the last 6 months

- Have you experienced pain during the last 14 days, incl. today? □ YES □ NO
  If Yes:
  - How many days have you experience pain during the last 14 days including today?
  - How long did the pain last?
  - In general, how much has pain interfered with your day-to-day activities in the last week?
  - How much did the pain influence/disturb your day-to-day activities?
    0 – 10 Numerical Rating Scale (ranging from 0 = "No interference" to a maximum of 10 = "Extreme interference") of pain interference with general activity.
    In general, how much has pain interfered with your overall mood in the past week? (NRS 0= no influence … 10 = "Extreme interference")
  - In general, how much has pain interfered with your ability to get a good night's sleep? (NRS 0= no influence … 10 = "Extreme interference")
  - Do you experience pain below your injury level, that is in body parts without sensation?
    □ YES □ NO
  - How many different pain problems do you have?

Description of the three worst pain problems:

Pain problem 1:

- Date of onset:
- Pain locations/sites (Use pain drawing assessment)
- Frequency of experienced pain during the last week:
- Pain intensity (NRS 0-10):
- Character (use descriptors if needed; for example, dull, aching, tender, cramping, hot-burning, tingling, pricking, pins and needles, squeezing, cold, electric, or shooting
- Factors that make the pain worse/better?
- Hyperalgesia (nociceptive stimuli cause more pain on a skin region, compared to other regions):
  □ YES □ NO
- Allodynia (experienced pain even due to normally non-painful stimuli)
  □ YES □ NO
- Treatment:

Pain problem 2 and 3:

Same questions as for "pain problem 1"

Spasticity:

- Have you experienced spasticity? □ YES □ NO
    - Describe! When do you experience most spasticity?
    - Triggers (What situations trigger your spasticity?)
    - In general, does spasticity have major impact on your quality of life, NRS 0 to 10
    - Treatment during that last 4 weeks:
    - Baclofen pump (ITP therapy)? □ YES □ NO

Bladder function:

- Do you have any sensation when your urinary bladder is full? □ YES □ NO □ DO NOT KNOW
    - If Yes, in a normal way "like before the injury", that is pressure over the bladder
    - Yes, differently. Describe.
- How do you empty your bladder?
- Normally, how often do you empty your bladder?
- Do you experience urinary urgency? When and how often?
- Do you leak urine? When and how often? What is the volume?
- Medical treatment and Botulinum toxin injections during the last year?
- Surgical intervention on the urinary tract? For what reason?
- Do you have problems with bladder function that are unrelated to spinal cord injury?
  □ NO □ DO NOT KNOW □ YES, Specify:

Bowel function:

- Do you feel your bowel movements? □ YES □ NO □ DO NOT KNOW
    - If Yes, in a normal way "like before the injury"
    - Yes, indirectly (unpleasant sensations or spasms in the abdomen, spasms in leg muscles, sweating, headache etc.)
- How do you empty your bowel? Frequency? Time required?
- Do you leak? When? How often?
- Surgical interventions? For what reason?
- Medical treatment?

Autonomic dysreflexia (relevant in patients with NLI above T6)
A marked increase in the sympathetic response to minor stimuli such as bladder or rectal distention, and nociceptive stimulation. Manifestations include hypertension, tachycardia (or reflex bradycardia), fever, flushing and hyperhidrosis.

- Do you experience autonomic dysreflexia? □ YES □ NO □ DO NOT KNOW
- If Yes, in what are the triggers (for example full bladder or painful (or tactile) stimulation below the NLL)
- What symptoms do you experience during the attacks?
- Treatment

Propensity for injuries on body parts innervated below NLI

- Do you often get injuries below the injury level? □ YES □ NO □ DO NOT KNOW
- If Yes, what kind of injuries?
- Did you have decubitus ulcers? □ YES □ NO □ DO NOT KNOW
    - Where?
    - How often?
    - Have you undergone a surgical intervention to treat an ulcer?
- Do you get any sensation from the body when seated on a firm surface for a prolonged period of time?

Body image

- How did the paralysis and sensory loss influence your image of your body parts below the injury level?
- Do have preserved sensation below the NLI (ZPP)? Where? Normal/disturbed?
- Do have preserved sensation in the perianal area? □ YES □ NO □ DO NOT KNOW
- Do have preserved sensation in genial regions? □ YES □ NO □ DO NOT KNOW
- Do you normally feel the surface that you sit on? □ YES □ NO □ DO NOT KNOW
- Body image (distortion?)

Current medications:

Contraindications for undergoing MRI scanning

- Do you currently or have you ever had an electric- or battery driven implant in your body? Pacemaker, medical pump (for example insulin-or chemotherapy pump), neurostimulator, hearing device (for example cochlear implant), other electric/battery driven implants □ YES □ NO
  If Yes, specify:
- Have you got any metallic objects in your body?Vascular stents (for example in your brain or heart), objects like a skin expander, screws, cardiac valve, shunt, prosthesis, dental braces, ear prosthesis? □ YES □ NO
  If Yes, specify:

- Have you got unremovable piercings? □ YES □ NO
- Pregnant? □ YES □ NO
- Claustrophobia? □ YES □ NO
- Morbid obesity? □ YES □ NO
- Problem with high volumes? □ YES □ NO

Clinical examination in study II (ISNCSCI worksheet)

Published with permission from American Spinal Injury Association (ASIA): International Standards for Neurological Classification of Spinal Cord Injury, revised 2011 and updated 2015; Richmond, VA.