Quantitative EEG and Neuromodulation for the Treatment of Central Neuropathic Pain in Paraplegic Patients

Muhammad Abul Hasan

A thesis submitted for the degree of Doctor of Philosophy (PhD)

Department of Biomedical Engineering

School of Engineering

University of Glasgow

September 2014

Abstract

Approximately, 2/3 of patients with a spinal cord injury (SCI) suffer from chronic pain, leading to a reduction in quality of life. The prevalence of chronic central neuropathic pain (CNP) in the SCI population is 40%. Recent neuroimaging studies provided evidence that CNP is accompanied by modified brain activity at surface and deep cortical levels and that CNP is resistant to different pharmacological and non-pharmacological treatments.

Our current knowledge on how CNP affects the brain activity of SCI patients is mainly based on fMRI studies. Although these studies provide precise spatial localisation of brain regions most affected by CNP, they indirectly measure brain activity through measuring blood oxygenation. Therefore they lack information specific to neuronal activity such as dynamic, time and frequency dependant oscillatory activity of cortical structures. Therefore, in Phase 1 of this study, electroencephalogram (EEG) activity of paraplegic patients with CNP (PWP) is compared with the EEG activity of able-bodied (AB) participants and paraplegic patients without CNP (PNP). It was found that CNP leads to frequency dependant EEG signatures both in the relaxed state and during motor tasks that are not restricted to the cortical representation of the body part perceived as being painful.

The pharmacological treatment of CNP has a number of side effects and does not provide significant pain relief. The effect of non-pharmacological treatments is inconsistent. Neurofedback (NF) is a non-pharmacological treatment, based on the voluntarily modulation of brain activity to control pain intensity. Using NF training the patient can learn and apply a mental strategy to control pain, without the need for an external device. However, NF requires a large number of training sessions to learn the necessary mental strategy. Therefore, in Phase 2 of this study, the effect on pain intensity of a large number

of NF sessions, using different NF training protocols, was assessed. The clinically and statistically significant reduction of pain observed in this study demonstrates that NF training has the potential to manage chronic CNP in paraplegic patients. This study also provides evidence that the reduction of pain achieved using NF training may not be due to a placebo effect. Furthermore, the study demonstrates the immediate global effect of NF training on power and coherence.

To date, no neuroimaging studies that have applied NF training with patients with CNP have shown changes in brain activity before the first and after the last training session. Therefore, in phase 3 of this study, the long-term neurological effect of NF training was assessed using EEG. This study provides evidence that NF training does not only induce an effect on spontaneous EEG activity, but also induces changes on evoked EEG activity.

In conclusion, this study compared the EEG activity of three groups (AB, PWP, and PNP) and found that CNP (PWP group) leads to frequency dependant dynamic oscillatory signatures. The study also reported that NF training has a potential to reduce pain and this reduction of pain might not be an effect of placebo. Furthermore, it was found that NF training induce long-term changes in the EEG activity recorded in relaxed state and during motor tasks. This long-term change in EEG activity was noticed at the surface and deep cortical structures.

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Acknowledgement

First and foremost, I thank Allah for reasons too numerous to mention; successful completion of this thesis through contribution of many peoples being just one of them. I wish to express my sincere thanks and appreciation to my supervisor, Dr. Aleksandra Vuckovic, for her commitment, helpful discussions and valuable feedback, which have been the most important factors in helping me to raise the quality of this thesis. I like to thank current and past competent authorities (chairman and dean biomedical engineering department, Prof. Neelofur Master, Prof. Dr. Ali Raza Jafri, and Prof. Dr. Sarosh Hashmat Lodhi; vice and pro vice chancellors, Late Engr. Abul Kalam, Prof. Dr. Muzzaffar Mehmood, and Prof. Dr. Muhammad Afzal Haque) of NED University of Engineering & Technology Karachi Pakistan for providing me a scholarship. I would like to thank the University of Glasgow and Queens Elizabeth National Spinal Injuries Unit (QENSIU) at Southern General hospital, Glasgow, Scotland, for providing me with the necessary facilities and conductive environment for carrying out this research.

My special gratitude goes to my parents (Mr. Pervaiz Akhter and MRs. Saeeda Bibi) who were always there to stand beside me, to motivate me and pray for me. My endless thanks go to my wife, Fatima Hasan, whose encouragement and unconditional support during the years of this PhD gave me the strength to complete this journey. Furthermore, I am thankful to our neighbour Mr Amjad Hussain and his family for their support to entertain my wife and son.

I am grateful to my current and past colleagues at the University of Glasgow and at NED University Pakistan for their valuable support throughout PhD; manly Syed Mohammad Noaman, Bilal Ahmad Usmani, Mohammad Jarjees, Henrik Gollee, Bethel Osuagwu, Sarah Comincioli, Rebecca Lightfoot, and Euan McCaughey. I am thankful to Mr Javaid Pervaiz

from the NED University for updating status of living expense, leave, and salary. I am also thankful to Elaine McNamara and Amanda Smith of the Glasgow University for arranging my visits to conference and courses, Mr Fraser (consultant at QENSIU) for his valuable moral support, and Dr Mclean and Dr Purcell for choosing participants. Professor Bernard Conway from the University of Strathclyde provided constructive feedback on results of the study and allowed us to use the device for performing experiments of the Phase 1 and Phase 3 of this study. Finally, yet importantly, I am thankful to all participants of this study, especially to those five patients who attend large number of training sessions.

Funding Sources

This PhD work has been supported by: (i) NED University Pakistan, Karachi for PhD scholarship under the scheme “Strengthening of NED University of Engineering and Technology, Mega-3”, (ii) MRC grant G0902257/1, (iii) Glasgow Research Partnership in Engineering, and (iv) GU68 for buying consumables to run the experiments.

Achievements

During PhD, I received GU68 award, three public awareness articles were published in different magazines, and a radio interview of a single patient was broadcasted.

2012 GU68 award (http://www.guengtrust.org.uk/awards_history)

Mar-2012 *'Easing the pain'* is published in University of Glasgow website Headlines. This article describes the effect of Neurofeedback Training for treatment of chronic central neuropathic pain. (http://www.gla.ac.uk/research/infocus/projects/headline_281501_en.html)

2012 *'Easing the Pain'* is published in Spinal Cord Injury Scotland magazine. This article reports the patient perspective after getting Neurofeedback Training for managing chronic central neuropathic pain. (http://www.sisonline.org/images/content_files/FINAL_APPROVED_VERSION_Summer_2012_SIS_News_A4_36pp.pdf , page 12)

Nov 2013 *'The Power of the Mind'* is broadcasted on Internet radio program 'Airing Pain' Episode 47. http://painconcern.org.uk/how-we-help/airing-pain/

April 2014 *'Training the Brain' under 'Exploring pathways of Pain'* is published in Horizons Magazine at University of Glasgow. (http://www.gla.ac.uk/research/horizons/spring2014/exploringpathwaysofpain/?utm_source=newsletter)

List of Publications

1. Vuckovic A, **Muhammad Abul Hasan**, Bahman Nasseroleslami, Bernard A. Conway, David B. Allan, Matthew Fraser. *Motor imagery in spinal cord injury with neuropathic pain: a component clustering method.* Proceedings of the 4th International Symposium on Applied Sciences in Biomedical and Communication Technologies. ISABEL 2011, October 26-29, Barcelona, Spain. ACM New York, NY, USA.

2. Vuckovic A, **Hasan, M.A.,** Conway, B.A., Allan, D.B., and Fraser, M. (2011) *Neurofeedback for treatment of neuropathic pain in SCI patients.* SCIence Research Update, 1 . p. 18.

3. Vuckovic A, **Muhammad Abul Hasan**, Matthew Fraser, David B. Allan. *Effects of Neurofeedback Treatment on Neuropathic Pain Following Spinal Cord injury.* 14th world congress on pain, IASP 2012 Milan. 27th-31st Aug 2012.

4. Muhammad Abul Hasan, Vuckovic A, David B. Allan, Matthew Fraser. *Voluntarily modulation of EEG rhyt**h**ms reduces Neuropathic pain in patients with Spinal Cord Injury.* 51st Annual Scientific Meeting ISCOS 2012 London- Advances in Spinal Cord Injury Management. 3rd-5th sep 2012. Abstract O26, page 78.

5. Vuckovic A, Muhammad Abul Hasan, Matthew Fraser, David B. Allan. *Design and experimental evaluation of Neurofeedback system for treatment of Central Neuropathic Pain.* National Health Informatics Scotland, Glasgow. 20th-21st Sep 2012.

6. Muhammad Abul Hasan, Vuckovic A, David B. Allan, Matthew Fraser. *On-line EEG Training Reduces Central Neuropathic Pain*. GRPe Conference 2013 Glasgow. June 2013.

7. A Vuckovic, B. Conway, M.A. Hasan, B. Kalman. *Source Information Flow study on EEG data during Motor Imagery*. Pg 67-68. Bioengineering conference 2013. Glasgow UK. 6^{th} -7^{th} September 2013.

8. A Vuckovic, **M A Hasan**, M Fraser, B A Conway, B Nasserolessami, D B Allan. *Dynamic Oscillatory Signatures of Central Neuropathic Pain in Spinal Cord Injury*. (Accepted) 2014. The Journal of Pain.

9. Aleksandra Vuckovic, **Muhammad Abul Hasan**, Matthew Fraser, B A Conway, B Nasserolessami, D B Allan. *Clinical and Neurological Effects of Neurofeedback Training for Treatment of Central Neuropathic Pain.* ICNR conference 2014. Denmark. 22-26 june 2014.

10. **Muhammad Abul Hasan**, Aleksandra Vuckovic, Matthew Fraser, B A Conway, B Nasserolessami, D B Allan. *Reduced Activation at Cortical Level Following Neurofeedback Treatment is Associated with Reduction in Central Neuropathic Pain Intensity*. 6th BCI conference 2014. Graz,Austria. 16-19 sep 2014.

11. Ren Xu, Ning Jiang, Aleksandra Vuckovic, **Muhammad Hasan**, Natalie Mrachacz-Kersting, David Allan, Matthew Fraser, Bahman Nasseroleslami, Bernie Conway, Kim Dremstrup, and Dario Farina. *Movement-related cortical potentials in paraplegic patients: abnormal patterns and considerations for BCI-*

rehabilitation. Accepted in Frontiers in Neuroscience.

12. Aleksandra Vuckovic, **Muhammad Abul Hasan**, Osuagwu B, Matthew Fraser, D B Allan, Conway, B Nasserolessami. *The Influence of Central Neuropathic Pain in Paraplegic Patients on Performance of a Motor Imagery Based Brain Computer Interface.* Submitted to Clinical Neurophysiology Journal.

Overview of Chapters

Chapter 1: Background

This chapter provides brief overview of physiology and anatomy of brain and spinal cord, and spinal cord injury. Pain is one a major consequences of the spinal cord injury, therefore this chapter also discussed pain pathways, types and mechanism of pain. Furthermore, this chapter also provides information of different neuroimaging techniques, neurofeedback, and mathematical methods involved in processing electroencephalogram signals.

Chapter 2: Brain Plasticity and Pain Management

This chapter first discuss changes in the brain in patients with only spinal cord injury and patients with injury and pain. This chapter also discussed effect of different pharmacological and non-pharmacological treatments on pain, focussed on non-pharmacological treatments. At the end of this chapter, we presented our three hypotheses.

Chapter 3: Dynamic Oscillatory signatures of Central Neuropathic Pain in Spinal Cord Injury

This is a first experimental chapter of this thesis. This chapter is called as a ‘Phase 1’ or ‘diagnostic phase’ of the thesis. In this chapter we will present frequency dependant brain dynamic signatures of central neuropathic pain in patients with spinal cord injury (objective 1).

Chapter 4: Experimental Evaluation of Neurofeedback Protocols for the Treatment of Central Neuropathic Pain Following Spinal Cord Injury

This is a second experimental chapter of this thesis. This chapter is called as a ‘Phase 2’ or ‘treatment phase’ of the thesis. In this chapter we present effect of neurofeedback training on pain and EEG (objective 2).

Chapter 5: Long-term Neurological outcomes of Neurofeedback Training on Central Neuropathic in Paraplegic Patients

This is a third experimental chapter of this thesis. This chapter is called as a ‘Phase 3’ or ‘neurological outcomes’ of the thesis. In this chapter we will discuss long-term effect of neurofeedback training on brain activity (objective 3).

Chapter 6: General Discussion

This chapter proposed different mechanisms of neurofeedback for treatment of pain. At the end of chapter we show limitations, applications of a study and future work. We also highlight how our research contributed to add new findings to the past literature.

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List of Abbreviations

AB	Able-bodied
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ASIA	American Spinal Injury Association
BA	Brodmann area
CES	Cranial electrical/electrotherapy stimulation
CNP	Central neuropathic pain
CRPS	Complex regional pain syndrome
DLPFC	Dorsolateral prefrontal cortex
EC	Eyes closed
EEG	Electroencephalogram
EMG	Electromyogam
EO	Eyes open
EOG	Electroocculogram
ERD	Event related desynchronisation
ERP	Event related potential
ERS	Event related synchronisation
ERSP	Event related spectral perturbation
F	Foot
FDR	False discovery rate
FFT	Fast fourier transform
fMRI	Functional magnetic resonance imaging
GUI	Graphical user interface
IASP	International Association for the Study of Pain
IC	Insular cortex

ICA	Independent component analysis
ISNR	International Society for Neurofeedback and Research
LH	Left hand
LORETA	Low resolution brain electromagnetic tomography
LTP	Long term potentiation
M1	Primary motor cortex
MCS	Motor cortex stimulation
MI	Motor imagery
MNI	Montreal neurological institute
NF	Neurofeedback
NP	Neuropathic pain
PCC	Posterior cingulate cortex
PENS	Percutaneous electric nerve stimulation
PET	Positron emission topography
PMC	Premotor cortex
PPC	Posterior parietal cortex
PSD	Power spectral density
PWP	Patient with Pain
RH	Right hand
rTMS	Repetitive transcranial magnetic stimulation
SCI	Spinal cord injury
S1	Primary Somatosensory cortex
S2	Secondary Somatosensory cortex
SMC	Supplementary motor cortex
SMR	Sensory-motor Rhythm
STT	Spinothalamic tract
TCD	Thalamocortical dysrhythmia
tDCS	Transcranial direct current stimulation

TENS	Transcutaneous electric nerve stimulation
TMS	Transcranial magnetic stimulation
VAS	Visual analog scale

Chapter 1. Background

This chapter is divided into three sections. The first section provides an overview of the physiology and anatomy of the brain and spinal cord, and the consequences of a spinal cord injury (SCI). Chronic pain is one of the consequences of SCI. Therefore, this section also provides information about pain pathways, the classification of pain and mechanisms of chronic neuropathic pain (NP). The second section briefly compares different neuroimaging technologies, focusing only on electroencephalogram (EEG). Following this, voluntarily brain modulation technique i.e. neurofeedback (NF) and its applications are discussed. The third section of this chapter describes different signal processing methods used in processing EEG.

Section I. Physiology and Anatomy

1.1. Brain

The brain is a part of the central nervous system and is protected by the skull, cranial meninges and cerebrospinal fluid. It is responsible for integrating and processing the cognitive, emotions, sensory and motor functions [1]. The brain is divided into four main parts [2]: cerebrum, cerebellum, diencephalon and brain stem (Figure 1.1). The ***cerebellum*** receives proprioceptive information from the spinal cord, and motor information from the cerebral cortex. It maintains balance and equilibrium [2]. The ***brain stem*** relays information from the cerebrum to the spinal cord and cerebellum, and vice versa. It controls autonomic

functions [2]. The ***diencephalon*** is a structural and functional link between cerebral hemispheres and brain stem. The walls and floor of the diencephalon are composed of the thalamus and the hypothalamus respectively [2].

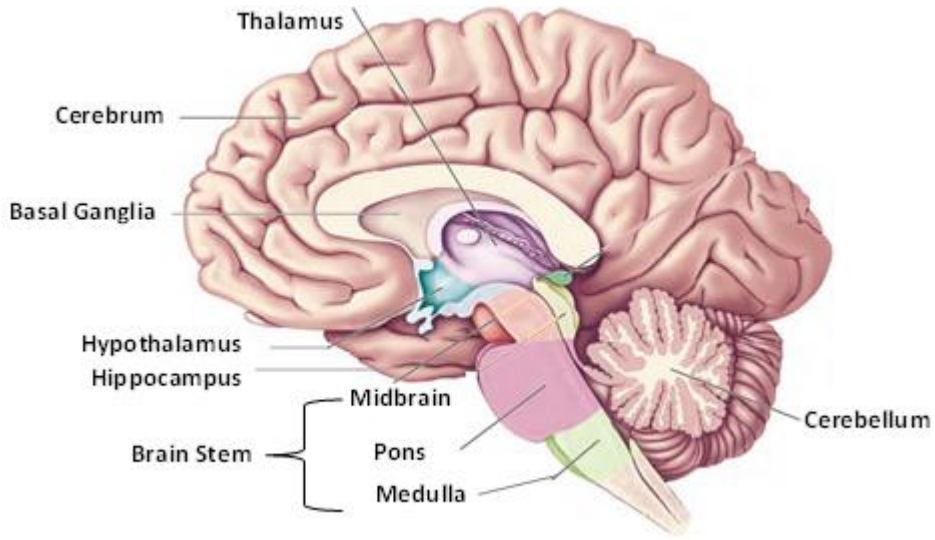


Figure 1.1: Parts of the brain [3]

The **thalamus** is responsible for conveying sensory information to the motor and sensory regions of cerebral cortex. Therefore, it is known as a 'gateway to the cortex'. There are five groups of thalamic nuclei [2]: the anterior, medial, ventral, posterior and lateral thalamic nuclei. The function of each group is listed in Table 1.1 [2].

The **hypothalamus** is involved in basic functions like eating, sexual function, temperature control and circadian rhythm, in addition to those associated with the limbic system [2].

The ***Cerebrum*** is the largest brain structure. It is involved in processing somatic sensory and motor information, problem solving, conscious thoughts, feeling and cognitive functions [2]. The cerebrum is divided into two hemispheres [2]: left and right. The left

cerebral hemisphere controls muscles of the right side of the body, while the right hemisphere control muscles of the left side of the body. The two hemispheres have different function, even though they look almost identical. The left hemisphere is involved in language processing and performing logical and exact mathematical computations. The right hemisphere is involved in face recognition, performing estimate calculations and emotions.

Table 1.1: Functions of thalamus nuclei [2]

Group/ Nuclei	**Functions**
Anterior	Part of the limbic system
Medial	Integrates sensory information for projection to the frontal lobe
Ventral	Projects sensory information to the primary sensory cortex; relays information from the cerebellum and basal nuclei to the motor area of the cerebral cortex
Posterior	Integrates sensory information and projects to the association areas of the cerebral cortex
Lateral	Integrates sensory information and influences emotional states

The cerebral hemispheres consist of [4]: (i) a heavily wrinkled outer layer gray matter called the cortex/ cerebral cortex, and (ii) a deep-lying structure called the subcortex. Each cortical and sub-cortical region can be represented by 'Broadman area (BA)'. The cortical map prepared by Korbinian Brodmann in 1909 is known as BA. It describes 47 patterns of cellular organization in the cortex based on cytoarchitectonics [2] (Figure 1.2).

The **cerebral cortex** is divided into four lobes [4] (Figure 1.3): frontal, parietal, temporal and occipital. It contains different functional areas [2]: the motor cortical areas, sensory

cortical areas, association areas, visual cortical area, auditory cortical area, cingulate cortical area and insular cortical area (Figure 1.4). The somatosensory input and motor output of each body part has its own somatotopical representations in the cortex called a homunculus [5] (Figure 1.5).

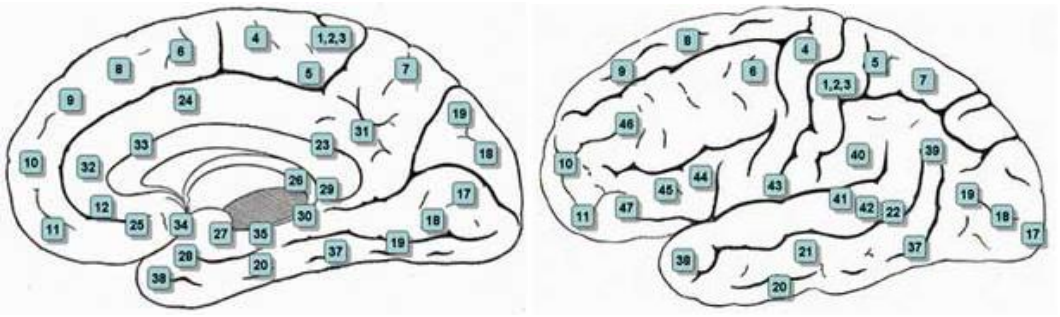


Figure 1.2: Brodmann areas representation [6]

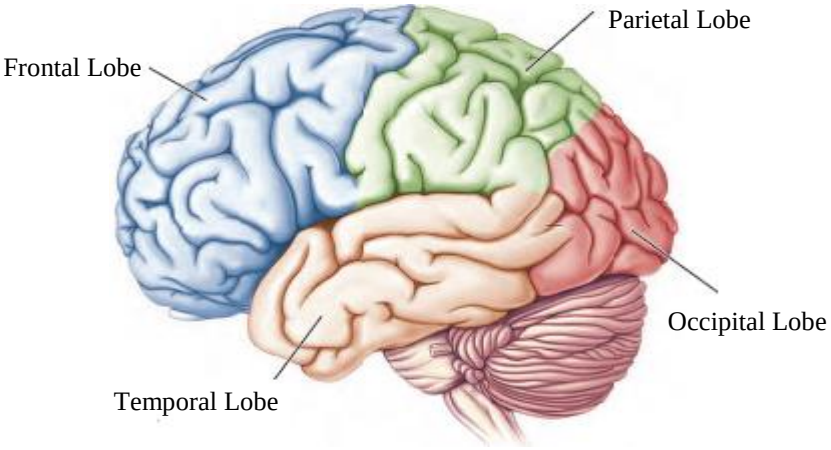


Figure 1.3: Lobes of the brain [3]

The **Motor cortex** is a term that describes regions of the cerebral cortex involved in the planning, control, and execution of voluntary motor functions. The main motor cortical areas include the primary motor cortex (M1), premotor cortex (PMC), Supplementary Motor cortex (SMC) [7].

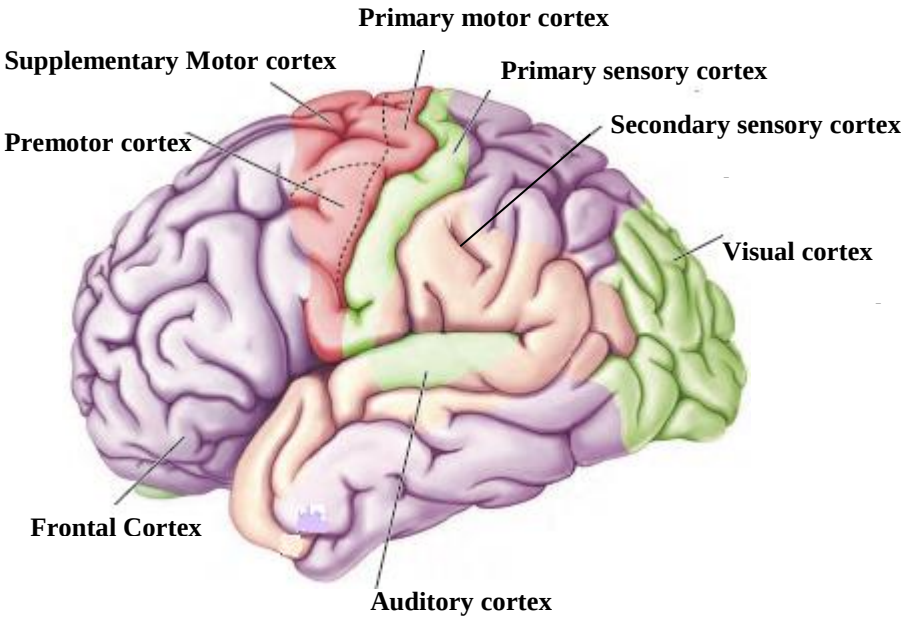


Figure 1.4: Motor and sensory cortical areas of the brain [3]

Primary Motor Cortex (M1): The surface of the precentral gyrus contains the M1. It is located in the frontal lobe and is represented by BA 4. It controls voluntary movements by controlling somatic motor neurons in the brain stem and spinal cord. The topographical representation of muscle areas of the body in the M1 are shown in Figure 1.5.

Premotor Cortex (PMC): The PMC lies 1-3 cm anterior to the M1 in the Frontal lobe and is represented by BA 6. The topographical representation is roughly the same as in M1 but movement patterns generated by the nerve signals in the PMC are complex (e-g position of the shoulder and arms). It is responsible for preparation of movements.

Supplementary Motor Cortex (SMC): The SMC is involved in planning complex movements and in co-ordinating movements involving both hands. It is represented by BA 8.

The **Sensory cortex** controls sensations such as touch, pressure, vibration, pain, temperature, sight, sound, smell and taste. The main sensory cortical areas include primary somatosensory cortex (S1) and secondary somatosensory cortex (S2)[7].

Primary Sensory Cortex (S1): The surface of the postcentral gyrus contains the S1 (BA 1, 2 and 3), and is located in the parietal lobe. The neurons in the S1 receive somatic sensory information of pain, temperature, touch and pressure from the thalamus.

Secondary Sensory Cortex (S2): The S2 (BA 40 and 43) cortex lies lateral to the S1 cortex in the lower parietal lobe. It receives connections from the SI neurons, however, its' response to sensory stimuli is less precise than the S1.

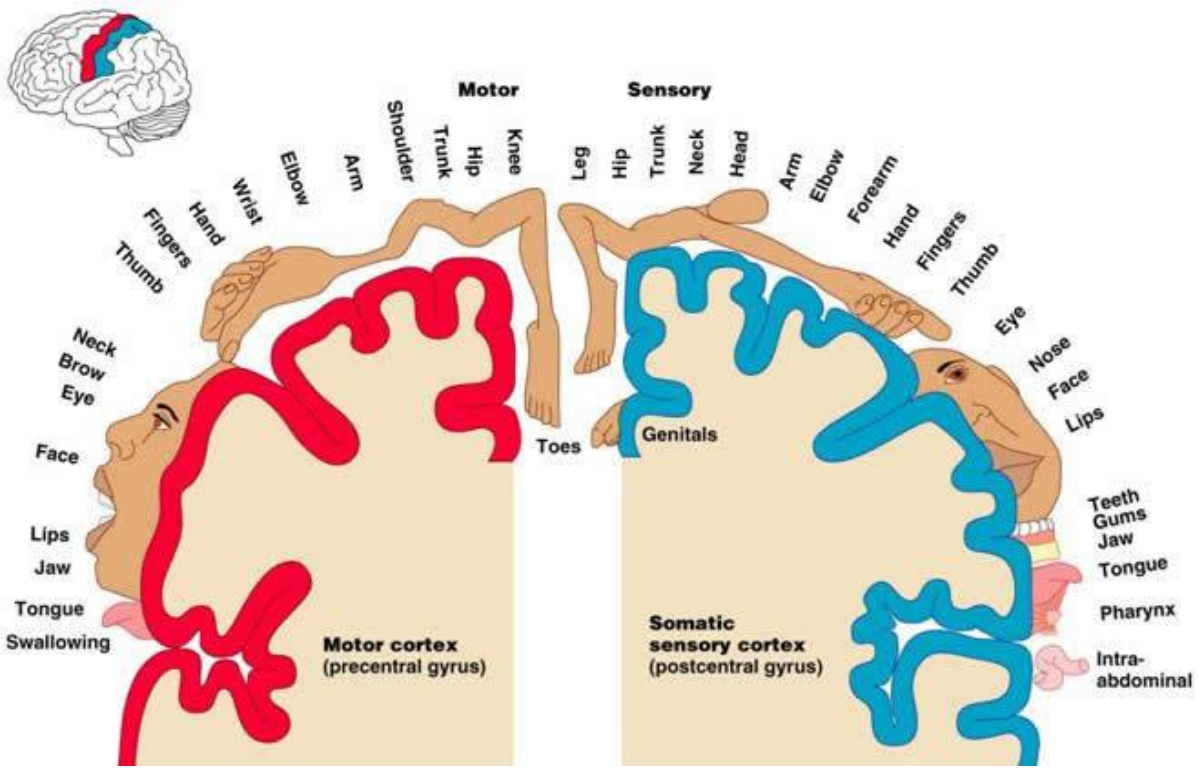


Figure 1.5: Cortical representation of sensory-motor areas [8]

The ***cingulate cortex*** is a part of the frontal cortex and is situated in the medial aspect of the cortex. It is shown by BA 23, 24, 29, 30, 31, and 32. It is a component of the limbic system. Therefore, it is involved in [2]: (i) producing and processing emotional responses to physical sensation of pain, (ii) linking the conscious function of the cerebral cortex with the unconscious functions of the brain stem, and (iii) facilitating learning and memory.

The **insular cortex (IC)** is involved in consciousness, perception, motor control, cognitive functions and control homeostasis of the body. It is represented by BA 13, 14, and 16.

1.2. Spinal Cord

The spinal cord is a part of the central nervous system [4]. It receives sensory information from the body, and contains motor neurons responsible for both voluntary and reflex movements. It also controls the involuntary activities of the body such as blood pressure, body temperature and sweating.

1.2.1. Spinal Nerves and Tracts

The spinal nerves carry information or messages from the spinal cord to the rest of the body (efferent nerves) and from the body back up to the spinal cord (afferent nerves) [9]. There are 31 spinal nerves grouped into four pairs (Figure 1.6) [4]: eight cervical nerves "C1-C8", twelve thoracic nerves "T1-T12", five lumbar nerves "L1-L5", five sacral nerves "S1-S5" and one coccygeal nerve. Each group of spinal nerves control signals of different parts of the body (Figure 1.6).

The white matter (outer layer) of the spinal cord is made up of tracts that form the ascending and descending pathways [4]. The two types of spinal tracts are ascending and descending tracts. The a**scending tracts or sensory tracts** carry sensory information from the body upward to the brain while **descending or motor tracts** carries information from the brain downwards to initiate movement and control body functions. The two common ascending tracts are spinothalamic tract (STT) and spinoreticular tract. The STT ascends to ventral posterolateral nucleus of the thalamus. The lateral part of the STT is associated with pain and temperature, while anterior part of the STT is associated with light touch, pressure and itch. The spinoreticular tract, positioned closely to the lateral STT, is projected to the reticular formation and the thalamus. It is mainly involved in arousing consciousness through cutaneous stimulation and responsible for autonomic response to pain.

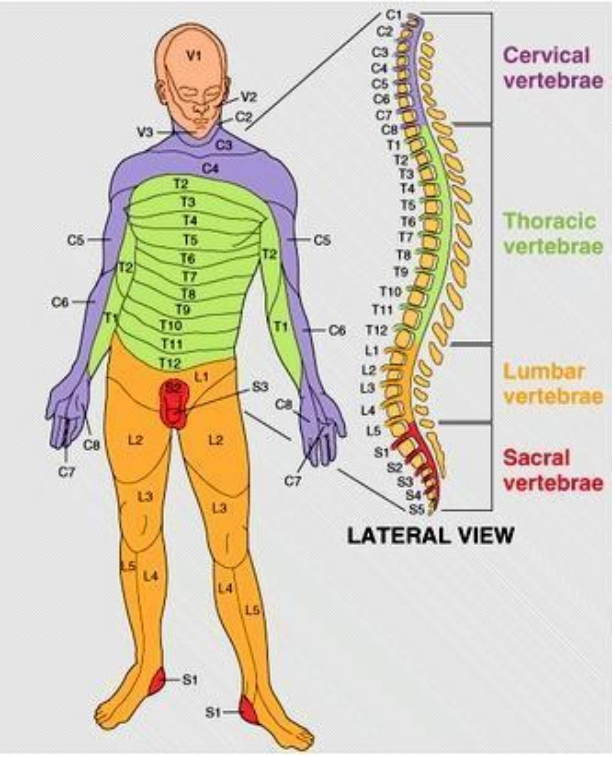


Figure 1.6: Spinal nerves [10]

1.2.2. Spinal Horn and Laminae

The grey matter (inner layer) of the spinal cord contains nerve cells, and it is divided into dorsal and ventral horns [4]. The dorsal horns are generally associated with sensory neurons that receive input from the periphery. The ventral horns are associated with motor neurons that innervate muscles.

The dorsal horn of the spinal cord can be subdivided into six distinct layers called laminae (lamina I to lamina VI) [11] (Figure 1.7). Nociceptive neurons located in the superficial dorsal horn, the marginal layer called lamina I, respond only to noxious stimulation, thus they are called nociceptive-specific neurons. These nociceptive specific neurons project to the higher brain centres. Lamina II contain interneurons which respond either only to noxious inputs or only to nonnoxious stimuli. Laminae III and IV are located ventral to the lamina II. The neurons in laminae III and IV are more related to the reception of tactile information. They receive monosynaptic input from Aβ fibers, and respond to non-nonxious stimuli. Lamina V neurons project to the brain stem and the thalamus, and they receive monosynaptic input from Aβ and Aδ fibers. They also receive input from C fibers, either directly or indirectly through excitatory interneurons.

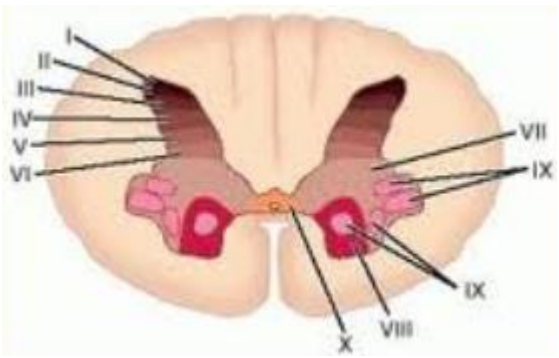


Figure 1.7: Laminae of the spinal cord [12]

1.3. Spinal Cord Injury (SCI)

A lesion to the spinal cord can be a consequence of an accident (traumatic SCI) or by disease (non-traumatic SCI) [13]. The injury may actually tear the spinal cord and/or its nerve fibers (spinal nerve).

1.3.1. Problems Associated with SCI

The primary consequence of SCI includes loss of motor (efferent) and/or sensory (afferent) functions, either completely or partially, below the level of lesion. Depending on the level of the lesion and severity of injury, an individual may also lose control of the bowel and bladder, breathing, sexual function, and spasms may also occur. Over time, the symptoms may be followed by secondary health complications, such as loss of bone mineral density, poor blood circulation, reduced control of body temperature, skin degradation, heart disease and pain [13].

1.3.2. Classification of SCI

The classification of SCI is based on a study of Marino [13]: (i) the level of lesion, and (ii) the amount of residual motor activity and sensation below the level of lesion (completeness of injury).

i. Level of Lesion

The SCI is divided into two types on the basis of the level of lesion: (i) tetraplegia and (ii) paraplegia. A lesion of a cervical nerve (above C8) causes paralysis of four limbs (upper and lower limbs) referred as “Quadriplegia” or “Tetraplegia”. Function of the arms, legs,

trunk and pelvic organs are affected in tetraplegics patients. Injury below the first thoracic (T1), lumbar or sacral spinal cord causes paralyses of lower limbs known as “Paraplegia”.

ii. Completeness of Injury

According to American Spinal Injury Association (ASIA), the SCI is divided into two types based on its completeness: (i) complete SCI and (ii) incomplete SCI. The extent to which a person’s sensory and motor functions are affected is described as completeness of injury. A *complete SCI* refers to an injury that results in the complete loss of function below the level of injury i.e. no motor and/or sensory functions (ASIA A). An *incomplete SCI* refers to a spinal cord injury in which some sensation or movement is still preserved below the level of injury. Hence, motor and/or sensory functions are partially preserved below the level of injury.

The completeness of injury is further classified into five degrees of impairment based on neurological level of injury known as ASIA classification [14] (Table 1.2 [15]). The ASIA classification provides information of motor and sensory function following SCI. The sensory level describes `the most caudal segment of the spinal cord with normal sensory function on both sides of the body', whilst the motor level is similarly `the most caudal segment of the spinal cord with normal motor function on both sides of the body'. A standard manual muscle test with muscle force rated on a scale of 0-5 (from total paralysis to active movement against full resistance) is used to assess the strength of the muscles for each spinal level [15]. The sensory function in all dermatomes is tested as light touch and pinprick sensation at defined key points on both body sides [15]. The sensitivity is scored as 0 (absent), 1 (impaired) or 2 (normal).

Table 1.2: ASIA classification of SCI [15]

ASIA type	Completeness of injury	Motor and sensory functions
ASIA A	complete	No motor or sensory function is preserved in the sacral segments S4-S5.
ASIA B	incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
ASIA C	incomplete	Motor function is preserved below the neurological level and more than half of key muscles below the neurological level have a muscle grade less than 3.
ASIA D	incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
ASIA E	normal	Motor and sensory functions are normal.

ASIA: American Spinal Injuries Unit; SCI: Spinal Cord Injury

1.4. Pain

Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [16]. According to International Association for the Study of Pain (IASP), in 1986, "Pain is unquestionably a sensation in a part or parts of body but is always unpleasant and therefore also an emotion experience" [17]. Hence, pain involves both pain perception (the subjective experience of

pain) and nociception (the neural mechanisms). Nociception is merely the sensory process that includes the activation of a nociceptor (a pain receptor) and transmission of pain message to the central nervous system [18].

1.4.1. Pain Pathways

Components involved in pain nociception can be split into peripheral afferents, the spinal cord, and the supra-spinal level (thalamus and cortex).

From the Periphery to the Spinal Cord: Nociceptive information from the periphery, through either myelinated A-delta (Aδ) or non-myelinated C-fibers, is transmitted primarily at the dorsal horn of the spinal cord (Figure 1.8) [19]. The fast/ first pain is carried by Aδ-fibers, while slow/ second pain is carried by C-fibers [20]. The fast pain is characterized as a sharp, burning and acute, while slow pain is characterized as a dull and annoying pain. Aδ-fibers projects to both superficial layers (laminae I-II) and deeper layers (lamina V). The peripheral C-fibers terminate in lamina I and send polysynaptic inputs to lamina V. Therefore, the lamina I receives more nociceptive-specific inputs, whereas the lamina V inputs represent integration of many afferent inputs. Nociceptive activity affects the processing of neural networks [21].

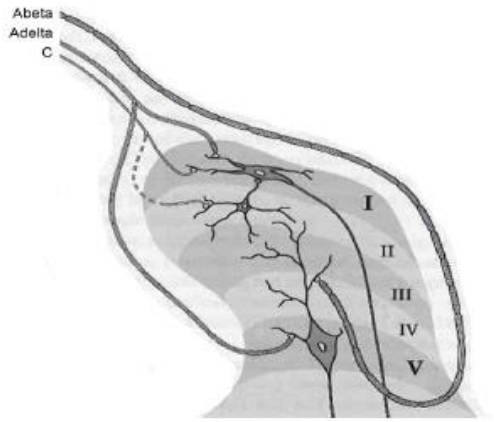


Figure 1.8: Pain pathway: From periphery to the spinal cord. Anatomical basis for the nociceptive afferent input via sensory nerves (Aδ, Aβ, and C fibers) to the dorsal horn (laminae I-V) of the spinal cord.

From the Spinal Cord to the Thalamus: Nociceptive and thermal information is transmitted from the second order dorsal horn neurons of the spinal cord to the thalamus directly through anterolateral STT or indirectly through spinoreticular tract [22,23]. The anterior part of the STT contains mainly lamina V neurons, and the lateral part contains mainly lamina I neurons. The nociceptive specific lamina I pathways are projected to the ventral posterior nuclei, posterior part of the ventral medial nucleus and the ventral caudal part of the medial dorsal nucleus [24] (Figure 1.9). Nociceptive information from lamina I, in addition to the thalamus, is also send to the homeostatic sites in the brainstem.

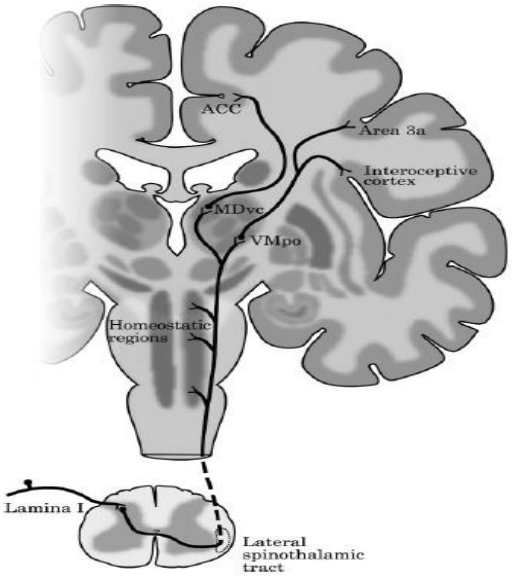


Figure 1.9: Pain pathway: From the spinal cord to the thalamus. Ascending projections of the lamina I to the thalamus via lateral part of the spinothalamic tract (spino-thalamo-cortical system).

From the Thalamus to the Cortex: Nociceptive information of the STT is mainly conveyed to the S1 and S2 cortices through posterior part of the ventral medial nucleus of the thalamus [25]. Thalamic nuclei project to cortical areas, which in turn send back information to different thalamic nuclei, forming thalamo-cortico-thalamic circuits [26]. The somatosensory cortices are responsible for the sensory-discriminative evaluation of pain (location and quality) [27], whereas anterior cingulate cortex (ACC) and IC are involved in

affective/emotional aspects of pain processing [28–31]. The posterior cingulate cortex (PCC) is involved in sensory vigilance processing [32]. The S1 neurons stimulate the secondary somatosensory cortex (S2) to encode the sensory-discriminative aspect of pain. The S2 projects to the insula which is thought to be involved in multidimensional experience of pain including autonomic aspects of pain processing [19] and pain intensity score [33,34]. Chronic pain activates many parts of the brain including the prefrontal cortex, while acute pain activates sensory parts of the thalamus projecting to the cortical homunculus [35]. In conclusion, the cortical regions activated in pain include thalamus, primary and secondary somatosensory cortices, frontal cortex, and cingular cortex. These cortical areas are known as the 'pain matrix'.

1.4.2. Classification of Pain

Pain is usually classified as nociceptive pain and neuropathic pain [16]. Both types of pain can be either chronic (pain more than 6 months) or acute (<6 months).

Nociceptive pain is caused by actual or potential damage to tissue e.g. a cut, burn, an injury and pressure from inside and/or outside the body [36]. The activated tiny nerve endings send a pain signal to the brain. This type of pain tends to be sharp or aching, and responds well to simple analgesics and opioids [37,38].

Neuropathic Pain (NP) is caused by a lesion or disease of somatsosensory system [39,40], defined by IASP in 2011. There is often no tissue damage that triggers the pain, but the affected nerve passes faulty information to the brain that causes NP [41]. The disturbance in homeostatic mechanism (state of balance in the body) may develop pain [42]. It can generally be described as allodynia, hyperalgesia sharp and burning pain [43,44]. This pain produces

sensations which feels as though it is coming from the body, however, sources of pain can be in peripheral nerves, spinal roots or the brain [45]. The different mechanisms compared to nociceptive pain make it difficult to manage this type of pain using traditional pain killers. Treatments to this type of pain will be discussed in Chapter 2. NP is classified as Central Neuropathic Pain (CNP) which is associated with central nervous system dysfunction or Peripheral neuropathic pain which is caused by a damage to the peripheral nerve, plexus, dorsal root ganglion, or root [41].

Peripheral neuropathic pain conditions are diabetic neuropathy, post-herpetic neuralgia, and post-surgical NP, while CNP conditions are stroke, multiple sclerosis, phantom limb pain following amputation, trigeminal neuralgia, and SCI [46]. The prevalence of CNP is highest in patients suffering from amputation (80%) [47] followed by patients with SCI (40%) [48,49], multiple sclerosis (27%) [50], parkinson disease (10%) [51], and stroke (8%) [52].

The SCI population experience chronic pain of different pathophysiological mechanisms [48,53–55]. Therefore, different classifications have been proposed [36,56,57]. NP is one of the most challenging problems that reduces the quality of life [58–60]. From review [61], 11% of SCI people give-up their work because of pain, not only from loss of motor functions. According to International SCI Pain Classification, NP following SCI is divided into three types [36]: (i) below level NP, (ii) at-level NP, and (iii) above level NP.

Above level NP is located above the level of injury and is caused by a peripheral nerve compression. At-level NP is located within 2 segments above and below the level of injury. Therefore, it is caused by a combination of both peripheral and central nervous system dysfunction. This type of NP may also be called segmental, transitional zone, or border zone NP. NP below the level of lesion is thought to be associated with the damage to the

central nervous system and is termed as CNP [62]. This pain is perceived as coming from three or more dermatomes below the level of injury.

1.4.3. Mechanisms of NP

NP is not a single disease, therefore, it is believed to be developed by multiple mechanisms [39], mainly due to the structural and functional changes in the pain pathways [63]. The mechanisms supposed to contribute to the development of NP include peripheral sensitization, long-term potentiation (LTP), central sensitization, central imbalance, central disinhibition and thalamo-cortical dysrhythmia (TCD).

Peripheral Sensitization: The sensitization of nociceptors produces changes in the number of sodium ions channels in the injured nerve and their dorsal root ganglia which reduces the threshold for depolarization. As a result, the nociceptors response to mechanical and thermal stimuli is increased.

Long-term Potentiation (LTP): It is the process of long-lasting increased synaptic strength [64,65]. At molecular level, LTP is noticed in pain pathways both in the brain and the spinal cord which might cause hyperalgesia in pain patients [66,67]. LTP in pain pathways might cause long-lasting pain amplification under conditions of inflammation, tissue damage or nerve injury long after the initial cause of pain has disappeared.

Central imbalance: The pain could be induced by imbalance of integration between spared dorsal column activity and damaged STT [18,62,68–73]. The damaged STT transmit nociceptive impulses from an alternate pathway (multisynaptic paleo STT) to the thalamus because Aβ fibers arriving to lamina 111-1V reach outer laminae. Therefore, the central

imbalance may imply that tactile and temperature information is processed abnormally in a nociceptive territory, constituting a potential mechanism for allodynia.

Central sensitization: The Aβ fibers arriving to lamina 111-1V can produce aberrant sprouting & reach outer laminae. Therefore, it is suggested that plastic changes taking place around the lesion level develops CNP [74]. The plastic changes to the injured nerve cause excessive firing of pain-mediation nerve cells, leading to central sensitisation of afferent pathways. Central sensitisation is the expression of an increased excitability of neurons in the spinal cord. The hyperexcitability is also caused by either increased excitation or reduced inhibition [43,62], grey matter loss at the rostral end of the lesion [70,75], alterations (increased) in N-methyl-D-aspartate, non-N-methyl-D-aspartate receptors, reduced g-aminobutyric acid, alterations (increased) in expression of sodium and calcium levels [76,77]. Consequently, the threshold for activation is decreased and response to stimuli is increased. The cellular changes, in addition to central sensitisation of afferent pathways cause second order dorsal horn neurons in the spinal cord to become hyperexcitable and thus develop pain.

Central Disinhibition: The *central disinhibition* at the thalamic level is considered as one of the important pathophysiological theories for the development of CNP [78–80]. The posterior part of the medial nucleus and ventral caudal part of the medial dorsal nucleus plays a role in central integration of temperature and pain sensation [42]. The central disinhibition due to reduced activity of posterior parts of the medial nucleus causes thermo-sensory loss and thus develops pain [76,81]. The phenomena of thermoregulatory dysfunction emphasize the concept that pain is not only a feeling but also a behavioural drive that signals a homeostatic imbalance.

Thalamo-cortical dysrhythmia (TCD): The damaged nerve fibers lead to a lack of excitation in VP nucleus of the thalamus which causes thalamic neurons to fire from high frequency to a low frequency bursting regime [82–84]. This process of abnormal firing of neurons by the thalamus is known as TCD. In addition to injury of the nerve fiber, the TCD can also be noticed when input from the cortical and sub-cortical regions to the thalamus affects the firing process of thalamic neurons [82]. In TCD, abnormal inputs to the thalamus hyperpolarizes thalamic neurons which reduces cortical inhibition or increases facilitation [70,76,81,85]. Hence thalamic integrative circuits behave as generators and amplifiers for nociceptive signals and thus induce long-lasting profound cortical and sub-cortical reorganization which in turn develops NP [86]. The TCD is characterized by a shift of dominant peak towards lower frequency. The formation of new cortico-cortical projections is also considered as a cause of NP [87]. The cortical reorganization, cortical over- and, de-activation and shift of dominant frequency are discussed in Chapter 2.

1.4.4. Assessment of NP

The assessment methods for NP are categorized into [18]: (i) pain questionnaire (verbal report), (ii) clinical Examination, and (iii) imaging of the brain.

Persistent pain is measured subjectively using several pain questionnaires. These include 'The Leeds assessment of neuropathic symptoms and signs' [88], brief pain inventory [89], 'the neuropathic pain questionnaire' [90], McGill Pain Questionnaire [91], and 'Douleur neuropathique en 4 questions' [92]. These pain questionnaires consist of several factors such as location, sign and symptoms of pain, mood, sleep and performance of daily activities. Patients also self-reported the pain intensity on 0 to 10 Visual Analog Scale (VAS) [93].

In a clinical examination, sensory response is tested. According to IASP, there are several clinical examination tools for screening NP [41]. These include: a piece of cotton wool or a soft brush for touch sensation, tuning fork (64 or 128 Hz) for vibration, wooden cocktail sticks for pinprick and sharp pain, cold object (20^0C) for cold sensation, and warm object (40^0C) for warmth sensation. The SCI patients are also tested for allodynia (painful sensation on a normally non painful stimulus) and hyperalgesia (increased sensitivity of pain) based on perceptual threshold in response to stimulation of feet and shank of both legs using monofilament [94,95].

Recently, brain imaging techniques have been used to objectively measure pain [96]. The brain imaging techniques will be discussed in next section where as changes in the brain activity following pain will be discussed in next chapter.

Section II. Technologies of the Mind

1.5. Neuroimaging Techniques

There are different imaging techniques used by researchers to record the brain activity, and to investigate the plasticity in the brain following injury to the nervous system. These tools include functional magnetic resonance imaging (fMRI), positron emission topography (PET), near infrared spectroscopy, electrocorticogram, magnetoencephalography and electroencephalogram (EEG) [97]. The summary of neuroimaging techniques is shown in Table 1.3.

Table 1.3: Summary of neuroimaging methods [97]

Neuroimaging Methods	Activity measured	Direct/ Indirect Measurement	Temporal resolution	Spatial resolution	Risk	Portability
EEG	Electrical	Direct	~0.05s	~10 mm	Non-invasive	Portable
MEG	Magnetic	Direct	~0.05s	~5 mm	Non-invasive	Non-portable
ECoG	Electrical	Direct	~0.003s	~1 mm	Invasive	Portable
Intracortical neuron recording	Electrical	Direct	~0.003s	~0.5 to 0.05 mm	Invasive	Portable
fMRI	Metabolic	Indirect	~1s	~1 mm	Non-invasive	Non-portable
NIRS	Metabolic	Indirect	~1s	~5 mm	Non-invasive	Portable
PET	Metabolic	Indirect	~ 30s	~4 mm	Non-invasive	Non-portable

EEG: Electroencephalogram, MEG: Magneto-encephalography, ECoG: Electrocorticogram, fMRI: functional Magnetic Resonance Imaging, NIRS: Near Infrared Spectroscopy, PET: Positron Emission Topography.

fMRI and PET have been used to measure localized changes in the oxygen content of the blood flow. The higher the volume of oxygen in the blood in one area, the more active that area [97]. The temporal resolution for both fMRI and PET is poor, however, fMRI compared to PET measures brain activity with much higher precision. The *near infrared spectroscopy* uses infra-red light to record brain activity. It is based on the principle of monitoring the changes in blood oxygenation and deoxygenation in the cerebral cortex [98].

Magnetoencephalography is an imaging technique used to measure the magnetic fields produced by electrical activity in the brain [99]. EEG can directly measure cortical electrical functional activity associated with different brain states. In contrast to fMRI and PET, EEG has a good temporal resolution but little spatial resolution. Electrocorticogram is an invasive procedure to record electrical activity of the cerebral cortex with a higher temporal and spatial resolution compared to EEG.

1.6. Electroencephalogram (EEG)

EEG is a non-invasive technique used to record brain activity with electrodes placed on surface of the scalp [100]. It cannot be used to analyse dynamics of the deep cortical structures, though activation of deeper cortical areas can be estimated using some source localisation method [101]. EEG recorded at the scalp is not the activity of a single neuron but made up of summations of billions of individual action potentials [102].

1.6.1. Electrode Placement

A standard placement of electrodes that is known as 10-20 International System of Electrode placements was established by Jasper in 1958 [103]. The term 10-20 refers to the placement of electrode placed 10% or 20% of the total distance between specified skull locations. Use of a percentage-based system allows for differences in skull size. The extension of 10-20 system are 10-10 and 10-5 systems which allow to use more electrodes on the scalp to improve spatial resolution (Figure 1.10) [100,104,105].

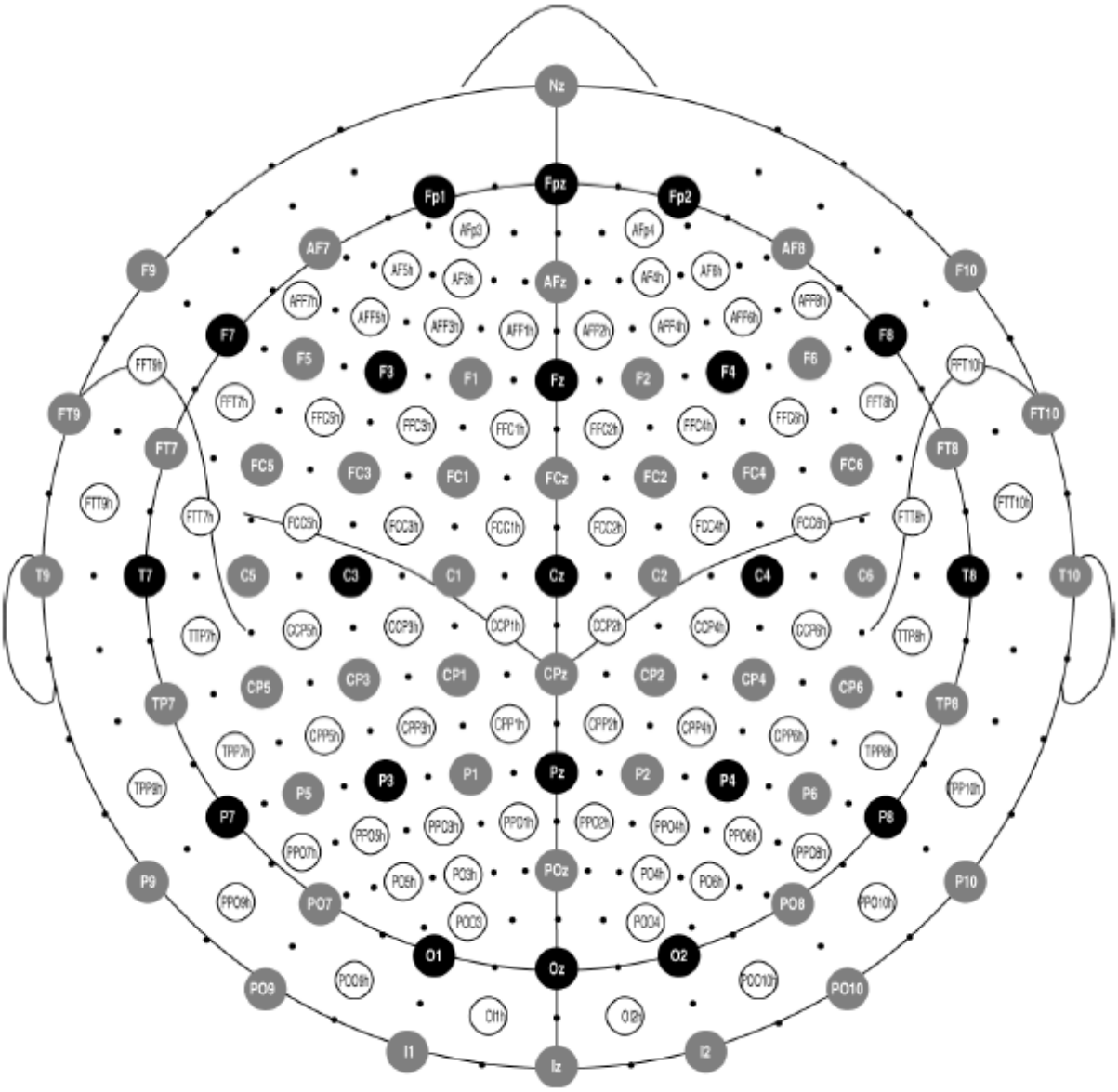


Figure 1.10: EEG electrode placement systems: 10-20 system (only black circles; 21 electrodes), 10-10 system (black and grey circles; 85 electrodes) and 10-5 system (circles and dots; 320 electrodes) [105].

1.6.2. EEG Montages

There are four basic types of EEG montage: (i) linked ears reference or monopolar, (ii) bipolar, (iii) common average reference, and (iv) local average reference or laplacian.

The **monopolar montage** provides information of active scalp site by comparing activity of active site with a common reference, such as ear lobes or nose tip. The main advantage of common referential montage is that common reference allows valid comparisons of activity in many different derivations. The disadvantage is that no reference site is ideal.

The **bipolar montages** compare activity between two active scalp sites, as shown with Eq.(1.1). The difference of two activities reduces noise, however some information is also lost.

$$V_{bipolar} = V_a - V_b \tag{1.1}$$

Where,

$V_{bipolar}$ = Potential between source 'a' and source 'b' with bipolar montage

V_a = Potential of a source 'a' without bipolar montage

V_b = Potential of a source 'b' without bipolar montage

In **average reference montage**, the EEG activity of all channels is averaged and this average is used as a common reference for each channel. Equation (**1.2**) is used to calculate the average reference.

$$V_i' = V_i - \frac{\sum_{j=1}^{n} V_j}{n} \tag{1.2}$$

Where,

V_i = Potential of an ith source without average reference

V_i' = Average potential of an ith source with average reference

V_j = Potential of other electrodes placed on head

n = Total number of electrodes placed on head used to calculate average reference

The term **local average or laplacian reference** represents a unique reference for each source. It provides information of active scalp site by comparing activity of active site with a weighted average of surrounding electrodes [106]. Equation (**1.2**) is used to calculate laplacian reference in which n ranges from 2 to 4 depending on number of electrodes in surrounding the active electrode. The laplacian is a high-pass spatial filter that increases localized activity and attenuates widespread (diffuse) activity [107].

1.6.3. EEG Frequency bands

Frequency refers to the rate at which a waveform repeats its cycle within 1 sec [108]. In EEG, the frequency range is divided into six frequency bands: delta (less than 4 Hz), theta (4-8Hz), alpha (8-13Hz), rolandic mu-rhythm, beta (13-30Hz) and gamma (> 30Hz). The description of frequency bands is provided by a Niedermeyer [109].

The **delta rhythm** refers to EEG activity within a frequency range of 1-4 Hz; the highest amplitude compared to other frequency bands. It is dominant in the posterior region of the brain in infants, while over the frontal region in adults. The increased power of delta rhythm is associated with sleep and neurological pathology such as tumour and brain lesion.

The **theta rhythm** refers to EEG activity within the 4-8 Hz range, prominently seen during sleep. During wakefulness, two different types of theta activity have been described: (i) widespread theta rhythm, and (ii) the frontal midline theta rhythm. The *widespread theta rhythm* has been linked to decreased alertness (drowsiness) and impaired information processing. This type of theta rhythm is common in infancy and childhood and

drowsy or sleepy state, it is less common in waking adult around age of 30 years. The theta rhythm is found in large number of brain structures: ACC, hippocampus, hypothalamus and medial dorsal nucleus of the thalamus. Furthermore, this wide spread theta rhythmic activity is thought to be a sign of maturity to link the cortex, thalamus and hypothalamus. The *frontal midline theta activity* (anterior to the vertex), is characterized by a frontal midline distribution and has been associated with focused attention, mental effort and mental task such as mathematical calculation, emotion, and effective stimulus processing. The ACC (BA 24 and 32) is thought to be a generator of this theta rhythmic activity.

The frequency range of **alpha rhythm** is 8-13 Hz. Topographically, the alpha rhythms are predominantly found over occipital, parietal, and posterior temporal regions during wakeful relaxation in eyes-closed (EC) state. This alpha rhythm can be greatly temporarily blocked or reduced during visual stimuli or eyes-open (EO) state. The process of alpha suppression is known as 'alpha blockage'. The posterior distribution of alpha and its attenuation in EO state demonstrate that functionally alpha might be associated with visual function system.

The frequency range of frontal **beta** is 13 to 30 Hz. Rhythmical beta activity shows symmetrical fronto-central distribution. The central beta rhythm is known as 'Rolandic rhythm' which will be discussed later on. The amplitude of the frontal beta activity is very small, seldom exceeds 30 μV. The beta activity is closely linked to motor behavior and is generally attenuated during active movements. Low amplitude beta with multiple and varying frequencies is often associated with active, busy or anxious thinking and active concentration.

There are two types of **rolandic rhythms** found over the sensorimotor cortex, one has a peak around 10 Hz called **'rolandic alpha rhythm' or 'mu' rhythm** and other has a peak of around 20 Hz called **'rolandic beta rhythm' or 'central' rhythm**. The frequency range for rolandic alpha is similar to posterior or occipital alpha (8-13 Hz), though it has different topography. The frequency range for rolandic beta rhythm is around 16-24 Hz. The rolandic alpha and beta rhythms are blocked or suppressed during motor tasks, such as overt (actual) or covert (imagined) movement. This suppression is bilateral but more pronounced on the motor cortical region contralateral to the site of movement. The spatial distribution is essentially confined to the precentral-postcentral region; some spread into parietal leads is not uncommon.

The frequency range of **gamma activity** is above 30 Hz. Gamma oscillations have been associated with attention, arousal, object recognition, modulation of sensory processes, and binding (the brain's ability to integrate various aspects of a stimulus) of different populations of neurons together into a network. This purpose being is to carry out a certain cognitive or motor function.

1.7. Biofeedback

Biofeedback is the process of learning to self-regulate physiological functions [110]. The trainee receives real time information of biological signal recorded via sensors placed on a body. The biological signals include breathing, body temperature and heart rate, as well as signals coming from muscles and the brain. The online information of biological signal may be provided in auditory or visual feedback such as digital or analog displays, or computer graphs.

1.8. Neurofeedback (NF)

According to International Society for Neurofeedback and Research, "NF is a process in which sensors are placed on the scalp and electronic devices are used to monitor and provide moment-to-moment information to the individual for the purpose of improving brain functions" [111]. NF, a modality of Biofeedback, is a method of acquiring feedback from the brain to voluntarily modulate brain activity in real time [112–114]. It is a non-invasive non-pharmacological approach which does not involve either surgery or medication [112,113].

NF is a form of operant conditioning. Operant conditioning is a type of learning in which individuals learn to elicit a new response following reinforcement to increase or decrease performance. In other words, the individual is required to actively perform an action in order to be rewarded or suppressed. Therefore, NF training requires 15-60 sessions, depending on application, learning ability and type of feedback [115].

1.8.1. Types of NF and history

There are three major forms of NF: (i) EEG, (ii) regional Cerebral Blood Flow or Homoencephalography (HEG), and (iii) fMRI based.

NF using HEG trains subjects to voluntarily control cellular activity of a targeted area of the brain [116]. There are two basic forms of HEG based NF [116–119]: (i) near infrared HEG, and (ii) passive infrared HEG. The near infrared HEG system was developed by Hershel Toomin in 1995. It involves the use of light in red and near infrared wavelengths (7-14 µm) and monitors changes in the cerebral blood flow by targeting small areas over the ventral lateral frontal sites (F7, F8, Fp1 and Fp2) [120]. The passive infrared HEG system was developed by Jeffrey Carmen. It involves the use of light in far infrared wavelengths (680-

850 nm) [116] and measures changes in the thermal waste products of cellular metabolism by targeting a wide variety of skull placements. Both types of HEG NF systems compared to EEG NF are less affected by noise [112].

The real-time fMRI feedback provides blood oxygenation-level dependant signal as a feedback to allow subjects to self-regulate brain activity [121–123]. The fMRI feedback compared to EEG feedback allows users to self-regulate deeper-cortical and sub-cortical structures but the delay is large. The fMRI feedback has a delay of about 1.3-2 s [121,122,124].

EEG based NF was first used in the beginning of 1950s by Dr Joe Kamiya, in which he explored that trainees could voluntarily modulate alpha brain activity under EC condition [121]. At same time, Barry Sterman carried experiments on cats to modulate the activity of sensory-motor rhythm (SMR). Later on, in 1970-1980s, the NF was applied in clinical studies to treat Attention Deficit Hyperactivity Disorder (ADHD) and through the 1990s to psychological and central nervous system disorders. At present, NF is used to improve peak performance of sports players, in addition to treating central nervous system disorders such as ADHD, pain and epilepsy.

1.8.2. Division of EEG based NF

EEG based NF can be divided into two types: (i) deep cortical activity feedback, and (ii) scalp EEG feedback.

The deep cortical feedback is provided by Low Resolution Brain Electromagnetic Tomography (LORETA) in which current source density is shown as a feedback signal. LORETA-based NF uses approximately 19 electrodes to train deeper cortical structures [125]. The LORETA feedback was first introduced in the 2001 annual meeting of ISNR [126],

however, it was not until 2004 that it was first validated [127]. LORETA feedback is more cost-effective than fMRI feedback to treat deep cortical structures, and more specific than scalp EEG NF [128]. According to Dr Thatcher: "An advantage of LORETA EEG biofeedback is that one can target anatomical regions related to "loss of function" or "weak" function related to the patients' symptoms and complaints" [129].

The scalp EEG-based NF can be divided into four types: (i) Spontaneous EEG NF [130–134], (ii) ERD-based NF [135], (iii) Event related Potential (ERP) based NF [121,136], and (iv) slow cortical potential feedback [121,137,138]. The ERD and ERP feedback types are applied for brain computer interface (BCI) and are not based on operant conditioning. In *spontaneous EEG-based* NF, a subject is asked to modulate the spectral absolute or relative amplitude/power in certain frequency band, ratio of power in two frequency bands over single electrode or ratio of power between two sites in single frequency band, coherence (NF parameter) between two sites in a given frequency band in both EO and EC modalities [121,130,131,139–142]. In *ERD-based* NF, the relative change in EEG power (NF parameter) in a given frequency band, in response to either real or imagery motor action, is provided as a feedback. In *ERP-based* NF, the amplitude or latency (NF parameter) of ERP component is provided as a feedback to a trainee [121,136]. In *slow cortical potential* NF, the trainee learns to control negative or positive shifts of slow cortical potentials (NF parameter) in response to warning stimuli.

In spontaneous EEG and ERD based NF training, a term 'dominant frequency band' is used when a trainee is asked to increase activity, whereas, 'inhibit frequency band' is used when a trainee is asked to decrease the activity in a particular frequency band [143–145].

1.8.3. Methods of Providing Audio/Visual Neurofeedback Information to a Trainee

The feedback information for each types of EEG-based NF (section 1.8.2) can be provided either in EO or EC modality in three different ways: (i) NF parameter directly, (ii) total time (percentage) patient achieved threshold condition, and (iii) Z-scores (also called classical NF) [133].

NF parameter can be directly shown as a feedback in the form of bars/videos or music [130–132]. The greater the amplitude/power, the higher or wider the bar and more intense the audio signal. The colour is also changed according to threshold value. In NF training with total time as a feedback information rather than NF parameter directly, the score of the trainee is increased once threshold condition is achieved. Therefore, the trainee is asked to maximize the score, which in general increases the percentage time the threshold is achieved [130,140,141]. In Z-score feedback, a trainee gets positive feedback as long as the targeted brain activity remains within a certain range of the standard activity [133,134]. These norms are derived from the extensive normative EEG databases. An excellent normative database was developed in 1987 for normal controls of all ages [146]. This database determines whether an individual with a head injury or ADHD differs significantly from matched normal controls. This database asked questions about power and coherence in different frequency bands at different scalp sites. Another database developed in 1999 stores information about power ratios of theta to beta at the Cz site and is calculated in four different conditions: EO state, reading, listening and drawing [146,147]. The smaller the value of the Z-score means a trainee is learning in the desired direction.

1.8.4. Frequency of Updating Training Variable

According to classical conditioning theory, the feedback lag (delay) should be less than 0.5 s [146]. The feedback delay depends on spectral analyses method and speed of the computer, in addition to the length of the EEG leads. The spectral analysis is performed using fast fourier transform (FFT) and filters methods. In contrast to the filter technique, the FFT takes more time to make initial calculations which can be resolved by taking small length epochs. The small length epochs decreases the frequency resolution which can be improved by shifting a window but there is still an initial delay. The delay caused by filters is usually less than 0.1 s. The delay in active bans pass filters can be further minimized by decreasing the order of the filter but this produced smooth spectrum. On the other hand, increased order induced oscillations or ripples which in turn might send wrong feedback.

1.8.5. Methods to Calculate the Threshold Value of Training Parameters

The threshold value for training electrode site is set either one of two ways [108]. (i) 1 to 2 units or 10-20% lower or higher than the mean spectral amplitude/ power or mean relative power, calculated in EO or EC state, for each training day [130,132,148], or (ii) spectral amplitude/ power or mean relative power at 50-80% of time for the whole baseline recording [131,149].

1.8.6. NF experimental procedure and assessment

NF procedure consists of initial assessment, NF training, and final assessment. The initial assessment is always before the first day of NF training and the final assessment is always after the last NF training day. The initial and final assessments mainly consist of EEG recordings using a large number of electrodes. The initial assessment EEG before NF is

also used to compare EEG of a subject with normative database or EEG of a healthy population, which also helps to design NF protocols. The final assessment EEG is used to find long-term neurological changes. The initial and final assessments also include patient history, current symptoms, medical information such as medicine intakes and injuries, discussion of diet, sleep and exercise, and goals of training. The behavioural changes are also assessed as part of the initial and final assessments, which mainly include questionnaires of related applications.

1.8.7. Placebo for NF Training

In any medical treatment, the psychological expectation might affect the therapeutic outcome. The effect of expectation is called placebo or sham effect [121]. The placebo effect has a real neurophysiological basis that can be revealed by neuroimaging techniques. The placebo effect can further prove the efficiency of any therapeutic method. Placebo effect can amount up to 30% from the pure effect of a medical drug or real non-pharmacological treatment. In NF training, the sham treatment to test the placebo effect can be performed in different ways [121,150]: (i) comparing effect of NF training with medical drug, (ii) showing feedback of other subject, (iii) showing feedback of other region of the brain which was not previously trained, and (iv) showing pre-recorded EEG as a feedback.

1.8.8. NF Protocols and Assessments

In NF, protocol refers to a selection of NF parameters, montage and electrode position to up-regulate NF parameters in ‘dominant frequency band’ and/or down-regulate in ‘inhibit frequency band’ with the EO or EC modality [151].

EEG-based NF is not only used in the optimal performance field but also used for the treatment of various neurological and psychological disorders [152,153] such as ADHD, autism, stroke rehabilitation, depression, anxiety, stress, obsessive compulsive disorders, epilepsy, schizophrenia, and pain reduction. However, well-established protocols only exist for the treatment of ADHD [154].

The *SMR protocol* along with *theta and beta inhibition protocol* have been used to successfully treat ADHD. In the field of NF, the range of SMR is 12-15Hz which was first studied by Barry Sterman on cats in 1960. The SMR protocol on ADHD patients was first tested by Lubar in 1970s. This protocol aims at increasing SMR activity, mainly over frontal (F3 and F4), central (Cz, C3 and C4), and parietal (P3 and P4) sites [120,121,149,155–159]. The feedback was provided both in visual and audio forms and a threshold condition was set to 80% of time or 1 to 2 units below/above the spectral amplitude/power [149,155]. Other applications of SMR reward protocol, though not standardized, include treatment of depression [160,161], improvement of sleep [162,163], obsessive compulsive disorder [108,164], Parkinson's disease [165]. The frontal leads were chosen for the treatment of depression and anxiety, and sensory-motor cortex was chosen for improving sleep.

The *SMR reward and theta-beta inhibit* protocol over sensory-motor cortex has been used also to manage pain [140,166–168]. The application of NF protocol for the management of pain will be discussed in Chapter 2.

The *alpha-theta EC protocol* from the occipital site was first used by Green Elmer [169] in 1975, but Peniston, later on, added temperature biofeedback and a protocol is known to be Peniston alpha-theta protocol [170]. The alpha-theta (Peniston) protocol aims at raising both theta (4-8Hz) and alpha (8-12Hz) bands activity from the occipital lobe following

temperature biofeedback. The alpha-theta biofeedback over the occipital site has been reported to be of clinical benefit in the treatment of addiction and posttraumatic stress disorder [121,171,172]. The alpha frequency range was 8-13 Hz and theta range was 4-8 Hz.

The *alpha asymmetry protocol* uses the ratio (F4-F3)/ (F4+F3) as a feedback parameter to reduce left alpha activity [108,173]. This protocol aims to normalize alpha asymmetry in the lateral frontal areas. The alpha asymmetry protocol has been used for the treatment of mood disorders and depression.

The *connectivity based protocol* is based on coherence between two brain sites [174]. The connectivity based protocol has been used for the treatment of autism disorder [174–176]. The electrode location and frequency bands were individualized.

The *self-regulation of slow cortical potential* has been used to establish communication in severely paralyzed people [121], to reduce seizure rate in patients with epilepsy [137], to treat psychiatric patients (schizophrenia) [138,177,178], and to reduce alcohol dependency [179]. The feedback was provided from Cz, C3 and C4 sites.

The ten sessions of Z-score LORETA NF, together with scalp EEG NF, improves speech, cognitive score and grades followed by reduction in theta and delta band activity in a single patient with autism spectrum disorder [180]. Other studies also reported improvement in cognitive functions and reduction in delta and beta band activity following 15 to 33 sessions of scalp EEG and 19-channel LORETA Z-score NF training [181,182]. The feedback was provided both in audio and visual forms from BA 32.

Currently, real-time fMRI NF is mostly applied on healthy subjects, showing that self-regulation of brain activity of different cortical and sub-cortical regions can be useful to

explore cognitive neuroscience and to improve various psychological disorders [124]. The feedback is mainly provided from areas including sensory-motor cortex [183], ACC [184], IC [185–187], subgenual ACC [188], auditory cortex [189] and inferior frontal gyrus [190]. The real-time fMRI NF study on healthy population suggested that upregulation of brain activity in the left amygdala can help to treat patients with neuropsychiatric disorders [191]. The downregulation of BOLD activity in ACC, IC, and sensory-motor cortices demonstrate that real-time fMRI can be used to manage pain [192]. The upregulation of brain activity of the SMC, IC, PFC and PMC has shown improvement in patients with parkinson's disease, schizophrenia, depression and stroke [186,193–195]. The down-regulation of brain activity in auditory cortex and ACC can reduce tinnitus symptoms, nicotine addiction, and pain intensity [150,196–198].

In the field of cognitive neuroscience, different protocols have been used to provide feedback with EEG-based NF. These protocols include upper-alpha, theta, gamma, alpha desynchronization, SMR/ theta, alpha/ theta, SMR and low beta protocols along with theta and beta inhibit, and peak alpha frequency [148,152,199,200]. The field or application of NF to improve cognitive performance of healthy participants is commonly called 'optimal' or 'peak performance' field [152]. In this area of cognitive neuroscience, NF has been used to improve peak performance of sports player, musicians, actors, and dancers, and to improve communication/ presentation skills [143,201,202]. The outcomes of NF training include improved memory, reaction time, large event-related P300b amplitude, and enhance visuo-motor skills. The details of each protocol and its application can be found from Gruzelier reviews paper [152,153].

Section III.Methods of Quantitative EEG Analysis

1.9. Spectral Analysis Methods of EEG

The spectral analysis provides information of a signal x(t) in frequency domain. The spectral analysis is often performed using fast fourier transform (FFT). The FFT describes a signal x(t) as a linear superposition of sines and cosines characterized by a frequency 'f'.

$$|X(F)| = \int_{-\infty}^{+\infty} x(t)e^{-i2\pi ft}\,dt \tag{1.3}$$

Equation (1.3) is the continuous fourier transform (X(F)) of the signal x(t) over each frequency point 'f'. Based on Eulers formula Eq. (1.4), the exponential function in Eq. (1.3) can be represented with sine and cosine function.

$$e^{-ix} = \cos x - i \sin x \tag{1.4}$$

The discrete FFT of a signal x(n) consists of N discrete samples is shown in Eq. (1.5).

$$|X(F)| = \frac{1}{F_s \times N} \sum_{n=0}^{N-1} x(n)e^{-i2\pi Fn} \tag{1.5}$$

Where,

$x(n) = Discrete\ Time\ Signal, x(n) = \{x_0, x_1, \cdots, x_{N-1}\}$

$X(F) = Fourier\ of\ a\ signal\ x(n)$

$F_s = Sampling\ Frequency$

$N = Total\ number\ of\ samples$

The frequency of FFT is calculated using Eq. (1.6). It shows that the frequency resolution is based on length of data epoch extracted for FFT.

$$F = \frac{F_s}{N} \tag{1.6}$$

Where,

$F = Frequency\ resolution\ of\ a\ signal\ x(n)\ whose\ fft\ is\ calculated\ in\ Eq.(1.5)$

$F_s = Sampling\ Frequency$

$N = Total\ number\ of\ samples$

Power of a signal: The power of a signal represents amount of energy or activity at different frequencies. Equation (1.7) shows that the power of a signal x(n) can be calculated by squaring the amplitude of the FFT output X(F) calculated in Eq. (1.5).

$$P_a(F) = \big(X(F)\big)^2 \tag{1.7}$$

Where,

$P_a(F) = Absolute\ Power\ at\ frequency\ 'F'$

$X(F) = Amplitude\ of\ a\ signal\ in\ frequency\ domain$

The absolute power is varied with many factors such as neurophysiological, anatomical and physical properties of the brain and surrounding tissues. The relative power for a frequency range of f1 to f2 Hz can be calculated using Eq. (1.8).

$$P_r(F) = \frac{P_a(F)}{\sum_{f=f1}^{f2} P_a(f)} \tag{1.8}$$

Where,

$P_r(F) = Relative\ Power\ at\ frequency\ 'F'$

$f = frequency\ range\ over\ which\ relative\ power\ is\ calculated$

Cross Power of two signals: The cross power is a measure of energy at different frequencies that is in common to the two different raw data time-series. Assume that x(n)

and y(n) are two different signals then the cross power between them is the product of the power of one signal with the conjugate of power of other signal Eq. (1.9).

$$P_{XY}(F) = \big(X(F)\big) \times \big(Y^*(F)\big) \quad \textbf{(1.9)}$$

Where,

$P_{XY}(F) = \ Cross\ Power\ between\ signals\ 'x'and\ 'y'at\ frequency\ 'F'$

$X(F) = fft\ of\ a\ signal\ x(n)$

$Y^*(F) = conjugate\ of\ fft\ of\ a\ signal\ y(n)$

Coherence between two signals: The coherence measures the linear relationship between two signals in frequency domain. Coherence provides information whether the same frequency components of two signals preserve their phase shift from one state to another. It can be represented as the ratio of the square of cross-spectrum of two signals to the product of the two auto-spectra Eq. (1.10).

$$Coh_{xy}(F) = \frac{|P_{XY}(F)|^2}{P_{XX}(F)P_{YY}(F)} \quad \textbf{(1.10)}$$

Where,

$Coh_{XY}(F) = \ Coherence\ between\ signals\ 'x'and\ 'y'at\ frequency\ 'F'$

$P_{XY}(F) = \ Cross\ Power\ between\ signals\ 'x'and\ 'y'at\ frequency\ 'F'$

$P_{XX}(F) = \ Auto\ Power\ of\ a\ \ signal\ 'x'at\ frequency\ 'F'$

$P_{YY}(F) = \ Auto\ Power\ of\ a\ \ signal\ 'y'at\ frequency\ 'F'$

1.10. Time-Frequency Methods of EEG

The time-frequency analysis provides information of a signal both in time domain and in frequency domain simultaneously. Due to the trade-off between time localization and frequency resolution, the resolutions in time and frequency domains cannot reach their

highest levels concurrently. However, it is better to have a smaller time resolution of higher frequencies and larger on lower frequencies. The two most widely used time-frequency methods are short time FFT and wavelet transform.

In **short time FFT** method, the signal of length N is first divided into K segments of length L using Eq. (1.11). Each segment is multiplied with a window prior to estimate the FFT using Eq. (1.12), then FFT output is averaged over all epochs.

$$K = \frac{N}{L} \tag{1.11}$$

Where,

$K = Number\ of\ segments$

$N = Length\ of\ original\ signal$

$L = Segment\ length$

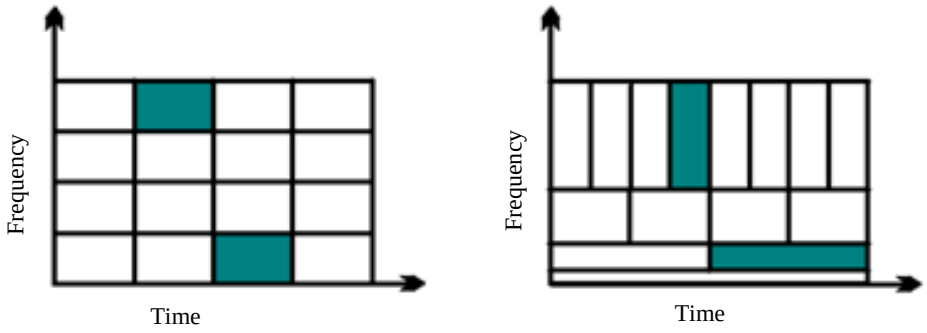
$$|X(F)| = \frac{1}{F_s \times N} \sum_{n=0}^{N-1} \left| x(n) w(n)\, e^{-i2\pi Fn} \right| \tag{1.12}$$

Where, w(n) is a window function.

There are different window functions [203], such as Bartlett, Hanning, Blackman, Kaiser-Bessel, Flat top, Tukey, and Hamming (Eq. (1.13)). In Eq. (1.13), 'n' is length of the window and 'N' is length of whole signal.

$$w_{hamming}(n) = 0.54 - 0.46 * \cos\left(2 * \pi * \frac{n}{N}\right) \tag{1.13}$$

The short time FFT method has disadvantage of same width of time-frequency windows for all frequencies (Figure 1.11 (a)), therefore the wavelet analysis is mostly used to study the time frequency dynamics of task-related EEG.



(a) short time FFT (b) Wavelet Transform

Figure 1.11: Short time FFT and wavelet transform breakdown of a signal. (a) The time-frequency window has fixed window length for all frequencies in short time FFT. (b) The time-frequency window length is large for lower frequencies and small for higher frequencies [204].

The **wavelet analysis** decomposes a signal into wavelets, instead of sinusoidal functions. The wavelet is shifted and scaled to match the input signal using Eq. (1.14). The process of shifting and scaling is shown in Figure 1.12. A figure shows that the length of the time-slice window is according to the frequency of the component extracted. The varying time-frequency window length allows smaller time resolution for higher frequencies and larger time resolution for lower frequencies (Figure 1.11 (b)). There are different wavelets families such as morlet, meyer, demyer, Gaussian and daubechies. The disadvantage of wavelet time-frequency method is an increased computational time and memory requirement.

$$\varphi_{a,b}(t) = \frac{1}{\sqrt{a}}\varphi\left(\frac{t-b}{a}\right) \quad \textbf{(1.14)}$$

Where,

$a = scaling\ factor\ (real\ number)$

$b = shift\ (real\ number)$

$\varphi = wavelet$ which can be shifted 'b' and width can be modified by factor 'a'

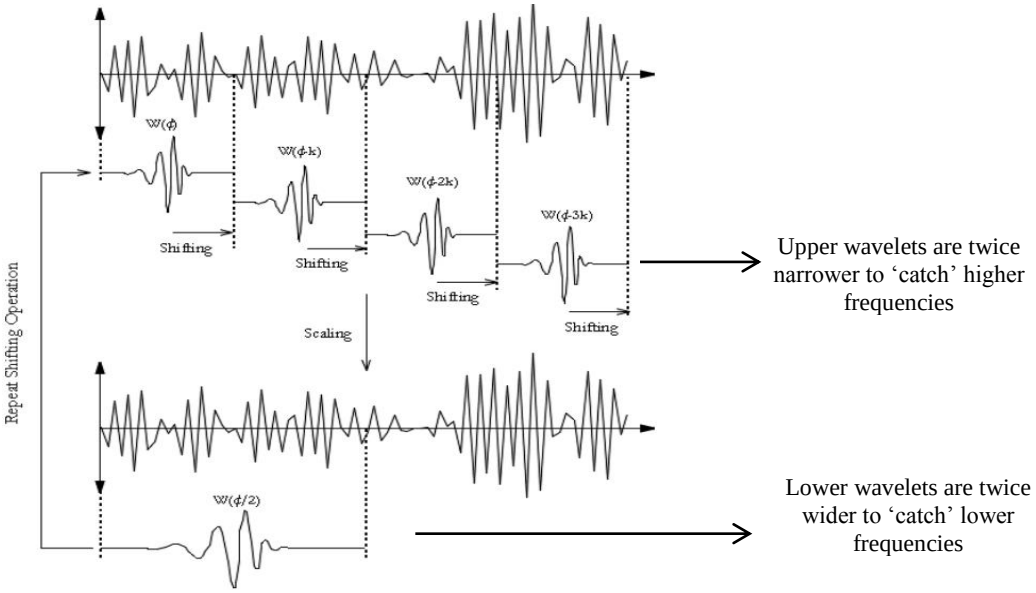


Figure 1.12: The scaling (dilated) and shifting (translated) process of wavelet [204].

The most widely used parameter to quantify task-related EEG activity is Event Related Spectral Perturbation (ERSP). The ERSP measures average dynamic changes in amplitude of the narrow band EEG frequency spectrum as a function of time relative to an experimental event. The ERSP is calculated using Eq (1.15) [205].

$$ERSP = \frac{P_{active} - P_{baseline}}{P_{baseline}} \quad \textbf{(1.15)}$$

Where,

$ERSP = Event\ Related\ Spectral\ Perturbation,$

$(-ve\ sign\ represents\ ERD\ and + ve\ represents\ ERS)$

$P_{active} = Power\ in\ active\ or\ task - related\ state$

$P_{baseline} = Power\ in\ resting\ or\ baseline\ state$

The two terms used to describe this phenomenon are Event Related Desynchronization (ERD) and Event Related Synchronization (ERS). The ERD/ ERS represent decrease

(negative ERSP)/ increase (positive ERSP) in energy during active or task related state compared to resting or baseline state. The ERD/ ERS are noticed in the alpha and beta bands. ERD can be interpreted as an increased cortical excitability in the cortical areas involved in processing of sensory or cognitive information or production of motor behavior. In other words, ERD is associated with enhanced processing of information in the brain i.e. active brain. The large negative ERD value represents strong desynchronization or more active brain. The strong ERD is based on many factors such as, complexity of the task, and tasks require more effort and tension. ERD over the sensory-motor cortex can be noticed during motor task and over the occipital cortex when processing visual information. ERS can be interpreted as a decreased cortical excitability which is associated with reduced information processing i.e. deactivated brain.

1.11. Independent Component Analysis and its Application to EEG

Independent Component Analysis (ICA) is a computational method for separating a multivariate signal into spatially fixed and temporally independent components [206]. The ICA represented with Eq. (1.16) shows that only a single variable x_j is known, therefore, few assumptions are taken to estimate the unknown mixing variable a_j and unknown sources/ ICs (u_n): (i) The ICs are statistically independent, (ii) the ICs must have non-Gaussian distribution, and (iii) the unknown mixing matrix is square.

$$x_j = a_{j1}u_1 + a_{j2}u_2 \cdots\cdots\cdots\cdots\ a_{jn}u_n \qquad \textbf{(1.16)}$$

Where,

$x_j = Known\ Random\ Variable\ measure\ at\ jth\ site$

$a_{jn} = weigted\ sum\ for\ activity\ measured\ at\ jth\ site\ from\ nth\ source$

$u_n = nth\ source\ (generated\ from\ unknown\ source)$

The EEG signal recorded at the scalp is a weighted sum of different rhythms produced at different frequencies by generators located at different cortical and subcortical areas. Furthermore, the scalp EEG is also affected with several types of non-brain artifacts which include eye movements, eye blinks, muscle activity and line noise. To extract real EEG sources or to remove non-EEG sources, source separation methods are applied. These methods include dipole fitting method, LOERTA, standardized LORETA (sLORETA), principal component analysis, common spatial pattern, and ICA. ICA has been widely used method to remove artifacts from EEG signals recoded at the scalp [207–210]. EEG signal recorded at each electrode can be described with ICA using Eq. (1.16) [211,212]. In case of EEG both weights (a_{jn}) and sources (generators and/ or noise, u_n) are unknown [208]. It is important to note that in terms of EEG u_n is the source generated by deep cortices and/ or sub-cortices or artifact, a_{jn} is the weightage matrix, j is the numbers of electrodes placed on the scalp, and x_j is the potential recorded at the scalp using EEG electrodes.

The whole process of ICA rejection and back-projection is shown in Figure 1.13 [213]. In terms of EEG, Eq. (1.16) can be rewritten as Eq. (1.17).

$$EEG_{M*N} = A_{N*N} \times U_{M*N} \quad \textbf{(1.17)}$$

Where, EEG_{M*N} and U_{M*N} are EEG recorded with 'N' electrodes and unknown 'N' sources for time M. A_{N*N} is a mixing square matrix (electrodes * components).

The unknown sources 'U' in Eq. (1.17) are obtained by multiplying the observed EEG signal 'EEG_{M*N}' with the inverse of a mixing matrix 'A' using Eq. (1.18).

$$U_{M*N} = W_{N*N} \times EEG_{M*N} \quad \textbf{(1.18)}$$

Where, W_{N*N} is inverse of mixing matrix 'A' or $W=A^{-1}$.

The bad components are set to zero before back projected the components to the corrected EEG. The corrected or artefact free EEG is obtained by multiplying the sources 'U' with inverse matrix 'W^{-1}' using Eq. (1.19).

$$EEG_{corrected\,M*N} = W^{-1}{}_{N*N} \times U_{M*N} \quad \textbf{(1.19)}$$

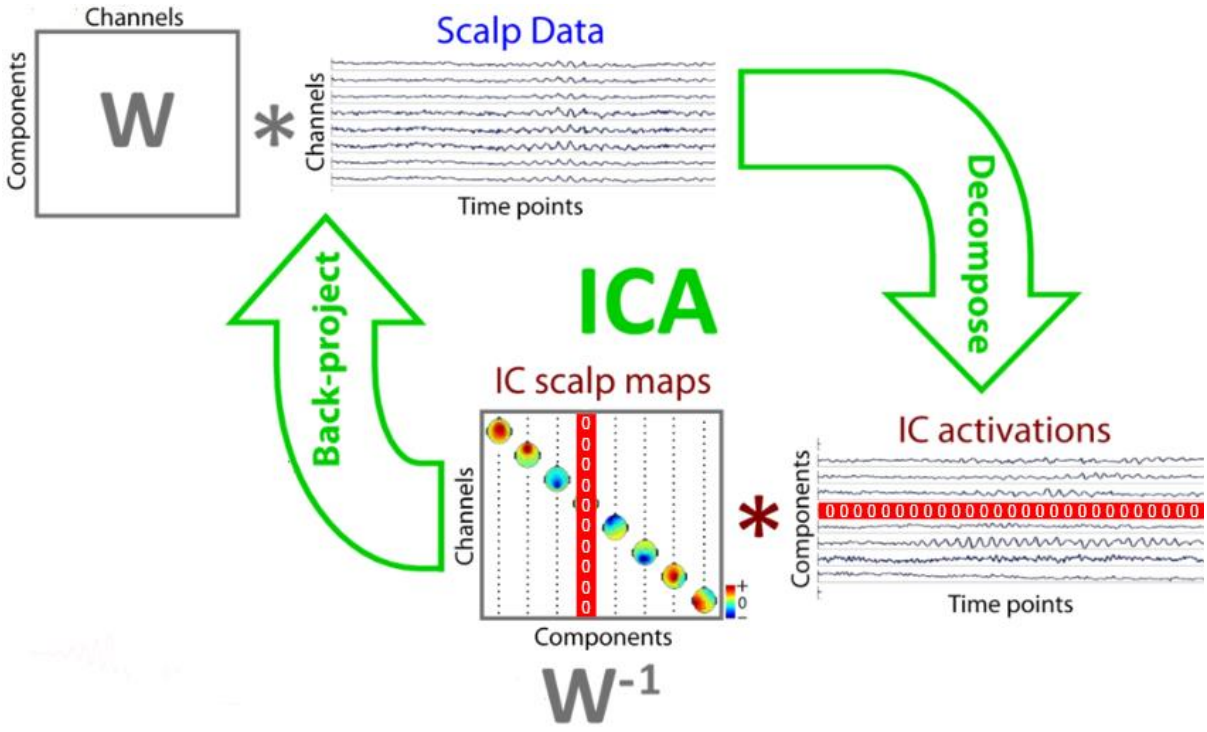


Figure 1.13: General block diagram for ICA rejection and back-projection to artefact-free corrected EEG [213].

Figure 1.14 shows application of ICA to remove noise from 3 sec EEG. The EEG was recorded in our lab using 61 channels but only ten channels are shown for simplicity

(subfigure ‘a’). The electroocculogram (EOG) artefact can be noticed on frontal leads while muscle artefact at electrode AF8. The subfigure ‘b’ shows derived independent components. The EOG artefacts and muscle artefacts in the EEG data are isolated in components 1 and 2 respectively. The bad components (non-EEG) are determined based on their temporal and spatial information, and frequency characteristics. In subfigure ‘c’ only 3 scalp components are shown in which first two components are EOG and muscle artefacts while last component is occipital alpha. The scalp components representing EOG and muscle artefacts in subfigure ‘c’ are set to zero before inverting the data to EEG domain shown in subfigure‘d’.

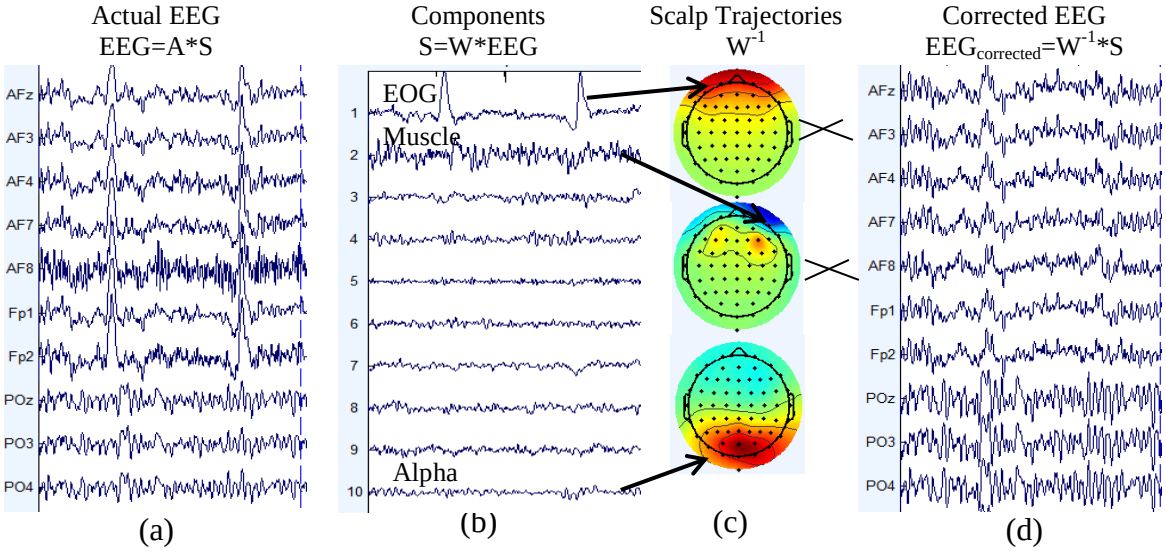


Figure 1.14: Example of ICA procedure on EEG data recorded with 61 channels in our lab, only 10 channels are shown for simplicity. (a) 3-sec portion of the recorded EEG time series. (b) ICA component activations for EEG, (c) the scalp topographies of three selected components (first two components are noise), (d) the artifact-corrected EEG signals obtained by removing two selected EOG and muscle noise components from the data.

Chapter 2. Cortical Plasticity and Pain Management

This chapter begins by discussing neuroimaging studies that describe the effect of spinal cord injury (SCI) on the brain. Following this, studies that considered the effect of pain in SCI patients, while analysing brain activity, are discussed. From the literature review of neuroimaging studies on SCI patients with and without pain, the limitations in existing studies are presented. Solutions are proposed to fill the lack in current knowledge about changes in the brain in patients with central neuropathic pain (CNP) following SCI.

Secondly, the effect of pharmacological and non-pharmacological treatments on pain in general population and patients with SCI are discussed. This chapter will focus on non-pharmacological interventions because in this thesis a non-invasive non-pharmacological approach was chosen to treat pain. From the literature review of studies describing effect of non-pharmacological treatments on pain in patients with SCI, the limitations in existing literature are highlighted and an alternative approach to treat CNP in patients with SCI proposed.

2.1. Brain Plasticity

Brain plasticity describes structural and functional changes in the cortices and sub-cortices in response to new tasks, normal development, lesions to the peripheral and central nervous systems, and neurorehabilitation (motor / sensory training either through external stimuli or mental practise) training following lesion [214]. It is caused by either physical wiring of new cortical circuits known as structural plasticity, or by change in strength of

existing connection known as physiological plasticity. In general, injury or paralysis of the body parts affects the sensory and motor functions that cause functional reorganization of the cortical region deprived of sensory input (deafferentation). The cortical/ subcortical plasticity can be described as shrinking/reduced and shifting of cortical representation of affected body part, and invasion by adjacent cortical representation. In this chapter, we will discuss cortical and subcortical plasticity following SCI and pain.

2.1.1. Brain Plasticity following SCI

It has been well documented that cortical and sub-cortical areas showed plasticity following SCI, due to disruption of the motor and sensory pathways between the brain and the periphery [215–231]. In few studies SCI patients either showed over- activation [215–219,232,233] or reduced activation of the cortex [220–223]. In addition to over- and reduced- activation, SCI patients have also displayed somatotopical reorganization [219,224–229,234]. On the contrary, few studies have not found differences in brain motor activation patterns between SCI patients and able-bodied people [235,236].

A Positron Emission Topography (PET) study comparing cortical activity of SCI population (paraplegics and tetraplegics) and able-bodied during hand movement (attempted movement by tetraplegics and actual movement by paraplegics) found strong activation in SCI group over supplementary motor cortex (SMC), insular cortex (IC), parietal cortex and thalamus [215]. The functional Magnetic Resonance Imaging (fMRI) studies also reported over-activation of affected and unaffected cortical and sub-cortical areas during motor imagery (MI) of paralyzed lower limbs and during motor execution of non-paralyzed upper limbs in chronic complete and incomplete paraplegics [216,217]. Another study also reported over-activation of primary motor cortex (M1), primary sensory cortex

(S1), premotor cortex (PMC) and SMC in chronic complete paraplegics during motor execution and MI of paralyzed toes [218]. The over-activation of primary and secondary motor cortical areas has also been reported in sub-acute tetraplegics (complete and incomplete) during extension of paralyzed wrist [233]. Also, electroencephalogram (EEG) studies reported strong beta frequency band (13-30 Hz) activation or high event related desynchronization (ERD) in SCI patients (complete and incomplete) during actual plantar-flex movement of toes [219].

Contrary to over-activation of cortical and sub-cortical areas in SCI population compared to able-bodied, reduced activation in sensory-motor areas and thalamus has been observed in both paraplegics and tetraplegics during motor execution of paralyzed and non-paralyzed parts of the body (wrist, foot and tongue) [221]. Similar to motor execution task, MI of paralyzed lower limb also reduced activity at the sensory-motor cortical region in SCI patients having complete injury based on American Spinal Injuries Association (ASIA) [220]. Spontaneous EEG studies have shown reduced alpha activity in relaxed eyes-closed (EC) state in SCI population compared to able-bodied [222,223].

The somatotopical reorganization in complete and incomplete paraplegics has been seen in the form of midline (towards paralyzed limb; Cz site) and posterior shift of cortical representation of non-paralyzed hands, thumbs and little finger [225,226]. Similar to fMRI studies, EEG studies also showed posterior shift of cortical representation of unaffected hands during movement of non-paralyzed hand [227,237].

The varying and conflicted findings are due to large variety in inclusion criteria, such as level of injury (Cervical [224,233,235]; cervical to thoracic [220,221,227,237,238]; thoracic to Lumbar [216–218,226]; cervical to lumbar [215]) completeness of injury (complete injury [216,220,226,236]; both

complete and incomplete injury [217,218,233,235,237]), motor and sensory functions (ASIA-A [216,220,236]; ASIA A-D [227,233,237], ASIA A-B [217,218], ASIA A-C [235]), type of SCI patients (paraplegic, tetraplegic), subjects characteristics (number of individuals; 4 to 44, age; 17-67 years, gender and time since injury; 0.25 months to 33 years), neuro-imaging techniques, motor tasks (attempted, actual and/or imagined movement of upper limb, lower limb and/or facial tasks), and frequency of motor tasks. In addition to the above mentioned variability, researchers did not actually consider the effect of presence of chronic Neuropathic Pain (NP).

2.1.2. Brain Plasticity following NP

Brain neuroimaging has been widely used to investigate the structural and functional changes in the brain associated with chronic pain [35,239]. A number of studies found that cortical and subcortical plasticity or reorganization were increased with chronicity and intensity of pain [239,240] in different chronic pain states, such as Complex Regional Pain Syndrome (CRPS) [241], fibromyalgia [240], trigeminal neuralgia [242], pain following amputees [243], and pain following SCI [87,244]. Also, the over- and reduced- activation of several brain regions, painful and non-painful cortical presentations, has been reported in chronic pain [87,245–247].

Cortical plasticity has been observed as a shift [248,249], invasion [243], expansion [250] and contraction [248,249,251,252] of cortical representation of affected body parts on the homunculus. The S1 and S2 representations of the affected arm shrinks in CRPS [249,253], and in patients with trigeminal neuralgia [242]. The invasion of cortical representation of the affected body part by the unaffected body part has been observed following phantom limb pain [243]. Also, the cortical shift of the painful body part towards intact body part has been observed in

chronic pain [248,249]. A shift of cortical representation of non-paralyzed little finger and thumb towards paralyzed painful leg cortical representation has also been observed in SCI patients with NP [244].

Numerous imaging studies also showed that regions of the brain such as the thalamus, S1 and S2, M1, SMC, IC, and anterior cingulate cortex (ACC) are overactivated in chronic pain [245,246]; other studies showed reduced activation and grey matter loss in rostral parts of the ACC and frontal cortex [35,248,254–256]. The fMRI studies found over- activation of thalamus, M1, SMC, S1, S2, Prefrontal cortex (PFC), ACC, IC and parietal cortex in patients with chronic CRPS and chronic back pain [245,246]. Similar to fMRI studies, spontaneous EEG studies reported overactivation (enhanced spectral power) of cortical and subcortical areas, mainly in the theta and beta frequency bands [257,258], which was not restricted to the cortical representation of the body part perceived as being painful [84,257–259]. A PET study on SCI patients reported that increased blood flow in the thalamus is related to NP [247]. A single fMRI study on complete paraplegics and a single scalp EEG study on SCI population (complete and incomplete) with below level chronic NP have found over-activation in the pain related cortical and subcortical areas in SCI patients with pain compared to SCI patients without pain [46,87]. Another EEG study found over-activation in the theta band in SCI population with chronic pain [260]. However, another fMRI study has not shown differences in cortical activity between two SCI groups (pain versus no-pain group) during imagination of brushing little finger, thumb and lips [261].

In addition to over- and reduced- activation, EEG studies provide information about peak theta-alpha frequency. The shift of peak frequency towards low frequency in neurogenic pain was reported in three studies [84,258,259], except a single study showing no change in

peak frequency [257]. This shift of peak frequency in relaxed state has also been reported in SCI patients with chronic pain, while this shift of peak frequency was not reported in SCI patients without pain and able-bodied [46,262]. Furthermore, it has been mentioned that reduced activity in EC state compared to eyes-open (EO) state shown by the pain group compared to able-bodied and SCI patients with no pain groups is associated with thalamo-cortical dysrhythmia (TCD) [262].

In conclusion, some studies showed reduced- [34,239,247] or over- [245,246] activation of the surface and deep cortical structures, others reported shift [248,249], invasion [243], expansion [250], and contraction [248,249,251,252] of the cortical representation of the affected limb. The varying and conflicting findings might be due to different reasons, such as patient selection criteria and types of pain (fibromyalgia, CRPS, trigeminal neuralgia, back pain, phantom limb pain, and pain after SCI), number of patients and neuroimaging technique (EEG, fMRI and PET).

2.2. Management of NP

Treatment of NP can be classified as pharmacological or non-pharmacological, both of which can be applied either by invasive or by non-invasive way. Some studies showed higher use of non-pharmacological than pharmacological treatments [263,264], while others reported opposite [265–267]. Here, pharmacological treatments will be described first followed by non-pharmacological treatments. The main focus will be on non-pharmacological treatments.

2.2.1. Pharmacological Treatments for Neuropathic Pain

The pharmacologic treatments include oral medicines, pumps for drug delivery and direct delivery of steroids invasively (using syringe) to alleviate pain. The two main categories of pharmacological treatment include anticonvulsants and antidepressants. The anticonvulsants and antidepressants decrease neuronal activity via many different mechanisms, such as blocking sodium channel, and enhancing modulatory systems [18,268–270]. The anticonvulsants decrease the peak alpha frequency and antidepressants increases activity of theta and beta activities along with slowed alpha frequency [271–274]. Past research [275,276] suggests tricyclic antidepressants and anticonvulsants as a first-line treatment, and opioids as a second-line treatment. A recent study suggested pregabalin (anticonvulsant) as a first choice for patients with anxiety, and antidepressants for the patients with depression [277]. The side effects and application of pharmacological treatment on different types of pain is shown in Table 2.1.

Anticonvulsants, such as gabapentin and pregabalin have shown efficacy in 54% patients for the treatment of postherpetic neuralgia [278–282] and diabetic neuropathy [283,284]. Carbamazepine has been used for the treatment of trigeminal neuralgia [285]. In patients with SCI, a single study supports the use of gabapentin for the treatment of NP (62% patients showed clinically significant i.e. >30% reduction of pain) [286], but other studies failed to show the efficacy of gabapentin [277,287,288]. Pregabalin is effective in reducing 25-40% pain intensity but with strong side effects [289–291]. Other anticonvulsants, such as duloxetine, were also not efficient for the treatment of chronic pain in patients with SCI [292–294]. In patients having chronic NP of mixed types, anticonvulsants reduce pain larger than 50% in 21% patients and larger than 30% in 61% [295,296]. In patients with CNP, the reduction of

pain larger than 30% was noticed in 42% patients only [297]. Common side effects of anticonvulsants include dizziness (19%), somnolence (14%), sedation, constipation, a dry mouth and drowsiness [298]. Due to these side effects, 10% patients stop taking anticonvulsants [296].

Table 2.1: Pharmacological treatment for pain and side effects

Types	Name	Pain Type	Side effects
Anticonvulsants	Pregabalin, gabapentin, carbamazepine, and duloxetine	Postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, post stroke pain, phantom limb pain, and pain following SCI	Dizziness, sedation, constipation, dry mouth, and drowsiness.
Antidepressants	Amitriptyline, nortriptyline	postherpetic neuralgia, painful diabetic neuropathy, central pain, and SCI	Drowsiness, dry mouth, constipation, and increased spasticity

Antidepressants, such as amitriptyline has been effective for few patients [277] but did not show its efficacy for mixed NP and nociceptive pain in SCI patients [299]. It has also been used for postherpetic neuralgia and diabetic neuropathy [300]. Common side effects of tricyclic antidepressants include drowsiness (17%), dry mouth (17%), constipation (14%) and increased spasticity (11%) [301].

Analgesics, such as, nonsteroidal anti-inflammatory drugs, acetaminophen, tramadol and opioids did not relieve NP, especially in SCI population [302–304]. However, a study supports use of opiods [305].

In conclusion, patients having chronic NP do not report sufficient pain relief with pharmacological treatments [264,266,306]. Moreover, it is difficult for patients to continue treatment because of strong side-effects. These shortcomings in pharmacological treatments call for the need of non-pharmacological treatments for NP.

2.2.2. Non-Pharmacological Treatments for Neuropathic Pain

It was mentioned previously in sections 2.1.1 and 2.1.2, multiple cortical and sub-cortical areas are over-activated and showed plasticity in chronic pain [307]. Therefore, it was hypothesized that interventions that directly or indirectly modulate the cortical and/or sub-cortical activity and reduces plastic changes can help to manage pain [307].

Brain modulation techniques reduce pain by altering the brain activity of the pain-related areas [307]. *Non-pharmacological* interventions that directly targets the brain either invasively or non-invasively to achieve neuro-modulation include transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), invasive motor cortex stimulation (MCS), and deep brain stimulation. The invasive MCS and deep brain stimulation are invasive procedure which requires surgery. The non-invasive brain stimulation techniques do not require surgery but work with defined protocols (frequency and current of stimulation, number of training sessions and duration of training) to achieve neuro-modulation. The *non-pharmacological* and *non-invasive* techniques in which neuromodulation is achieved using peripheral stimulation include cranial electrical\

electrotherapy stimulation (CES), acupuncture, transcutaneous electrical nerve stimulation (TENS) and percutaneous electrical nerve stimulation (PENS). These neuromodulation techniques also work with defined protocols (frequency and current of stimulation, number of training sessions and duration of training). The *non-pharmacological* approaches in which brain is not physically stimulated from external stimuli rather trained/ teach to achieve neuro-modulation include NF, visual illusion (VI), hypnosis, cognitive behaviour therapy, and meditation training and practise.

Invasive stimulation of motor cortex has shown significant improvement in chronic central pain [308], refractory NP [309], central deafferentation pain [310], CRPS [311], central pain [312], neuropathic facial pain [312], neuralgia [313] and phantom limb pain [314]. Evidence showed that invasive procedure for motor cortex stimulation (MCS) relieves trigeminal NP, but CNP was not reduced [315]. There was a study which proposed somatosensory cortex stimulation apart from motor cortex to treat deafferentation pain [316]. Invasive MCS has shown promising results (75% response rate) [312], however, less invasive or pure non-invasive stimulation techniques are required to provide cost effective pain treatment without surgical procedure.

rTMS, a noninvasive brain stimulation technique involves stimulation of the cortex by a stimulating coil applied to the scalp to cause depolarization or hyperpolarization in the neurons of the cortex [317–320]. Changing magnetic fields induces electric currents in the neurons of the targeted region [321]. Low-frequency rTMS (< 1Hz) decreases cortical excitability at the site of stimulation, whereas high-frequency stimulation (> 5 Hz) increases cortical excitability or causes synchronization [320]. In rTMS studies, cortical areas such as M1 [78,312,322–324], S1 [325], frontal cortex [325,326] and parietal cortex [327] are mainly

targeted, though stimulation over primary motor cortex is more effective in reducing pain [324,328–330]. The frequency of stimulation is varied from 0.2-20 Hz [322,324]. It is believed that stimulation with frequencies in a range 10-20 Hz, that has the largest effect on reducing pain, restores the intracortical inhibition and causes increase in EEG power [324]. Through lateral cortical connections between the stimulated and other cortical sites, rTMS affects not only the stimulation site but also other cortical areas involved in pain matrix, such as PFC, S1, and S2 cortical areas [324,330], possibly activating inhibitory circuits involved with pain reduction [326]. Evidence supports the clinical efficacy of rTMS (1 Hz – 20 Hz) in patients with trigeminal neuralgia and post-stroke pain syndrome [331], CRPS [332], and fibromyalgia [333]. Compared to placebo, active 20Hz stimulation over the M1 representing contralateral painful zone induced significant reduction in pain [320,323,334]. There are three crossover rTMS studies (both active and sham groups) for the management of NP in SCI population [335–337]. All studies reported clinically non-significant reduction of pain. However, in addition to improvement in quality of life, statistically significant reduction in average pain and worst pain has been noticed. The stimulation was applied with a frequency of 5-10 Hz over the cortical representation of paralyzed and painful lower limb in a study having only paraplegics while over the hand and leg cortical representations in studies with mixed SCI population (paraplegics and tetraplegics, complete and incomplete injury). In two other rTMS studies with heterogeneous group of pain patients [334,338], only a single SCI patient was enrolled but authors did not discuss the individual response. In summary, rTMS induced 25-30% reduction in pain in non-SCI patients [319] and 15-21% in SCI population [335–337].

tDCS, a noninvasive brain stimulation technique, uses constant low current (<2 mA) via small electrodes applied to the scalp for the modulation of the brain activity [339–342]. The

current induced from anodal stimulation causes a depolarization of the resting membrane potential, thus increases the neuronal/ cortical excitability of the area being stimulated, while cathodal stimulation causes hyperpolarization which decreases the neuronal excitability analogous to mechanisms supporting long-term potentiation (LTP) and depression [343]. Increased neuronal excitability increases synchronization. The dorsolateral prefrontal cortex (DLPFC) and M1 have been stimulated at 1-2 mA for pain treatment using tDCS [344–349]. The anodal tDCS (1 mA – 2 mA for about 20 min) compared with sham over the M1 corresponding to painful zone showed efficacy in patients with chronic NP following multiple sclerosis [350], refractory chronic pelvic pain [346], fibromyalgia pain [351] [344] [347] and other chronic pain syndromes (trigeminal neuralgia, poststroke pain syndrome, back pain) [352]. There were two tDCS studies on NP in SCI population [345,353]. In one study, five sessions of active anodal tDCS (2mA) over M1 compared to sham tDCS induced statistically significant reduction in pain [345]. However, the clinically significant reduction in pain in active group was noticed in 63% subjects (7/11) only. This reduction in pain was negatively correlated with the duration of pain. The other study did not find reduction in pain following a single session of both active anodal tDCS and sham tDCS [353]. However, theta and alpha amplitude increases and gamma amplitude decreases significantly.

Reduction in level of NP in five paraplegics has been evaluated using visual illusion in three modes (virtual walking, motor imagery and watching movie) in which greater and longer time pain reduction was observed with virtual walking mode in four out of five patients [354]. Contrary to Moseley [354], noticeable improvement of NP was not observed in visual illusion group [355]. Studies showing increased activation of ACC and right DLPFC in patients with NP prevents using MI for the treatment of NP [261,356,357].

The combined effect of both tDCS and visual illusion on NP in SCI population has been assessed in two studies [355,358], where reduction in pain was high in combined therapy compared with a single intervention. The study provided evidence that combinational treatment group (tDCS + visual illusion) than other three groups (tDCS alone, visual illusion alone and sham/placebo) reported largest and longer lasting (12 week follow-up) reduction in pain intensity and quality of life [355]. In other study with combinational therapy, 72% (13 out of 18) patients reported clinically significant reduction in NP [358].

The mechanisms of NF is not completely known, but is believed that it facilitates global connectivity and after a prolonged practice induces neuroplasticity [359]. It has been suggested that NF can provide benefit to both NP and nociceptive pain by affecting the pain experience indirectly through enhanced central nervous system stability and improved homeostatic control [360]. Since, the goal of NF is either to activate or suppress EEG activity; the mechanism is also based on selection of protocol. NF treatment of chronic pain is typically based on increasing dominant activity (e.g. alpha) and decreasing theta and beta frequency activity [361]. It is believed that sensory-motor rhythm (SMR) enhancement facilitate thalamocortical inhibitory mechanisms and reduce hyperactivity [362]. Alpha and theta suppression are associated with increased corticospinal excitability, increased excitation of sensory cortex, decreased intra cortical inhibition, cortical metabolism, attention, behavioural and increased neural activation of the cortex [363–365]. Further, the suppression in alpha amplitude induced up-regulation of functional connectivity within the ACC [366].

It has been reported that scalp EEG-based NF showed positive results in 95% patients with 19 or more NF sessions and in only 12 % (3 out of 25) patients with 11-19 NF

sessions [167]. NF training has shown promising results in treating individuals with chronic pain of different origins but there is no single recommended protocol (frequency bands and scalp locations) [353,360,361,367–369]. The early NF study on pain management found that occipital alpha enhancement did not reduce pain, though alpha activity was increased in both EC and EO modalities [168]. SMR reinforcement, and theta and beta suppression at Cz and C4 following few (more than 20) sessions of NF reduced fibromyalgia pain syndrome [140,141,370,371]. It has been reported that tailored protocols, such as enhancement of SMR and theta using bipolar T3-T4 and P3-P4 respectively reduced CRPS [367], whereas alpha reward reduced trigeminal neuralgia [368]. Other protocols include alpha-theta training, bipolar Cz-Fz, F3-F4 and F7-F8, and theta (2-7Hz) and beta inhibits training at C3, C4 and T4 sites. In addition to reduction in pain intensity, improvement in other symptoms, such as physical and psychological functioning, sleep quality, depression, anxiety and muscle tenderness has been reported [140,141,367,371]. To the best of our knowledge, there is only a single scalp EEG NF study comparing the effect of scalp EEG feedback with the control group [141]. The control group were given escitalopram and NF group received 20 sessions of SMR enhancement training from the C4 site for a period of four weeks. Compared to control group, the NF group showed largest reduction in pain and improvement in depression and anxiety.

NF studies uses fMRI to provide real time feedback showed that chronic pain can be controlled by controlling rostral ACC activation [150,198]. In these studies, the control groups compared to active group did not report reduction in pain intensity. The control groups in these studies either did not receive feedback, received feedback from a different brain region, or feedback from other person brain activity. There are two groups working on LORETA feedback for the management of pain. A group at University of Alberta has been

working on LORETA based feedback since 2006 for the treatment of chronic pain but we found only one news article and one magazine article [372,373]. In these articles it was reported that down-regulation of activity of ACC (BA24) and PFC (BA9) reduced pain intensity. Another group at "Tallahassee Neurobalance Center, Florida, USA" reported positive effects of LORETA Z-score feedback in four case studies [374]. In that study patients achieved clinically significant reduction in chronic pain accompanying reduction of EEG power and reduced activity in IC and ACC in theta and beta frequency bands.

Table 2.2 shows list of protocols tested for the treatment of pain with NF. The table also provides information about sample size and total number of sessions.

Table 2.2: Details of NF studies for management of pain

Feedback Type	Protocols			Sample Size	Total sessions	Reference
	Electrode/ Brain region	Frequency bandwidth				
		Reward	Inhibit			
Scalp EEG	Oz (EO, EC)	A		1	67	Gannon 1971[168]
	C4	SMR	T	3	10	Kayiran 2007 [371]
	Cz, C3, C4, T3-T4, P3-P4, Cz-Fz, F3-F4, F7-F8	SMR, T, A/ T	B	18	30	Jensen 2007 [367]
	C4	SMR		18	20	Kayiran 2010 [141]
	C3, C4, P3, P4, T3-T4	A	T, B	13	12	Jensen 2013 [142]
	T3, T4	A	T	30	1	Jensen 2013[353]
	Cz	SMR	T, B	67	40	Caro [140]
fMRI	ACC		✔	4	3	Decharms 2005 [150]
LORETA	BA: 9, 13, 24		T, B	4	4	Koberda 2013 [374]

EO: eyes open, EC: eyes closed, A: alpha, B: beta, T: theta, SMR: sensory-motor rhythm, A/T: alpha over theta ratio, BA: broadmann area.

Recently, the effect of scalp EEG NF on SCI patients with chronic pain (either nociceptive or NP or both) has been assessed in two studies [142,353]. In both studies, patients reported clinically non-significant reduction in pain. The non-significant reduction in pain might be due to small number of NF sessions (12 sessions [142] and only 1 session [353]) [167]. However, in addition to improvement in pain symptoms, significant decrease in theta and significant increase in alpha amplitude has been reported [142]. The three different protocols were tested: reinforce alpha and inhibit beta at T3-T4 bipolar; reinforce 10-15 Hz and suppress beta and theta at C3 and C4; and reinforce 10-15 Hz and suppress beta and theta at P3 and P4.

Hypnosis is usually induced by a procedure known as hypnotic induction involving a series of preliminary instructions and suggestions, defined by 'The Society of Psychological Hypnosis'[375]. Hypnotic treatment for chronic pain mainly includes suggestions to create a comfort and relaxation by changing the pain experience or pain related thoughts and behaviours [376,377]. A number of studies show that hypnosis can reduce the pain experience [376–378]. Evidence supports the clinical efficacy of hypnosis in treating individuals having chronic pain following SCI, however, it has not been mentioned whether individuals had NP or other type of pain [379–381]. In a study with four SCI patients receiving hypnotic treatment, two patients reported short term while two patients reported a long-term (1 year follow-up) positive effect [379]. In another study using hypnosis with large number of population with chronic pain (13 SCI subjects), significant improvement in average pain intensity has been reported by a subset of patients [380]. SCI participants receiving hypnosis compared to participants receiving biofeedback reported significant decrease in pain intensity that was maintained at 3 month follow-up [381]. A recent hypnosis study (only single session) on SCI population also showed significant reduction in pain

following significant increase in theta and alpha amplitude and decrease in gamma amplitude [353].

Meditation is a technique that involves internal effort (practise) to self-regulate the mind to promote relaxation [382]. Meditation has shown positive outcomes on patients with chronic pain of different origins [34,383,384]. It has been reported that meditation reduces pain by modulating brain activity in the pain-related areas (S1, S2, ACC, IC and PPC), in addition to, brain areas not related to pain [34]. Recently, it has been shown that a single session of meditation could significantly reduce chronic pain in SCI patients [353]. The patients also showed significant increase in alpha and beta bands amplitude.

The electrical current in CES is applied as a pulse (100 μA) via clip electrodes attached to the earlobes. It is suggested that CES reduced pain by modulating activity of the hypothalamus and limbic system [385]. CES significantly reduced pain of mixed types (NP, nerve root entrapment, visceral and musculoskeletal) associated with SCI (paraplegic and tetraplegic) [386,387]. The short-term statistically significant reduction in pain, though clinically significant only in 14%, has been reported in a sham double-blinded study with large number of SCI population (128 subjects) with NP [388].

In acupuncture, 6-12 needles are inserted at different acupoints (body location) [389]. Also, electro acupuncture technique is used in which a small amount current is applied at acupoint or at the needle. Recently, it has been suggested acupuncture is effective for some but not all kinds of pain [390]. Acupuncture has been used with good results to reduce NP following SCI [391–393]. In studies [391,393] 46% patients reported reduction in pain following treatment, however, 27% also reported increased pain [393]. Moreover, Norrbrink [391] compared the effect of massage therapy with acupuncture therapy and found it less

effective. Of the 36 SCI participants with below level NP, 24 patients reported reduction in pain [392].

The mechanism of TENS is based on Gate theory in which large diameter afferent fibers are activated that overlap the area of injury and pain [11]. There are two variants of TENS: 1) low-intensity (1–2 mA), high-frequency (50–100 Hz) TENS; and 2) high-intensity (15–20 mA), low-frequency (1–5 Hz) [394]. PENS is a technique involving insertion of an ultra-fine acupuncture needle probes into the soft tissues or muscles to electrically stimulate peripheral nerve fibers [395,396]. PENS is related to both electro acupuncture and TENS [396]. NP of different origins have been treated using PENS and TENS in patients with diabetes [395], [397]. In SCI patients with NP, the significant reduction in pain has been reported in 38% patients with low frequency TENS (2-4 Hz pulse frequency) and in 29% patients received high frequency TENS (80 Hz pulse frequency) [398,399].

The outcomes of above studies varied from patient to patient because of using different techniques in a heterogeneous population of patients with different origins and duration of NP. Some subjects achieved short term relief while others did not benefit. In the context of cortex stimulation techniques, the variability of results could be related to inaccurate positioning of stimulation electrode, stimulation parameters (frequency and site of stimulation), active or sham stimulation. Further, most studies did not discuss neurological outcomes of treatment.

2.3. Limitations in the Literature

Previous brain imaging studies with SCI patients did not show a consistent change in brain activation patterns during motor tasks (see Section 2.1.1). The inconsistency in these findings may be due to the large variety of inclusion criteria, including ignorance of pain. Current knowledge of changes in brain activity following chronic pain in patients with SCI is mainly derived from fMRI studies. These studies do not provide information about dynamic changes in brain activity. EEG studies with SCI patients who have CNP have so far been limited to the analysis of relaxed states (EO and EC states). Additionally, it has been mentioned that different pharmacological and non-pharmacological treatments have been used to manage chronic pain (see Section 2.2). These studies found that non-pharmacological treatments compared to pharmacological treatments reduces pain with less side effect. NF is a non-pharmacological treatment approach that has the potential to reduce pain. However, there is no standard NF protocol and effect of large numbers of training sessions was not assessed. Furthermore, previous NF studies did not show the immediate global effects of NF training. Most non-invasive non-pharmacological treatments showed behavioural changes and few studies discussed the effects of long-term changes in brain activity following treatment.

2.4. Objectives of the Study/ Research Problem

The aim of this thesis is to address the limitations described above. This will be accomplished using four main objectives: (1) to detect frequency dependant CNP signatures in paraplegics with CNP by recording EEG in relaxed and during MI states, (2) to test different NF protocols for the treatment of CNP in paraplegic patients, (3) to find

the immediate global effect of NF training on power and coherence, and (4) to find long-term neurological changes in pain related cortical and sub-cortical areas following long-term NF training.

The study outlined in this thesis is divided into three phases to achieve the four main objectives.

Phase 1 (Diagnostic phase): Phase 1 of the study is intended to achieve objective 1. Here, scalp EEG will be used to compare frequency dependent dynamic changes in the brain activity of three groups: (i) paraplegic patients with CNP, (ii) paraplegics without pain, and (iii) able-bodied subjects.

Phase 2 (Treatment Phase): Phase 2 of the study is intended to achieve objectives 2 and 3. Here, NF training will be provided to seven patients, selected from the patients recruited for phase 1 of the study, to assess the effect of NF on CNP in paraplegics. The NF protocols will be designed based on the results of phase 1 in combination with neurostimulation techniques that mainly target the cortex to achieve neuromodulation. Furthermore, whole head EEG with 16 channels was also assessed during NF to find the immediate global effects of NF training.

Phase 3 (Neurological Outcomes): Phase 3 of the study is intended to achieve objective 4. Here, whole head EEG analysis with 61 channels will be performed after the last training session to compare cortical and deep cortical changes before and after NF.

Chapter 3. Dynamic Oscillatory Signatures of Central Neuropathic Pain in Spinal Cord Injury

3.1. Abstract

Objective: To define electroencephalogram (EEG) signatures of Central Neuropathic Pain (CNP) in paraplegic patients.

Methods: Three groups of ten participants took part in the study: Able bodied (AB), paraplegic patients with no pain (PNP) and paraplegic patients with CNP (PWP). EEG was recorded in the eyes open (EO) and eyes closed (EC) relaxed state and during cue-based motor imagery (MI) of upper and lower limbs. Power and event-related desynchronization/ synchronization (ERD/ERS) were analysed.

Results: In the relaxed state, CNP is characterised by the increased power in the theta (4-8 Hz) and alpha (8-12 Hz) band and shift of the dominant alpha frequency towards lower values. During motor imagery (MI), CNP is characterised with dynamic, frequency dependant increase of ERD over the sensory-motor and parietal cortices, not somatotopically restricted to painful parts of the body.

Conclusion: Increased ERD, not restricted to MI of painful body parts, might be a signature of CNP.

3.2. Introduction

CNP is believed to be accompanied by functional and structural changes in several cortical and sub-cortical structures [239,307,400]. The cortical and sub-cortical areas show plastic changes include primary and secondary sensory-motor cortices, anterior cingulate and insular cortices, and dorsal lateral part of the frontal cortex [261,400]. It has been mentioned in section 2.1.2 that the plastic changes can be observed in the form of either increased or decreased activation of the cortical representation of the painful and non-painful parts of the body during motor task. The cortical plasticity can also be noticed in the form of expansion, invasion, and shift of the cortical representation of the body part perceived as being painful. Our knowledge on this interaction is mainly based on functional magnetic resonance imaging (fMRI) studies which can provide information about sub-cortical structures but could not provide frequency-dependant dynamic changes in the brain activity [27,401]. Previous studies also suggested that chronic pain may be related to changes in brain activity measured with EEG [46,257–260,262]. Limitation of these studies was that they provided information about brain activity in a relaxed state only. However, a study demonstrates that dynamic oscillations of EEG are associated with empathy for pain [402].

The objective of this study was to detect frequency-dependant dynamic oscillatory signatures of chronic pain in the brain. The objective was achieved by comparing task-related and task-unrelated EEG activity of paraplegic patients having CNP with the EEG activity of able-bodied and paraplegic patients without CNP. The methods, results and discussion presented in this chapter are based on our published study in the journal of pain [403].

3.3. Methods

3.3.1. Participants

A total of 30 age-matched adult (between 18 and 55 years old) volunteers were recruited in three groups of 10. The three groups were:

1. Paraplegic patients, with diagnosed below level CNP (**PWP**) (3F, 7M age 45.2±9.1)
2. Paraplegic patients with no chronic pain (**PNP**) (2F, 8M age 44.4±8.1)
3. Able-bodied (**AB**) volunteers with no chronic pain (3F, 7M age 39.1±10.1)

Informed consent was obtained from all participants and the ethical approval was obtained from the University Ethical Committee for the able bodied group and from National Health Service ethical committee for patients' groups. Information of both patients' groups is shown in Table 3.1. The location on the body perceived as being painful is shown in Figure A.1 (Appendix).

The neurological level of SCI was determined using the American Spinal Injury Association (ASIA) Impairment Classification [14] . All SCI patients were at least 1 year post injury and had a spinal lesion at or below T1 level. Inclusion criteria for patients with CNP was a positive diagnosis of CNP, reported a pain level ≥ 5 on the visual analog scale (VAS) and a treatment history of CNP for at least 6 months The general exclusion criteria for all three groups were a presence of any chronic (non CNP) or acute pain at the time of the experiment; brain injury or other known neurological impairment that would affect EEG interpretation or would prevent patients understanding the experimental task.

Table 3.1: Information about both patients groups

Nr	Injury Level	ASIA	Injury time (years)	Pain VAS	Pain time (years)	Medications
Patients with pain group (PWP)						
1	T5	A	7	7	7	Baclofen Carbamazepine Gabapentin
2	T5/6	A	11	6	11	/
3	T5	A	7	8	7	Pregabalin Gabapentin
4	L1	B	15	7	15	Gabapentin
5	T6/T7	D	4	7	3	Pregabalin
6	T7	B	6	8	5	/
7	T6/7	B	25	10	24	Gabapentin
8	T1	A	25	5	10	Pregabalin
9	T5	A	14	5	13	Amitriptyline, Baclofen, Diazepams
10	L1	B	5	5	4	/
Patients with no pain group (PNP)						
1	T7	A	7			
2	T7	B	7			
3	T12	A	7			
4	L1	A	6			
5	T2	A	2			
6	T5	B	15			
7	T11	A	11			
8	T4	A	9			
9	T7	A	15			
10	T7	B	22			

ASIA: American Spinal Injuries Association, CNP: Central Neuropathic Pain, PWP: Patient with pain group, PNP: Patient with no pain group, VAS: Visual Analog Scale.

3.3.2. Recording Equipment

A 61 channel EEG (Synamp 2, Neuroscan, USA) was used to record with electrodes placed according to standard 10-10 locations [100] using an ear-linked reference and AFz ground. Electrooculagram (EOG) was recorded from 3 channels around the right eye. All channels were sampled at 1000 Hz. Individual electrode impedance was below 5kΩ. In addition, electromyogram was recorded from the right and the left wrist extensor muscles and right shank using the bipolar inputs to the Synamp device. The purpose of electromyogram recording was to check for the absence of any evidence of voluntary movements when subjects performed MI.

3.3.3. Experimental Study Design

Participants were instructed not to drink coffee or alcohol on the day of the experiment. EEG was recorded in two paradigms: spontaneous activity and induced activity during cue-based motor imagery. Before starting the experiment participants with pain were asked to fill out 'brief pain inventory' [89] to establish the level and location of pain.

3.3.4. Spontaneous EEG Recording

Spontaneous resting EEG was recorded under the EO and EC condition in a quiet room. During the EO state, participants were asked to visually fixate on a small cross presented on a computer screen, while in EC state they had to close their eyes and relax. EEG was recorded for 2 min for each condition repeated 3 times, alternating between the conditions.

3.3.5. Cue Based Motor Imagery

An experimental protocol that instructed participants to imagine hand or lower limb movements was devised using visual cues. Participants were seated at a desk, approximately 1.5 m in front of a computer monitor. Participants were instructed to look at the centre of the monitor and were instructed to respond to a sequence of visual cues. The cues comprised at t= -1s a readiness cue (a cross +) which remained on for 4s (Figure 3.1). At t=0s an initiation cue, presented as an arrow was displayed for 1.25s, pointing to the left ←, to the right → or down ↓ and corresponding to imagination of the left hand waving (LH), right hand waving (RH) and tapping with both feet (F). Participants were asked to continue to perform real or imaginary movements until the cross disappeared from the screen (3s after the initiation cue appeared). In total 60 trials of each movement type were presented to subjects and cues were collected in randomised sequences comprising 10 trials with rest periods between.

3.3.6. Data Pre-processing

For pre-processing of spontaneous EEG, a high pass filter (IIR, 12db cut off frequency) was set to 1 Hz and a notch filter was applied between 48-52 Hz, to remove line noise at 50 Hz. Filtering was applied forwards and then backwards to avoid phase shift. Signals were then down-sampled to 250 Hz. EEG was visually inspected and sequences containing EOG artefact and other types of noise (amplitude exceeding approximately 100 μV over all channels) were manually removed. For EO and EC state for each volunteer after noise removal a minimum of 3 min of data was required for data inclusion. For pre-processing EEG data during MI, signals were pre-processed as explained above and were then exported to EEGLab [208]. Independent Component Analysis (ICA) was performed using the

Infomax algorithm [210] implemented in EEGLab for advanced noise removing purposes to avoid excessive EEG removal from a limited number of trials. In this way no more than 2 (out of 60) trials had to be removed per dataset.

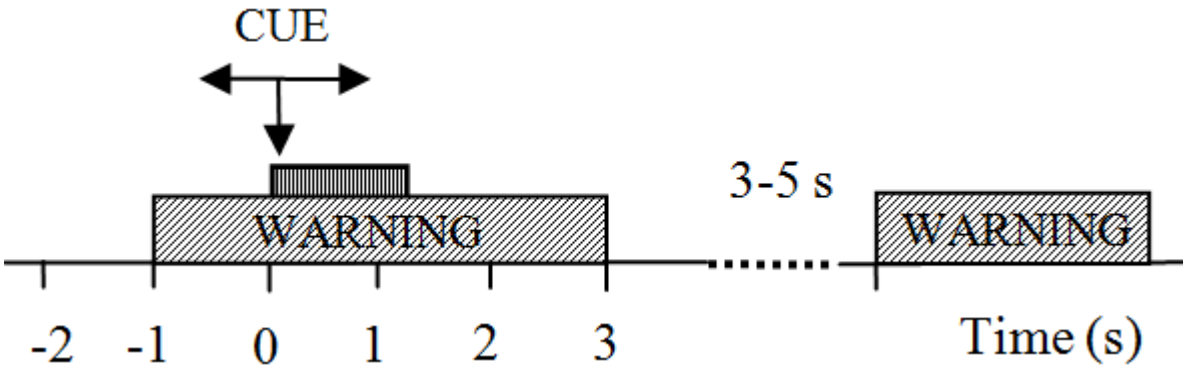


Figure 3.1: Experimental setup for cue based motor imagery (MI) tasks: At t=-1 s a readiness cue (a cross) appeared on a computer screen, followed by a cue (an arrow) at t=0 s. The cue stayed on the screen till t=1.25 s while the warning stayed until t=3 s. A volunteer was asked to perform repetitive imagination of movement from t=0 s till readiness cue disappeared at t=3s. Different arrows indicate motor imagery of different limbs.

3.3.7. Analysis of Spontaneous EEG

Data were re-referenced to an average reference. For each volunteer, a power spectral density (PSD) was calculated over 2 s windows overlapped for 1s using Hamming windows. Logarithmic PSD was calculated as $10 \cdot \log_{10}$PSD for normalisation purposes. The location of the dominant alpha peak was determined based on PSD. Location of a peak frequency was additionally confirmed by a visual inspection. A dominant peak frequency for each volunteer was normalised and averaged over all electrodes.

A 'Study' structure was created in EEGLab to compare on a group level between different conditions. 'Groups' were three groups of volunteers (AB, PWP, and PNP) while

'conditions' were EO and EC state. PSD was averaged over different frequency bands and compared for each electrode location between Groups and between Conditions. To compare between means of two variables a non-parametric permutation test [404] based on resampling was implemented in EEGLab with a significance level set to p=0.05. A non-parametric two-way ANOVA based on permutation analysis was also applied to compare between Groups and Conditions and to check for their interaction. A correction for multiple comparisons was performed using the False Discovery Rate (FDR) [405]. All procedures were implemented in EEGlab.

3.3.8. EEG Analysis of Motor Imagery

Before performing the analysis, EEG data were re-referenced to the average reference. A 'Study' structure was designed in EEGLab to allow EEG analysis on a group level. 'Groups' were PWP, PNP and AB groups and 'Conditions' were motor imagery of LH, RH and F. Data analysis was based on ERD/ERS phenomena [406].

For calculating the ERD/ERS of each single volunteer a reference period from -1.9 to -1.1s (before the cross) was adopted, time-frequency decomposition was performed in a frequency range 3-55 Hz using a sinusoidal wavelet with minimum 3 wavelet cycles per data window at lowest frequencies. Overlapping Hanning tappers windows were applied.

In order to find regions of significant ERD/ERS for each condition (on a single electrode site), a significance level was set to p=0.05 and nonparametric bootstrapping procedure (N=2000 trials) [407] was performed, comparing ERD/ERS maps between groups. A FDR correction was applied to correct for multiple comparison from multiple time-frequency windows.

Scalp maps were created based on ERD/ERS averaged over certain frequency bands and short time windows (0.2 s). Comparison between scalp maps of different groups or conditions was performed based on a permutation statistics (p=0.05) as previously described and FDR was applied to account for comparison from multiple electrode sites.

3.4. Results

3.4.1. Spontaneous EEG Activity of Three Groups

To assess the dynamic response of the motor cortex to CNP in an imagined movement task, we first characterised the relaxed states, using EO and EC states. The power spectral density in the theta and the alpha band was compared amongst each of two groups (AB versus PNP, AB versus PWP, PWP versus PNP) over all 61 electrode locations (Figure 3.2). The subfigure 'a' and subfigure 'b' shows difference in the theta band (4-8 Hz) and alpha (8-12Hz) band separately in EO and in EC state. Because of multiple comparisons across 61 electrodes, a FDR method was used to avoid Type II error. These may lead to more conservative results than in previous studies which haven't used FDR. PNP group had lowest theta and alpha power in EO state, significantly lower than PWP and AB. Results confirmed that in EO state PWP patients had increased theta PSD compared to PNP group [257,259,260,262] (Figure 3.2a) and comparable theta PSD to AB group. No difference among groups was found between theta PSDs in the EC state (Figure 3.2a). The intensity of the alpha PSD in PWP was comparable with the alpha PSD in AB group in both EO and EC state (Figure 3.2b). PWP had larger alpha PSD in EO state than in PNP group over most of recording sites (Figure 3.2b). However in the EC state there was no difference between PWP and PNP group in the parieto-occipital region (Figure 3.2b),

which is normally an area of largest alpha activity in the EC state. This effectively means that PWP group had a reduced EC/EO ratio in the parieto-occipital region. Reduced EC/EO ratio has already been reported in paraplegic patients with CNP and is believed to be an indicator of the thalamocortical network involved in CNP processing [262]. There was no significant difference between groups in the beta range. In PWP, the dominant frequency 9.1±0.8 Hz was significantly lower compared to 10.1±0.6 Hz in the AB (Wilcoxson p= 0.008) and 10.4±0.9 Hz in PNP (Wilcoxson p= 0.0085).

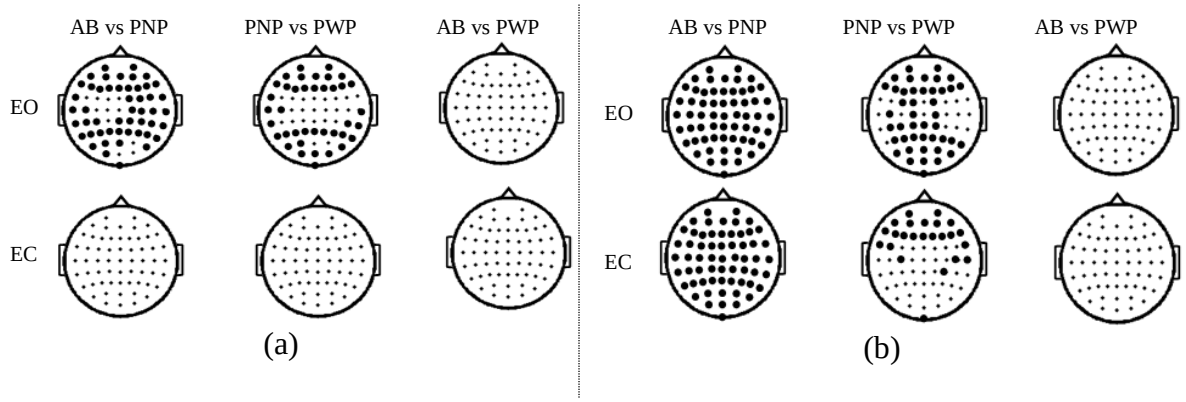


Figure 3.2: Comparison of PSD in relaxed state between each two groups (p=0.05) with FDR correction for multiple comparison. Large black dots mark electrode locations with statistically significant differences between groups (AB: able bodied, PWP patients with pain, PNP patients with no pain) in eyes open (EO) and eyes closed (EC) states. (a) Theta band 4-8 Hz; (b) Alpha band 8-12 Hz.

3.4.2. Dynamic Activation of Sensory-Motor Cortex during Motor Imagery

Figure 3.3 shows ERD/ERS at electrode location Cz, being of pimary somatotopic relevance to the leg area. PWP patients showed the most significant ERD, spreading over all frequency bands (being most pronounced for the movements of the feet), being

statistically significant larger than ERD in the other groups. This strong ERD persisted during motor imagery of both painful and non-painful limbs.

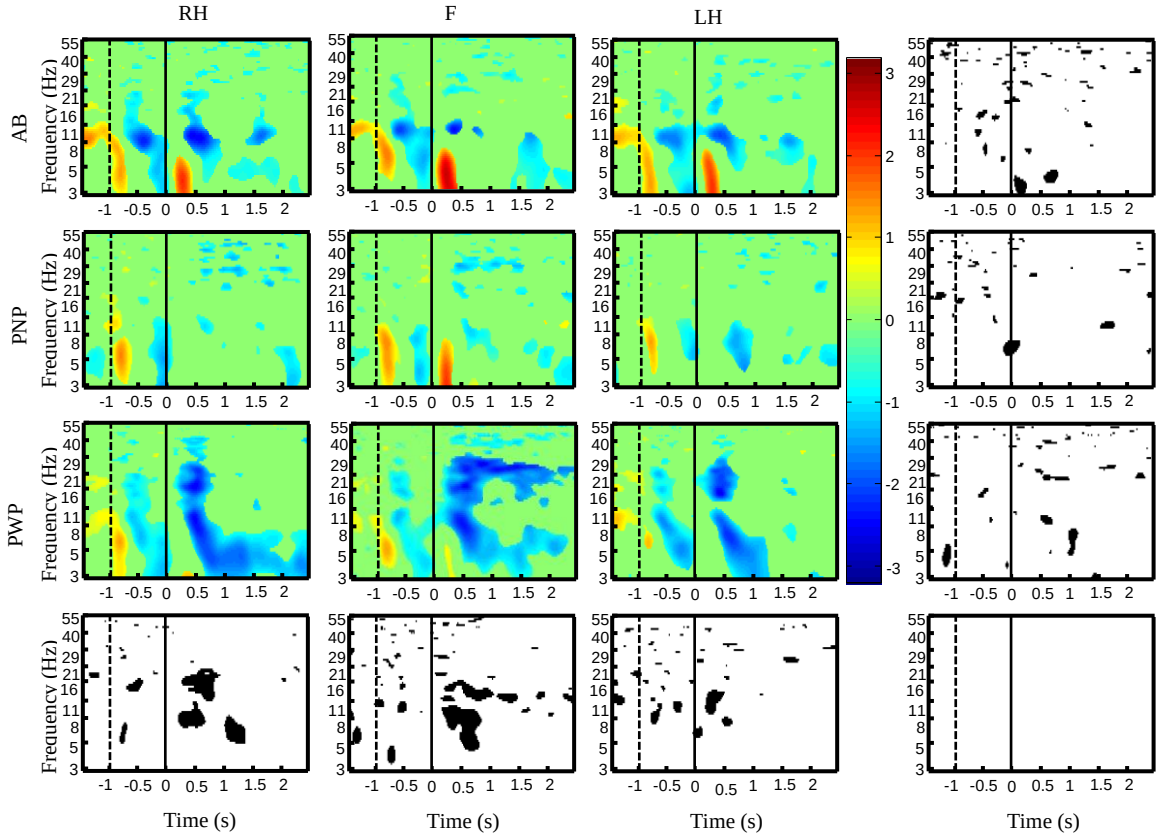


Figure 3.3: ERD/ERS time frequency map at Cz site for all three groups (AB: able bodied, PWP patients with pain, PNP patients with no pain) and for all three motor imagery (MI) tasks (RH: right hand MI, F: feet MI, LH: left hand MI. Figures far right show areas of statistically significant differences among three MI tasks, while figures at the bottom row show areas of statistically significant differences among three groups (p=0.05) with FDR correction for multiple comparison. At t=-1 s (dashed line), a warning cross was appeared. Participants were asked to start with motor imagery when a cue appeared at t=0s (solid line) and to continue with motor imagination until t=3 s. ERD/ERS map shows a time period starting at t=-2 s before the cue and ending at t=2.5 s after the cue in a frequency range 3-55 Hz.

The comparison of ERD/ ERS between each two group (AB versus PNP, AB versus PWP, PWP versus PNP) corresponding to Figure 3.3 is shown in Figure A.2 (Appendix). Also, the ERD/ ERS time-frequency maps for all three groups for all three MI tasks at C3 (Figure A.3) and C4 (Figure A.4) sites are shown in the Appendix.

3.4.3. CNP Leads to a Distinctive Cortical Activation

Cortical activation during imagined movements in patients with CNP was stronger and spatially different from that of the other groups (AB, PNP). Figure 3.4a show ERD/ERS scalp maps averaged over the SMR1 band (8-12 Hz) and over a period 0.4-0.6 s after presentation of a cue on the computer screen, for all groups and all three tasks. As this latency period exceeds what would be a normal reaction time to a movement we believe that this period, 0.4-0.6 s after MI cue corresponds to the covert i.e. 'mental' execution of the MI task. This period is also the time point where intensity of ERD is maximal (Figure 3.3).

In PWP ERD was not limited to the cortical presentations of the painful legs. They had a wide-spread ERD, strongest for MI of the right hand and weakest for MI of the left hand, with no ERS in 'the surrounding' areas, (Figure 3.4a). Although shifted posteriorly, the ERD spatial distribution in PWP still follows the somatotopic presentation, where the movement of the right hand causes a strongest ERD at electrode locations placed over the left hemisphere, over the centro-parietal area for the feet and over the right hemisphere for the left hand. In contrast, AB participants and PNP both exhibited similar spatial distributions, central ERD accompanied with weak ERS in the areas surrounding the central area (a phenomenon known as 'central ERD with surrounding ERS') [408] .

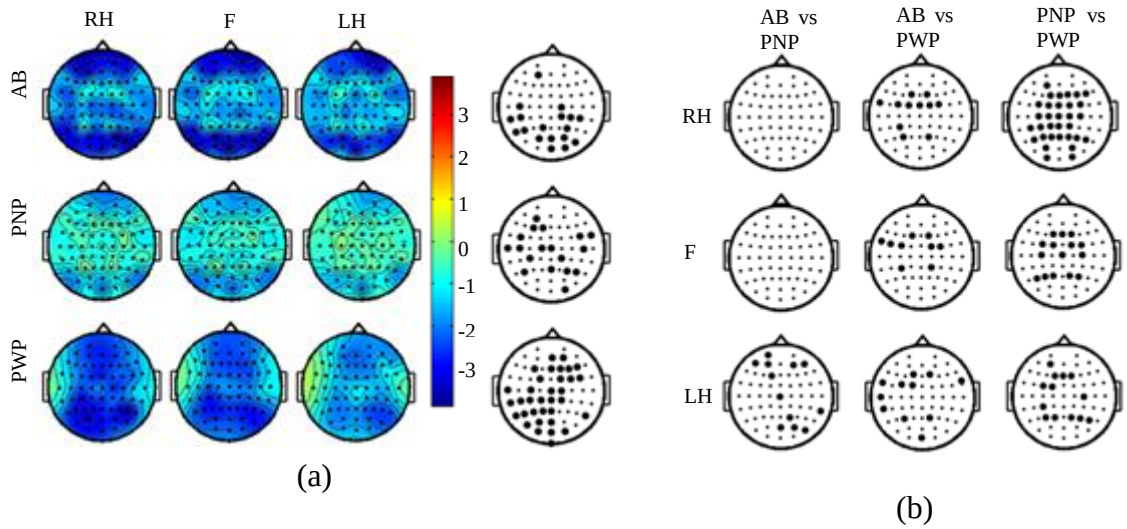


Figure 3.4: Comparison of ERD/ERS over whole scalp among groups and conditions. (a) Scalp maps of ERD/ERS in SMR1 band at 0.4-0.6 s post cue for all three groups and all three tasks. ERD shows areas of increased cortical activity, as compared to the period before motor imagery. Column far right shows areas of statistically significant differences (p=0.05) with FDR correction for multiple comparison among three tasks AB: able bodied, PWP patients with pain, PNP patients with no pain; RH: right hand, F: feet, LH: feet. (b) Areas of statistically significant difference between groups and tasks shown in Figure 4a (p=0.05) with FDR correction for multiple comparison.

In contrast to relaxed state, where AB and PNP alpha PSD showed statistically significant difference over all cortical areas (Figure 3.2a), during MI AB had stronger responses than PNP for MI of the LH only (Figure 3.4). The largest difference between PWP and PNP patients was found for MI of the RH although areas of statistically significant difference existed for motor imagery of both hands and feet (Figure 3.4b column PWP versus PNP). While there was no statistically significant difference in the normalised alpha power in EO state between AB and PWP (Figure 3.2), there was a statistically significant difference in the SMR1 ERD during MI (Figure 3.4). Statistically significant differences between AB participants and PWP were found for MI of F, RH, and LH - again indicating that CNP

produces a widespread increased activity in the sensory-motor cortex. In AB group strongest ERD could be noticed in the frontal and in the occipital areas. This might be attributed to visual processing of the target and movement planning. Similar but weaker tendency can be noticed in the PNP group. In the PWP group however, ERD can be noticed over almost all cortical regions from which EEG was measured. A relatively conservative correction for multiple comparisons, which does not take into account spatial correlation of measured values, might explain why relatively few EEG locations show statistically significant difference between the groups.

3.4.4. EEG of Patients with CNP Reveals Frequency-Specific Temporal Signatures

MI induces dynamic cortical responses that cannot be captured using fRMI. In addition to showing that CNP causes a frequency specific activation pattern over several cortical areas, we show that this activation has a specific temporal pattern. As an example of this, a response to imagined movement of the feet is shown for all three groups for theta (Figure 3.5) SMR1 (Figure 3.6) and SMR2 (16-24 Hz) (Figure 3.7) band activities. Although participants repetitively imagined movement for 3s, we show first 2 s only as this captures the important initiation of the task.

In the theta band (Figure 3.5) and in the period 0.2-0.4 s, all three groups exhibited ERS. Following this, in a period from 0.4 to 0.6 s, PWP group showed widespread ERD from the occipital to the frontal area until 0.8 s. In the period 0.8-1.2 s, weak ERD was noted over the parietal (sensory) area. In the other two groups theta ERD could not be noticed in the central area of the cortex. Thus theta ERD over sensory-motor cortex appears to be an observation only seen in patients with CNP.

In the SMR1 band, Figure 3.6, strongest ERD in PWP group was in a period t=0.2-0.8 s dominantly located posteriorly but for t>0.8 s SMR1 ERD can be noticed at the lateral areas of the central region only. In other two groups, distinctive ERD in the central area of the cortex could be noticed until t=0.8 s. In AB group ERD can also be noticed in the frontal and occipital area until the end of the analysed period. PNP group had weaker ERD in the frontal and occipital areas compared to the other two groups, and almost no visible ERD after t=0.8 s.

Finally, in the SMR2 band, (Figure 3.7) all three groups had strongest ERD in a period t=0.2 to 0.4 s. In a period t=0.2 to 0.6 s, ERD in PWP group can be noticed over the central, parietal and occipital areas but for t>0.6 s remained only at the central areas (Figure 3.7). ERD in the AB and PNP group is wide spread. No visible ERD can be noticed in the AB group after t=0.8 s while some ERD over the central area could be noticed for both PNP and PWP groups till the end of the analysed period.

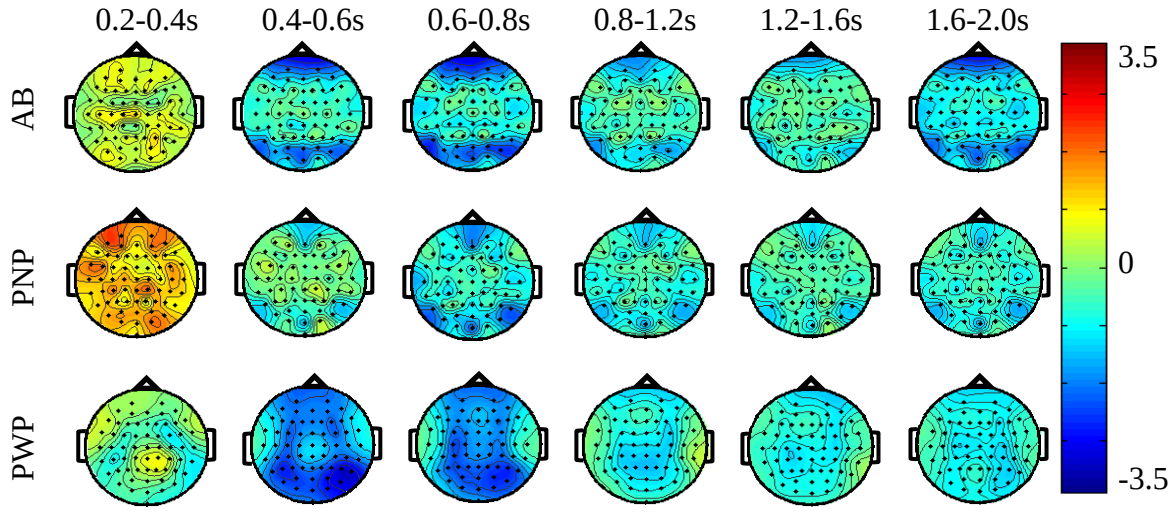


Figure 3.5: Spatio-temporal changes in ERD/ ERS of three groups in the theta band. AB: able-bodied, PNP: patients with no pain, PWP: patients with pain. The motor imagination task was a repetitive tapping of F from t=0s till t=0.3 s.

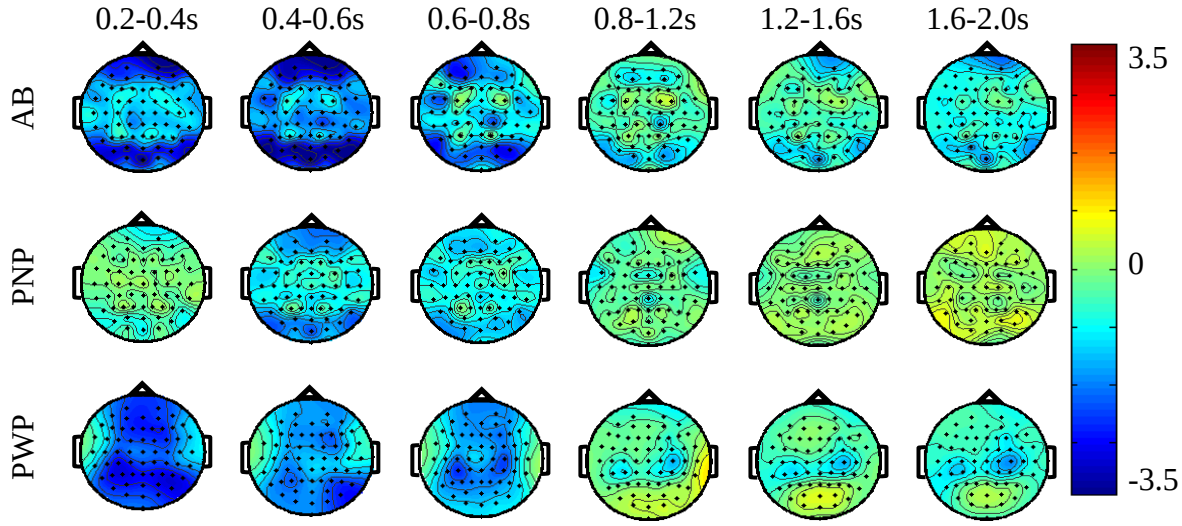


Figure 3.6: Spatio-temporal changes in ERD/ ERS of three groups in the SMR1 band. AB: able-bodied, PNP: patients with no pain, PWP: patients with pain. The motor imagination task was a repetitive tapping of F from t=0s till t=0.3 s.

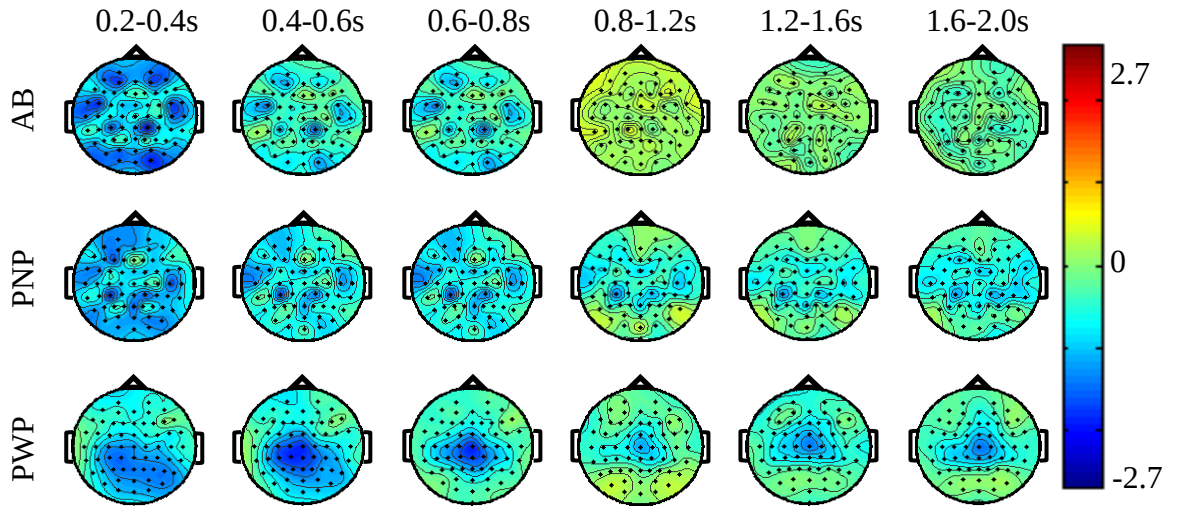


Figure 3.7: Spatio-temporal changes in ERD/ ERS of three groups in the SMR2 band. AB: able-bodied, PNP: patients with no pain, PWP: patients with pain. The motor imagination task was a repetitive tapping of F from t=0s till t=0.3 s.

3.5. Discussion

The study provides evidence of altered spontaneous and evoked cortical activations in patients with CNP in the absence of peripheral nociceptive stimulation as a way to identify what aspect of the EEG might reflect a long lasting alteration in brain behaviour associated with chronic pain, thus further expanding on indicative results from fMRI studies [87,244].

Spontaneous EEG Activity of Three Groups: In the relaxed EO state, PWP had higher alpha and theta power than PNP group. The occipital alpha power in EC state was comparable between PWP and PNP groups. PWP and AB group showed similar EEG energy levels in both the EO and EC state. PWP group also had a significantly lower dominant frequency in the alpha band than both AB and PNP groups. Increase in the theta power in presence of CNP is in accordance with previous studies [257,259,260,262], while increase in the alpha power mirrors the observation of Sarnthein et al. [259] on a mixed patient group, but disagrees with study by Jensen et al. [260] who reported a decrease in the alpha power. PWP group had a reduced reactivity in the occipital alpha between EO and EC state, which in this patient group has been attributed to a thalamo-cortical dysrhythmia [262]. The low alpha power in the PNP group confirms results of previous studies on this patient group [222].

EEG of Three Groups during MI: During MI, PNP group had weaker ERD than the AB group while PWP had distinctive strong EEG signatures. PWP group had significantly stronger alpha ERD over multiple electrode locations compared to both AB and PNP group; this contrasts between group analysis of spontaneous alpha power in EO state where no difference was found between AB and PWP group. Taken together, this indicates that strong ERD in PWP group was not a simple consequence of a high alpha power in the

reference period but can rather be attributed to the more intensive activation of the sensory and motor cortex. Of interest is that PNP group had weakest alpha ERD not only over central cortical areas but also over the frontal, parietal and occipital areas which are involved in higher order cue-based movement planning. Beta band ERD in PWP group also had a distinctive parietal location and was of a stronger intensity than in the other two groups at equivalent sites. From all three groups, AB group had the shortest lasting beta ERD.

A striking characteristic of PWP group was a wide spread ERD in the theta band. Theta is not a EEG frequency band commonly associated with movement related ERS/ERD and it's ERSP is likely to reflect the underlying CNP condition and may therefore be a putative signature of this disorder in both the relaxed [259] and active state.

Although in this study we were not able to separate the influence of sensory loss and pain in PWP group, EEG analysis between PNP and PWP group showed statistically significant difference in both relaxed state and during MI. This supports a novel theory of distinctive effect of sensory loss and of pain initiated by trauma leading to sensory loss [409].

Noteworthy finding of this study is that increased ERD over the sensory-motor cortex in PWP group is wide spread, indicating a possibility that MI in presence of CNP equally affects cortical presentation of painful and non-painful limbs. This wide spread affect indirectly supports the results of neuromodulation/ neurostimulation studies, which showed that although it is important to modulate activity of the motor cortex, it is not necessary to target cortical areas corresponding to the painful part of the body [142,324,410].

It should be mentioned that while this EEG study demonstrated distinctive brain activity in patients with CNP it could not confirm any related anatomical or functional changes. Therefore it is possible that different factors such medication, disuse reorganisation, anxiety or depression influenced brain activity recorded by EEG. A disuse reorganisation unrelated to CNP should be present in both PWP with PNP groups but these two groups had distinctive EEG responses in both relaxed state and during MI. Anxiety and depression might have contributed to EEG signatures of PWP group [411], though these patients showed no statistically significant difference in EEG power in a relaxed state compared to AB group. Antiepileptic drugs and antidepressants which were used by patients for treatment of CNP might have affected their relaxed state EEG, in particular in the theta band [274,412]. Antidepressants increase EEG amplitude in the theta and the higher beta (>20 Hz) [274], while antiepileptic drugs are known to slow down the dominant frequency and increase the energy in the theta and the delta band [412]. The antispastic drug taken by two patients targeted GABA receptors, and could potentially also increase energy level in the theta and delta band [413]. However evidence from the literature show that theta band power is reduced in patients undergoing surgery for CNP [259], suggesting that increased power in theta band is most likely related to pain, not to medications alone.

3.6. Conclusion

The results showed that the presence of CNP itself leads to frequency-specific EEG signatures that could be used to monitor CNP and inform neuromodulatory treatments of this type of pain.

Chapter 4. Experimental Evaluation of Neurofeedback Protocols for Treatment of Central Neuropathic Pain following SCI

4.1. Abstract

Objective: This study had two main objectives: To develop and test a neurofeedback (NF) protocol for the treatment of central neuropathic pain (CNP) based on electroencephalogram (EEG) signatures of CNP and to assess the global effect of NF training on modulation of EEG activity and connectivity of wider cortical structures.

Methods: Seven paraplegic patients with chronic CNP were asked to voluntarily modulate their brain activity provided feedback from one EEG electrode at a time. The electrode was located over the sensory-motor cortex. The task was to simultaneously regulate relative power spectral density (PSD) in three frequency bands: inhibit theta (4-8 Hz), inhibit beta (20-30 Hz), and reward alpha (9-12 Hz) or reward sensory-motor rhythm (SMR: 12-15 Hz) band. Patients were also tested for placebo effect: a) by showing a pre-recorded session with a feedback, and b) by providing NF from electrode location which had not previously been used for training. Patients learning ability to modulate the EEG PSD was analysed by comparing change in EEG PSD during NF with EEG PSD while practising NF without feedback information i.e. no GUI.

Results: Five out of seven patients completed the study. All five patients showed a statistically significant reduction of pain while four patients reported a clinically significant

reduction of pain (>30%). NF from one electrode site was accompanied by a widespread modulation of PSD. The effect of training on pain intensity was strongest when patients modulated PSD from C4 site, reducing the power of the theta and beta band and increasing power of the alpha band. Patients also learned to modulate PSD without graphical user interface (GUI).

Conclusion: Although NF therapy has been shown to have a potential to reduce chronic CNP in paraplegics, study on a larger number of patients is needed to further confirm the effectiveness of NF on CNP and to introduce this protocol in clinical practice.

4.2. Introduction

Chronic CNP in patients with spinal cord injury (SCI) is resistant to treatment [60,414]. Neuroimaging studies (section 2.1.1) and results found in Chapter 3 provided evidence that chronic pain is associated with the plasticity in the cortex. The insufficient reduction of pain and intolerable side-effects with pharmacological treatments suggests to test non-pharmacological treatments [264] (see section 2.2.2). The effectiveness of various non-pharmacological treatments were discussed in a review paper; reducing pain for some group of patients [264]. The inconclusive results for non-pharmacological treatments of NP might be due applying it with varied protocols on heterogeneous group of patients (see section 2.2.2). Recently, Jensen *et al.*[142] found inconsistent effect of different protocols of NF training, but suggested to test the effect of large number of training sessions with different protocols.

NF training is based on voluntarily modulation of brain activity (discussed in section 1.8). There are no standard protocols (electrode sites and frequency bands) for the treatment of chronic pain with NF (discussed in section 2.2.2). However, the feedback is mainly provided from the sensory-motor cortex to decrease the activity of theta and beta frequency bands [140–142] and to increase the activity of alpha and SMR frequency bands [140–142,367,368,371]. Furthermore, the immediate global effect of training on power and connectivity was not presented in previous NF studies. Also, past NF studies did not focus on changes in full spectrum PSD, changes in baseline PSD and pain intensity, patients learning ability to modulate brain activity without feedback, comparison of modulation of local versus distant sources, and suggestions for placebo training [415].

The two main objectives of this study were: (1) to test the effect of different protocols on pain reduction in paraplegic patients with large number of training sessions, and (2) to test the immediate global effect of NF training on power and connectivity among different electrode site. Moreover, this study addresses the mentioned limitations of previous NF studies of pain management.

4.3. Methods

4.3.1. Participants

Seven out of the 10 paraplegic patients with CNP (PWP: patients with pain) who participated in the diagnostic phase of the study (Phase 1) also received NF training (Training Phase or Phase 2) in a single-blinded manner. The numbers of NF sessions were set to 40 based on recommendation of past NF studies on pain management [167]. CNP

produces long term changes in cortical activity and therefore long term training is required to potentially reverse the effect. The demographics for the seven patients are shown in Table 4.1. Each patient had chronic CNP rated 5 or more on Visual Analog Scale (VAS). Three patients had a complete injury (ASIA A) and four had an incomplete injury (ASIA B). During the study patients were not treated using other non-pharmacological treatments, however, they continued their pharmacological treatment with anticonvulsant drugs gabapentin or pregabalin. Four patients completed all 40 training sessions, one patient received only 20 training sessions (greater than minimum recommendation of 19 sessions [167]). This patient who received 20 sessions lived outside of Glasgow and had to live in the hospital for the purpose of training for three weeks. This patient received NF training every day, while others received NF training 2 to 3 times per week. Therefore, total numbers of week each patient received training was depend on total number of times per week they received training. Patients six and seven left training after three sessions due to transport and family problems, though one of them reported reduction of pain.

Table 4.1: Demographics of PWP who received NF training

No	Level of Injury	Completeness of Injury	ASIA Level	Years with Injury/ Pain	Pain on VAS	Total sessions	Total weeks	Description of pain	Medicaions
1	T8	cSCI	A	7/ 7	6	40	19	pricking/ es	G
2	T7	cSCI	A	7/ 7	7	40	16	burning	P
3	T6/T7	iSCI	B	3/ 3	6	40	19	pricking/ es	P
4	T6/T7	iSCI	B	25/ 24	9/10	40	20	squeezing/ es	P
5	T8	iSCI	B	11/ 11	9	20	3	burning/ es	P
6	T5/6	cSCI	A	11/ 11	6	3	2	burning	G
7	T12/L1	iSCI	B	33/ 4	6	3	1	tingling	P

cSCI= complete SCI, iSCI= incomplete SCI, VAS= visual Analog Scale, ASIA= American Spinal Injuries Association, es= electrical sensation, G= gabapentin, P= pregabalin.

The exact location of perceived pain for each patient is shown in Figure 4.1. It can be noticed that except PWP7, all patients had pain on legs, buttocks and shank. PWP7 had pain on feet only.

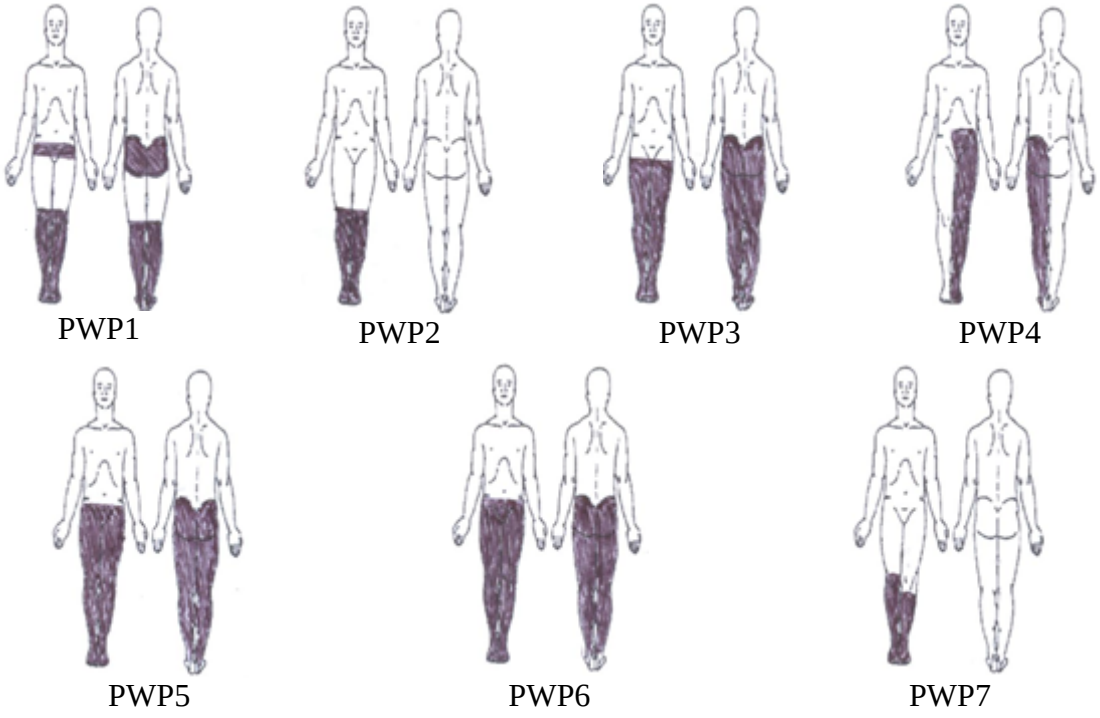


Figure 4.1: Locations on the body perceived as being painful

The ethical permission to conduct this study was granted by the NHS for the Greater Glasgow and Clyde, and NF experiments were performed at the Queens Elizabeth National Spinal Injuries Unit, Southern General Hospital, Glasgow, Scotland.

4.3.2. Assessment/ Clinical Evaluation

The self-reported pain and EEG parameters were assessed and evaluated on every training day under three conditions: (i) immediately before a training (Pre NF or baseline EEG) (used to set thresholds for the training), (ii) during each sub-session of NF training (during NF), and (iii) three to four minutes after the last sub-session of training (Post NF) (used to

assess a short-term carry-over effect). The EEG parameters that were analysed post-hoc included full spectrum PSD, coherence and dominant EEG frequency.

4.3.3. Experimental Procedure

Each daily training session lasted approximately 45 min and was split into three steps: (i) two min EEG recordings in both eyes open (EO) and eyes closed (EC) relaxed state (Pre NF) (ii) two, 3 min long sub-sessions of EC audio feedback followed by six or seven 5 min long sub-sessions of EO visual feedback, and (iii) two min EEG recordings in EO and EC relaxed state (Post NF). The purpose of EC training on every training day was to provide relaxation [169] before starting NF sessions for the treatment of CNP.

4.3.4. Experimental Paradigm

The experimental paradigm for a whole NF study is shown in Figure 4.2. There were four different experimental paradigms: (i) actual NF training, (ii) placebo test, (iii) mental Task, and (iv) practising NF strategy without feedback.

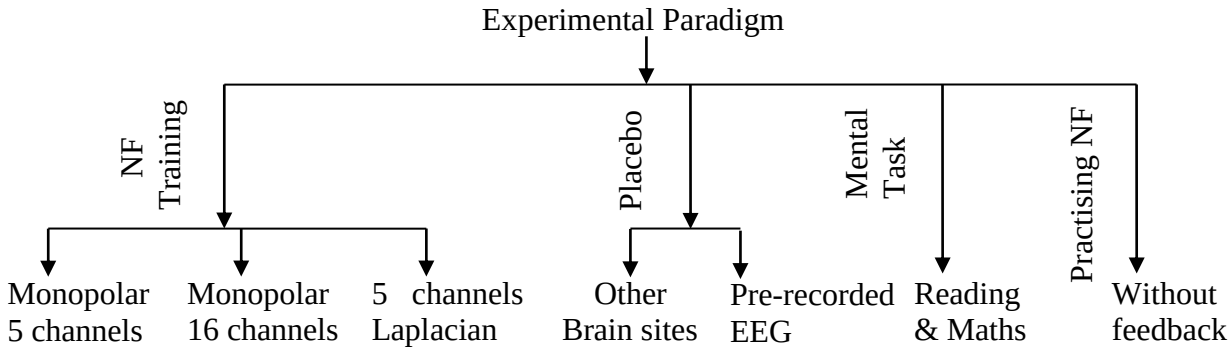


Figure 4.2: Experimental Paradigm for NF training

i. NF Training

There were three different experimental setups that were used to provide NF training. These setups are based on different numbers of EEG recording electrodes (five and sixteen channels) and different referencing montage (monopolar and Laplacian). These include: (i) monopolar five channels, (ii) monopolar sixteen channels, and (iii) laplacian five channels.

Five EEG Channels Setup: The five channel EEG setup was tested on each day of training. The commonly used locations were over the primary motor cortex (C3, Cz and C4), visual cortex (Oz), and over the area of sensory cortex (P4 or CP4).

Sixteen EEG Channels Setup: We have chosen location of the following 16 EEG channels: F3, Fz, F4, C7, C3, Cz, C4, C8, CP3, CP4, P3, Pz, P4, O1, Oz, and O2) to cover most of the cortex. In this way it was possible to assess the global effect of NF training on the other areas of the surface cortex. Scalp maps PSD and coherence between each electrode pair were measured. The sixteen EEG channels used for recording are shown in Figure 4.3.

Laplacian Derivation: To test whether patients modulated the widespread or local EEG sources, we provided a feedback from laplacian derivation. The laplacian for C4 site was calculated from four channels (C2, C6, CP4, and FC4) using Eq **(4.1**). In studies which analyse motor control for the purpose of BCI, this derivation is often used to extract local 'mu' rhythm and to separate it from the wide-spread alpha rhythm which can be present at the same frequency range and at the same location as the mu rhythm [106,107].

$$C4_{Lap} = C4 - \frac{C2 + C6 + CP4 + FC4}{4} \quad \textbf{(4.1)}$$

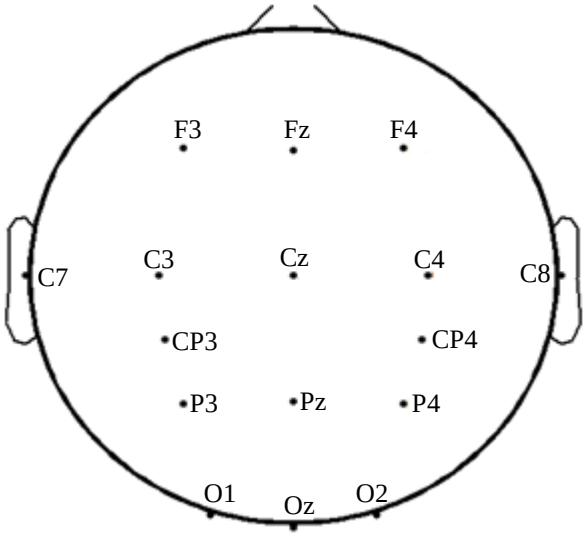


Figure 4.3: Electrode locations for sixteen channels experimental setup

ii. Testing for a Placebo Effect of NF Training

In this study, two different tests for a placebo effect were applied: (i) feedback from a pre-recorded EEG, and (ii) feedback from a cortical area which is not a part of the pain matrix.

A single-blinded placebo which was administered by showing pre-recorded PSD as a feedback was used to confirm whether modulation of EEG PSD during NF was an effect of NF training. This feedback placebo was tested only on PWP5 on the last day of training.

The occipital region is not a part of the pain matrix. Therefore, we chose the occipital region for providing a NF in EO state to test whether reduction of pain was a consequence of a particular NF protocol. The modulation of occipital 7-10 Hz activity with EC that was

a part of everyday training for the purpose of relaxation was also used to test whether reduction of pain was consequence of a particular NF protocol.

iii. Mental Tasks

A reduction of the alpha power during an active mental task (reading and mental arithmetic) is a well-documented phenomena [416,417] . The effect of these tasks should be opposite to the effect of the NF protocol on the alpha rhythm. Therefore, the purpose of comparing modulation of EEG PSD during NF with EEG PSD during mental tasks (reading and mathematics) was to confirm whether changes in EEG were a consequence of a particular NF protocol or is caused simply by a distraction. In the mental arithmetic task, patients were asked to subtract seven starting from 100 until reaching a minimum number greater than zero. This task usually took one to two min. In the reading task, patients read an article of their interest from a magazine for three min. Patients were tested for mental task on the following dates (PWP1: date36, PWP2: date25, PWP3: date09, PWP4: date09, PWP5: date16).

iv. Mental NF Practise

One of the purposes of long term NF training was to enable patients to learn the strategy to modulate their EEG activity in a direction that reduces pain without using feedback information (no GUI). Patients' EEG was recorded during mental practise (without feedback) and was compared with their EEG during actual NF to test whether patients modulated the PSD in same direction in both conditions.

4.3.5. Creating NF Protocols

i. Electrode Positions and Frequency Bands for EC Training

For a successful NF therapy it is necessary that trainees are relaxed. To assure that patients were relaxed before starting NF treatment of pain, at the beginning of each daily training session, patients received audio feedback training. The occipital alpha is an indicator of a relaxed state [109]. Therefore, reward 7-10 Hz frequency band over the occipital region was chosen to achieve relaxation.

ii. Electrode Positions and Frequency Bands for EO Training

There is no widely accepted recommendation for selecting a brain site and a frequency band for pain management, therefore, consistent with other studies [367,368] tailored protocols were tested. Four different protocols were tested based on results of Chapter 3 and past neuroimaging studies defining the cortical areas involved in pain, past neurostimulation (tDCS and TMS) studies, NF studies on pain management, and correspondence with Mark P Jensen (Department of Rehabilitation medicine, University of Washington) [418], who was running a study on treatment of chronic pain in SCI patients [142,419]. However, the reason for each frequency band and electrode location is discussed in detail in discussion (section 4.5 under heading 'Design of NF Protocols'). Four frequency bands were considered, that corresponded to parts of the standard EEG rhythms: theta (4-8 Hz), alpha (9-12 Hz), SMR (12-15 Hz) and beta (20-30 Hz). The four different protocols are listed below:

Protocol 1: Reward SMR, inhibit theta and inhibit beta from the Cz site.

Protocol 2: Reward alpha, inhibit theta and inhibit beta from the CP4/ P4 site.

Protocol 3: Reward alpha, inhibit theta and inhibit beta from the C3 site.

Protocol 4: Reward alpha, inhibit theta and inhibit beta from the C4 site.

Figure 4.4 shows total number of training days and sequence of training with each protocol. It can be noticed that apart from PWP1, other patients received feedback with Protocol 4 for most of training days. PWP1 received feedback with Protocol 1 for first 28 days followed by feedback with Protocol 4 for last 12 training days. However, Protocol 3 was also tested within session with Protocol 4 for two training days (Day 37 and Day 38). PWP2 initially received feedback with Protocol 1 for first 4 training days than practised to modulate the EEG with Protocol 3 for next three days (Day 5 to Day 7). Also, Protocol 4 was used within session for three training days (Day3 to Day5). Following this, Protocol 4 was used for most training days. However, Protocol 3 was again tested for two training days (Day 13 and Day 36) and within session with Protocol 4 for four training days. Protocol 2 was tested only in two training days (Day 24 and Day 25). In total, feedback with Protocol 4 was provided for 31 training days. PWP3 was initially tested with all four protocols for first 11 training days (Day 1 to Day 11); 2 to 4 training days with each protocol. Following 11 days, Protocol 4 was used to provide feedback for most training days and Protocol 3 was tested again for two training days (Day 26 and Day 35). Protocol 2 was tested again within sessions with Protocol 4 for four training days (Day 17 to Day 20). In total, Protocol 4 was used for 31 training days. Similar to PWP3, PWP4 was also tested with all four protocols for first 13 days. For the remaining training days, Protocol 3 was used for five days and Protocol 2 was used for a single day. Altogether, PWP4 received feedback with Protocol 4 for 31 training days. In PWP5, feedback with Protocol 4 was provided for 14 training days out of 20 days and other protocols were used for remaining training days.

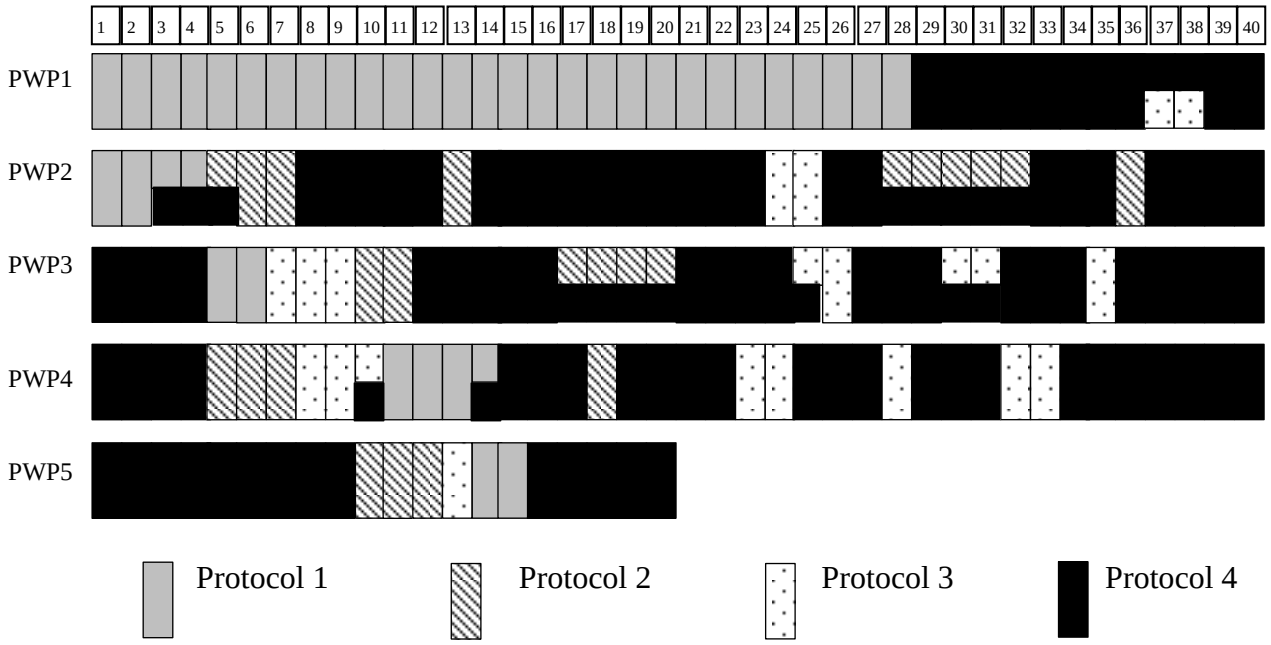


Figure 4.4: The number of sessions and sequence of training with each protocol.

iii. Choosing a Feedback Parameter and Threshold Value

As previously mentioned, a relative PSD was chosen as a feedback parameter [121,131]. It is shown in Eqs (4.2) and (4.3) that the training threshold for NF was set 10% above the mean baseline PSD value for the reward bands, while 10% below the mean baseline PSD value for the inhibit bands [121]. The threshold value was calculated for every NF training day due to the natural variation in the baseline EEG. Attempts were made to perform all NF training sessions at the same time of day, with patients were instructed not to have food or tea/coffee 1-2 hours prior to training.

$$P'_{dom} = P_d \times 1.1 \quad \textbf{(4.2)}$$

$$P'_{inhibit} = P_i \times 0.9 \quad \textbf{(4.3)}$$

Where,

P_d and P_i are mean PSD value for dominant and inhibit bands respectively

P'_{dom} and $P'_{inhibit}$ are threshold values for dominant and inhibit bands respectively

4.3.6. Design of NF system and GUI

A biosignal amplifier (usbamp, Guger technologies Austria), Simulink/MATLAB 2009 (USA), and Labview 9 (USA) were used for NF training. A real-time communication between Simulink and Labview was achieved by using 'Simulation interface toolkit' (V 5.0).

EEG was processed in Simulink using purpose made software package g.RTanalyzer (Guger technologies, Austria). The EEG feedback parameter (relative PSD) for EO visual training were displayed in Labview GUI.

EEG was recorded with 256 Hz sampling rate using a fifth order finite impulse response (moving average) filter. A notch filtered at 50 Hz was applied to remove the artefact coming for the mains. Filtering was provided within the device. The power and relative power was calculated for each recorded channel in five frequency bands (theta, alpha, SMR, beta and 2-30 Hz) with respect to 2-30 Hz band. The initial delay was 19.5ms (model order/ sampling frequency; 5/256) but later-on sliding window of 128 samples (0.5 s) was updated (shifted) for every sample. For EC training system, the same NF system was used but the relative power was calculated only for 7-10 Hz.

i. NF Task for Audio (EC) NF training

For EC training, the intensity of instrumental music during NF was inversely proportional to the relative power of the occipital alpha. The volume of the music was lower when

patients' alpha power was above the threshold value and increased when patients' alpha was below the threshold value. Patients were instructed to relax to increase the occipital alpha and to decrease the volume of music.

ii. GUI and NF Task for Visual (EO) NF Training

Figure 4.5 shows the GUI used to provide visual NF. There were two screens, one for that provided feedback to the trainee (right screen) and the other that allowed the operator to set the feedback parameters i.e. thresholds and electrode site (left screen).

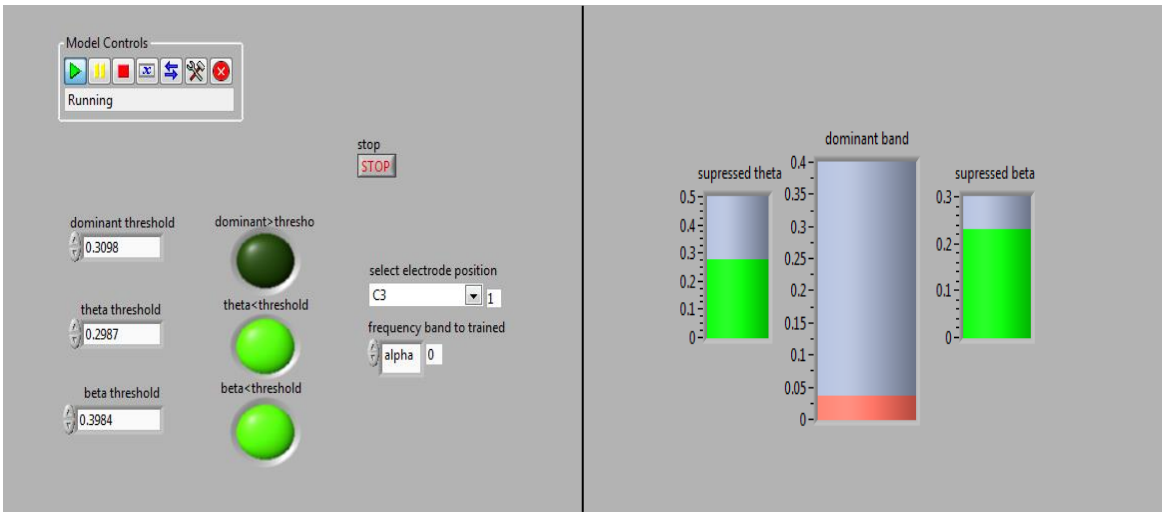


Figure 4.5: Graphical User Interface for EEG real-time feedback. The left side window is for the operator and the right side window is for a patient.

Four different protocols were tested (section 4.3.5) in which electrode locations and dominant bands (either alpha or SMR) were varied but inhibit bands (theta and beta) were the same in all protocols. Therefore, on the left screen the operator was asked to insert '*electrode position*' and '*frequency band to train*'. Furthermore, the threshold value for dominant and inhibit bands was inserted into the boxes 'dominant threshold', 'theta threshold' and 'beta threshold' on the left screen. The LEDs were green only when

threshold conditions were satisfied. On the right screen, there were three bars; two lateral bars representing inhibit bands (left bar: theta, right bar: beta) and one central bar representing the reward band (centre: alpha or SMR). The height of the bar represents the total relative PSD, and colour (either red or green) represents the status of a trainee's PSD with respect to the threshold value. The colour of the bars was green when the threshold condition was satisfied and red when the threshold condition was not satisfied. Therefore, patients were informed that in order to achieve successful training (all three bars green) the level of the dominant band bar should be increased, whereas the level of the inhibit bands bars should be decreased. There was no special instruction provided as to how to make bars green, however, patients were suggested to relax as increased concentration would decrease the alpha and increase the beta power [109]. The patients were always presented with the same GUI irrespective of the experimental paradigm and training protocol.

4.3.7. Data Processing

i. PSD Processing for a Single Training Session

The PSD was calculated using the Welch modified periodogram method (4 s epochs, 50% overlapping). For statistical analysis to compare between PSD of different conditions (Pre NF vs during NF, Post NF vs during NF), the following procedure is applied: the whole EEG recording of the chosen condition was divided into 4 s long epochs and a full spectrum PSD was calculated for each epoch separately. For each 1 Hz of the full spectrum PSD, a parametric unpaired t-test was applied between two different conditions to find statistically significant differences over the whole frequency spectrum. A $p<0.05$ was regarded as statistically significant.

For a particular frequency band, the PSD was averaged over that frequency band then a parametric unpaired ttest was applied between two different conditions to find statistically significant differences.

ii. Baseline Pain Intensity and EEG Parameters Processing

The linear regression analysis was performed to estimate the trend of change in baseline values for pain intensity and EEG parameters over all training days in Pre NF state only. The EEG parameters include PSD and dominant frequency at Cz, C3 and C4 sites.

iii. Analysis of Pain Intensity During NF Training Over all Training Days

For each patient, self-reported pain intensity was averaged during each sub-session of NF for each training day. A non-parametric Wilcoxon paired two tailed test was applied to find a statistically significant change in pain intensity between two conditions (Pre NF versus during NF) over all training days. Following this, the pain intensity over all training days was averaged separately for both Pre NF and during NF states.

iv. Relative PSD Processing

The relative change of PSD represents change in EEG PSD during NF compared to EEG PSD in Pre NF state. For each patient, PSD was averaged during each sub-session of NF for each training day. Following this, a relative change in PSD was calculated using Eq (4.4) for each training day. This relative change in PSD was calculated for all three frequency bands (inhibit theta, reward alpha, and inhibit beta). A Wilcoxon paired two tailed non-parametric test was applied to find a statistically significant change in PSD during NF compared to PSD in Pre NF state. Therelative change in PSD was averaged in two ways: (i) over consecutive ten days, and (ii) over all training days. Averaging ten days

means average from Day1 to Day10, Day11 to Day20 Day21 to Day30 and Day31 to Day40.

$$\Delta PSD_i = \frac{PSD_{NF_i} - PSD_{Pre_i}}{PSD_{Pre_i}} \times 100 \quad \textbf{(4.4)}$$

Where,

i= 1, 2, 3… n (n= total number of training days)

ΔPSD_i= Percentage change in PSD for i^{th} training day

PSD_{NF_i}= Average PSD during all sub-sessions of NF training for i^{th} training day

PSD_{Pre_i}= PSD in Pre NF training for i^{th} training day

v. Dominant Frequency Processing During NF Over All Training Days

The dominant frequency was analysed in 7-13 Hz. The reason for selecting 7-13 Hz came from EEG studies showing shift of dominant peak frequency towards low frequencies in patients with pain [46,257–259,262]. The change in dominant frequency over all training days was processed in a similar way to the change in pain intensity over all training days (section 4.3.7, Part iii).

vi. Processing of a Total Time Patients Followed Training Rules

The progressive learning of patients with NF training was also assessed by calculating total time (percentage) each patient followed the training rules. In this study, a post-hoc analysis was performed to find total time patients followed training rules. Analysis was performed, similar to relative change in PSD (section 4.3.7, Part iv), for all three frequency bands of EEG over all training days. The higher the value of time percentage means more time a person achieved threshold condition.

vii. PSD and Coherence Processing for a Sixteen Channels Experimental Setup

In a sixteen channel setup, PSD at training site during NF is first calculated for five time periods of two min length overlapping for one min rather than whole five min training period to choose the period in which each patient best followed the NF training protocols. The reason for choosing an optimum period was to provide a representative EEG for analysis of PSD spectral scalp maps.

For coherence analysis, a representative two min period EEG was further split into four s long epochs. Following this, coherence among each electrode pairs (16*16) was calculated using Welch's method (0.5 s hamming window, 50% overlapping) both in Pre NF and during NF states. A parametric unpaired ttest was applied over each four s epoch to find significant change in coherence during NF compared to Pre NF for theta, alpha and beta frequency bands. Also, Holms-Bonnifernoi correction was applied to reduce Type II error dues to multiple comparisons. Following this, a difference of coherence (NF-Pre) over all epochs was calculated for electrode pairs showing significant change ($p<0.05$).

4.4. Results

First, the influence of each single protocol (Protocol 1 to Protocol 4) on the full PSD spectrum and the intensity of pain is shown for a single representative day. Following this, the longitudinal effect of Protocol 4, used on majority of training days, is demonstrated on: (a) Pain intensity, (b) PSD over the training site (C4) and adjacent central sites (Cz and C3), (c) dominant alpha frequency, and (d) post-hoc analysis of the time-percentage during which NF training rules were followed. Finally, the following phenomena were analysed: (a) the global effect of NF training on other sites, (b) the effect of placebo training, (c) the

effect of NF modulation of local versus wide-spread sources, and (d) the effect of mental practise effect without feedback on pain and full spectrum PSD.

4.4.1. Immediate and Short-term Effects of Each Protocol

The *immediate* and *short-term effect* represents the effect of NF training on full spectrum PSD and on self-reported pain intensity during NF (*immediate*) and two to four min Post NF (*short-term*) for a representative training day.

The full PSD spectrum for a single training day was analysed: (i) to find the most effective training protocol for reducing pain by modulating a PSD, and (ii) to assess the effect of NF training in one frequency band on the rest of the PSD spectrum.

Protocol 1: Reward SMR, and Inhibit Theta and Beta from Cz Site: This protocol was practised by each patient. Four patients (PWP1, PWP2, PWP3 and PWP5) did not show short-term change in PSD in the desired direction in any training frequency band. Patient PWP4 was able to modulate the PSD in the desired direction but did not report a reduction in pain.

Figure 4.6 shows the 'immediate' and 'short-term' effects of Protocol 1 on PSD of PWP4 on fourth training day. A statistically significant immediate increase in PSD in the reward SMR and inhibit beta bands is noticed, while the short-term increase of PSD is not noticed in either band. In the inhibit theta band, only a short-term statistically significant decrease in PSD is noticed.

The effect of increase in SMR band PSD during NF is widespread to higher beta range, up to 22 Hz, though PSD returns back to the baseline beyond the training (Post NF).

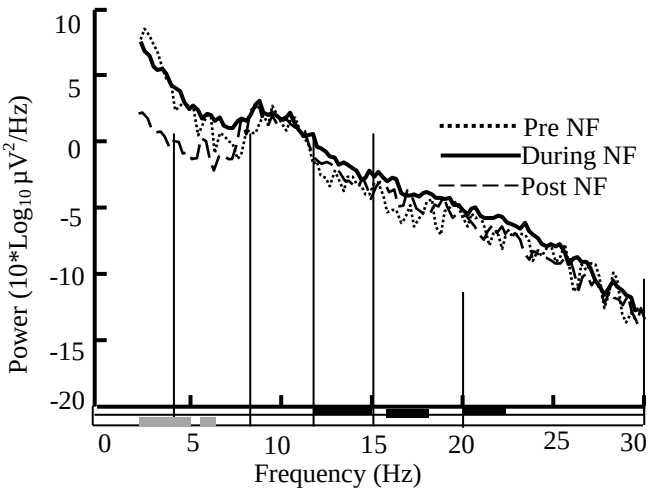


Figure 4.6: 'Immediate' and 'Short-term' effect of Protocol 1 on PSD of PWP4 at Cz site. Pre NF (dotted line), during NF (solid line) and Post NF (dashed line). The immediate significant change is shown with thick black line and short-term significant change is shown with thick grey line above x-axis.

Protocol 2: Reward Alpha, and Inhibit Theta and Beta from CP4/ P4 Sites: Four of five patients, except PWP1, practised Protocol 2. Two patients (PWP3 and PWP4) failed to modulate PSD while two patients (PWP2 and PWP5) modulated the PSD in the desired direction and reported a reduction in pain (PWP2: 6 to 5, PWP5; 8 to 7 on VAS). The modulation of PSD by PWP2 was not significant while PWP5 showed significant change in PSD in the desired direction.

Figure 4.7 shows 'immediate' and 'short-term' effects of Protocol 2 on PSD of PWP5 on the eighth training day. A statistically significant immediate and short-term increase in PSD is noticed in the reward alpha band, while this significant increase in PSD in the inhibit beta band is noticed in short-term only. In the inhibit theta band, a statistically significant decrease in PSD is noticed both in immediate and short-term.

In Post NF state, a statistically significant increase of PSD can be noticed in smaller frequency bands over delta, alpha, and beta bands.

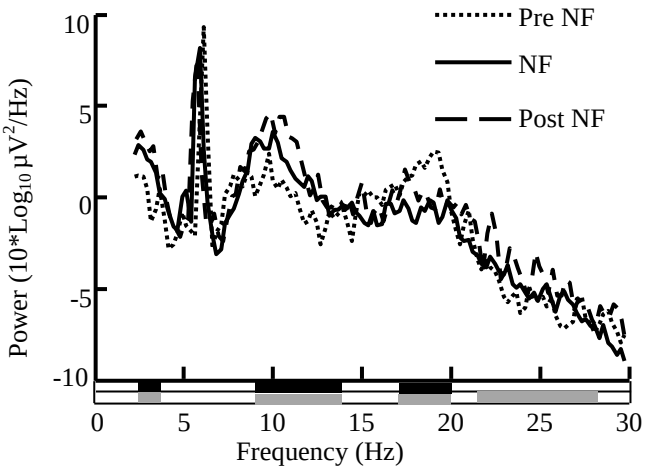


Figure 4.7: 'Immediate' and 'Short-term' effect of Protocol 2 on PSD of PWP5 at P4 site. Pre NF (dotted line), during NF (solid line) and Post NF (dashed line). The immediate significant change is shown with a black thick line and short-term significant change is shown with gray thick line above the x-axis.

Protocol 3: Reward Alpha, and Inhibit Theta and Inhibit Beta from C3 Site: Each patient practised Protocol 3 to modulate PSD in order to control pain. Two patients (PWP1 and PWP2) failed to modulate PSD in the desired direction in any frequency band. Although three patients modulated the PSD and reported a reduction in pain, the increased spasms did not allow patients to continue training with this protocol.

Figure 4.8 shows 'immediate' and 'short-term' effects of Protocol 3 on PSD of PWP5 on 12^{th} training day. A statistically significant increase in PSD is noticed in the inhibit theta and reward alpha frequency bands both in immediate and short-term, while statistically significant decrease in PSD is found in the inhibit beta frequency band. The increase in PSD can also be noticed in 2-9 Hz both in Post NF and during NF states.

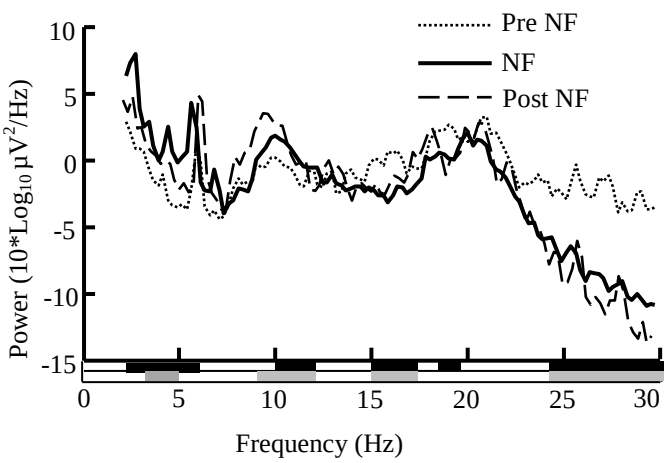


Figure 4.8: 'Immediate' and 'Short-term' effect of Protocol 3 on PSD of PWP5 at C3 site. Pre NF (dotted line), during NF (solid line) and Post NF (dashed line). The immediate significant change is shown with a black thick line and short-term significant change is shown with gray thick line above the x-axis.

Protocol 4: Reward alpha, and inhibit theta and beta from C4 site: Each patient practised this protocol to modulate the PSD in order to control pain. The reduction of pain was accompanied by a pleasant warm sensation over the body parts that were previously perceived as being painful. As each patient reported reduction of pain with this protocol, this protocol was used to provide feedback for the majority of training days. The PWP1 first received training with this protocol after 25 training sessions because of testing with different protocols (Protocol 1 to Protocol 3) in the early stages of training. Three (PWP2, PWP3 and PWP4) out of five patients reported both immediate and delayed reduction of pain. PWP1 reported only immediate reduction of pain while PWP5 reported delayed reduction of pain. Figure 4.9 shows 'immediate' and 'short-term' effects of Protocol 4 on PSD of each patient (PWP1: date28, PWP2: date30, PWP3: date27, PWP4: date10, PWP5: date18).

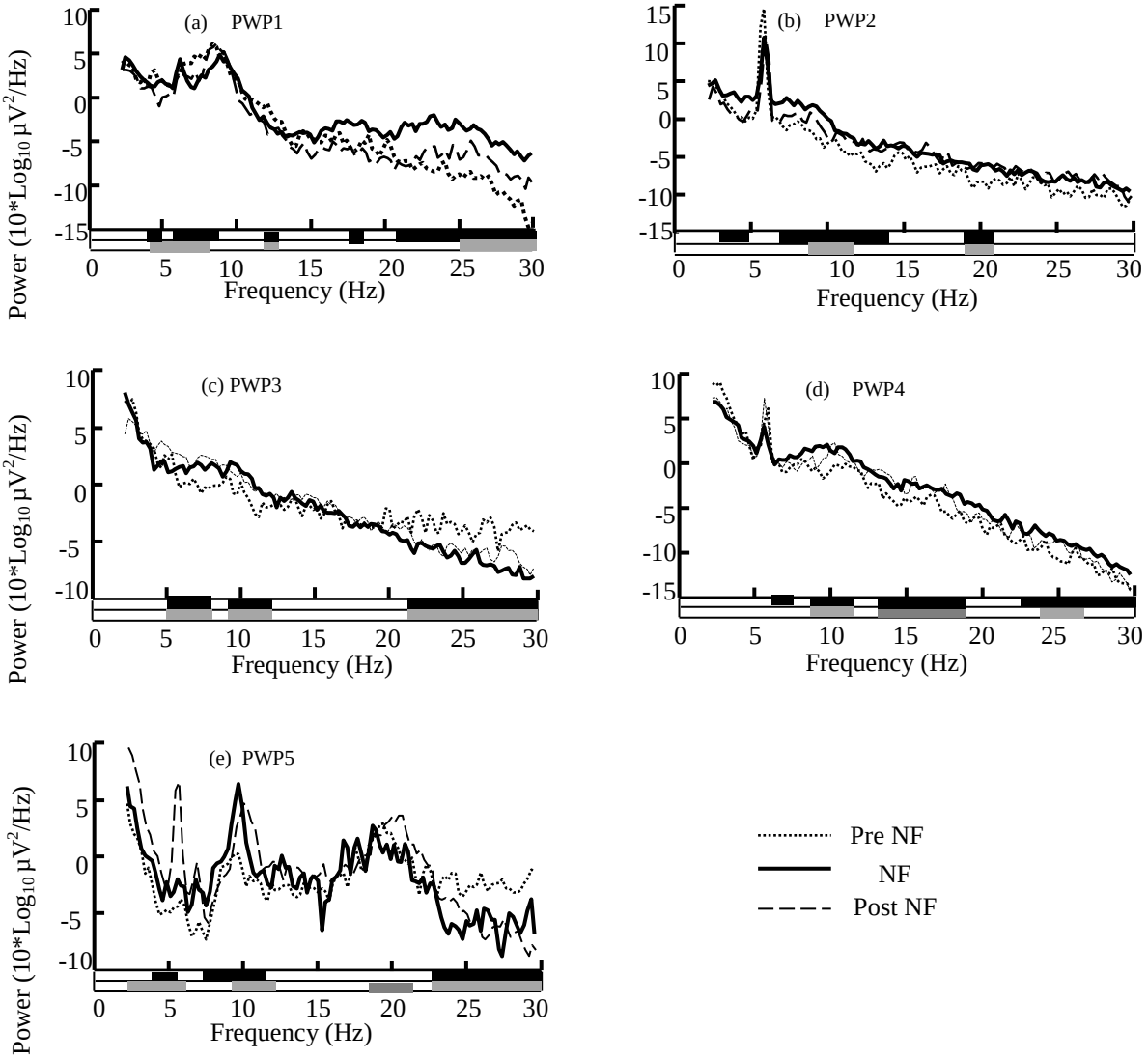


Figure 4.9: 'Immediate' and 'Short-term' effect of Protocol 4 feedback on PSD at C4 site of each patient (PWP1: 'subfigure (a); PWP2: 'subfigure (b); PWP3: 'subfigure (c); PWP4: 'subfigure (d); PWP5: 'subfigure (d)). Pre NF (dotted line), during NF (solid line) and Post NF (dashed line). The immediate significant change is shown with black thick line and short-term significant change is shown with grey thick line above the x-axis.

In the inhibit theta band, a statistically significant increase of PSD both in immediate and in short-term is noticed in two patients (PWP3 and PWP5) and only an immediate increase of PSD is noticed in two patients (PWP2 and PWP4), while both immediate and short-term decrease of PSD is noticed in PWP1 only.

In the reward alpha band, a statistically significant increase of PSD is noticed in four patients (except PWP1) both in immediate and short-term, while no change of PSD is noticed in PWP1.

In the inhibit beta band, both immediate and short-term change of PSD is noticed in each patient. Three patients (PWP1, PWP2 and PWP4) showed statistically significant increase of PSD, while two patients (PWP3 and PWP5) showed statistically significant decrease of PSD.

In conclusion, PWP1 followed rule in the inhibit theta band only, PWP2 and PWP4 followed rule in the reward alpha band only, and PWP3 and PWP5 followed rule in the reward alpha and inhibit beta bands.

The effect of modulating PSD in a single frequency band over other frequency bands was patient specific. In three patients (PWP1, PWP3, PWP5) the spreading effect of increased/ decreased PSD in the alpha band was noticed over 2 to15 Hz band, while other two patients showed global increase (over all frequencies) in PSD. Furthermore, the change in PSD during NF was sustained beyond the training (Post NF).

In addition to reduction of pain with Protocol 4; patients with incomplete injury often reported being spasm-free for the rest of the training day. A single patient (PWP3) reported improved dorsi-flexion of the foot, spasm-free while stretching a body at bed time, and a

pleasant warm sensation that lasted for some hours after training. Some patients had a complete SCI and could not possibly feel real changes in temperature, therefore this sensation was most likely been generated in the brain. As these results were mostly subjective, they were not investigated in a systematic way.

4.4.2. Effect of Training on Pain intensity

The effect of training with Protocol 4 on pain intensity is presented as: (i) change in baseline pain intensity, and (ii) cumulative change in pain intensity over all training days.

i. Change in Baseline Pain Intensity

Table 4.2 shows the clinical change in pain intensity and a linear trend in baseline pain intensity (slope, r and p values) for each patient when Protocol 4 was used for NF training. Each patient, except PWP1, shows clinically significant reduction (> 30%) in pain. Furthermore, the significant negative slope (from regression analysis) supports the observation that the baseline pain intensity is significantly reduced over the period of training.

Table 4.2: Pain Intensity and trend in baseline pain intensity. The significant reduction in pain is shown in bold with italic.

	Clinical Change in Pain intensity			Trend in baseline Pain Intensity		
Code	First Day	Last Day	Percentage Change in pain	Slope Direction	r-value	p-value
PWP1	6	4/5	-25	-	0.74	***0.023***
PWP2	7	5	***-30***	-	0.66	***2.5e-5***
PWP3	6	2	***-67***	-	0.61	***0.001***
PWP4	9/10	5/6	***-55***	-	0.83	***6.85e-8***
PWP5	9	5	***-40***	-	0.64	***0.005***

ii. Change in Pain Intensity Averaged over all Training days

Table 4.3 shows the value for pain intensity in Pre NF and during NF states averaged over all training days. The significant value is set to $p<0.05$. Each patient shows statistically significant reduction in pain intensity.

Table 4.3: Cumulative Change in Pain Intensity. A significant change is shown in bold with italic. A non-parametric Wilcoxon paired test was applied.

	Pre NF Mean ± SD	NF Mean ± SD	p-value
PWP1	5.3±1.2	4.3±1.1	***0.05***
PWP2	6±0.83	5±1.3	***0.0004***
PWP3	5±1.6	2.4±2.8	***0.0001***
PWP4	6.4±1.1	5.4±1	***0.0002***
PWP5	7.9±0.7	7±1.6	***0.006***

4.4.3. Effect of Training on PSD Modulation

The effect of training on PSD at training site (C4), contralateral (C3) and adjacent sites (Cz) to the training site is presented in two ways: (i) relative change in PSD over ten consecutive days and over all training days, and (ii) change in baseline PSD on each day before NF training.

i. Relative Change in PSD

Averaging Over Ten Training Days: The relative change in PSD averaged over ten consecutive days for each patient in three frequency bands is shown in Figure 4.10. The positive bars represent increased PSD and negative bars showed decrease PSD during NF compared to Pre NF.

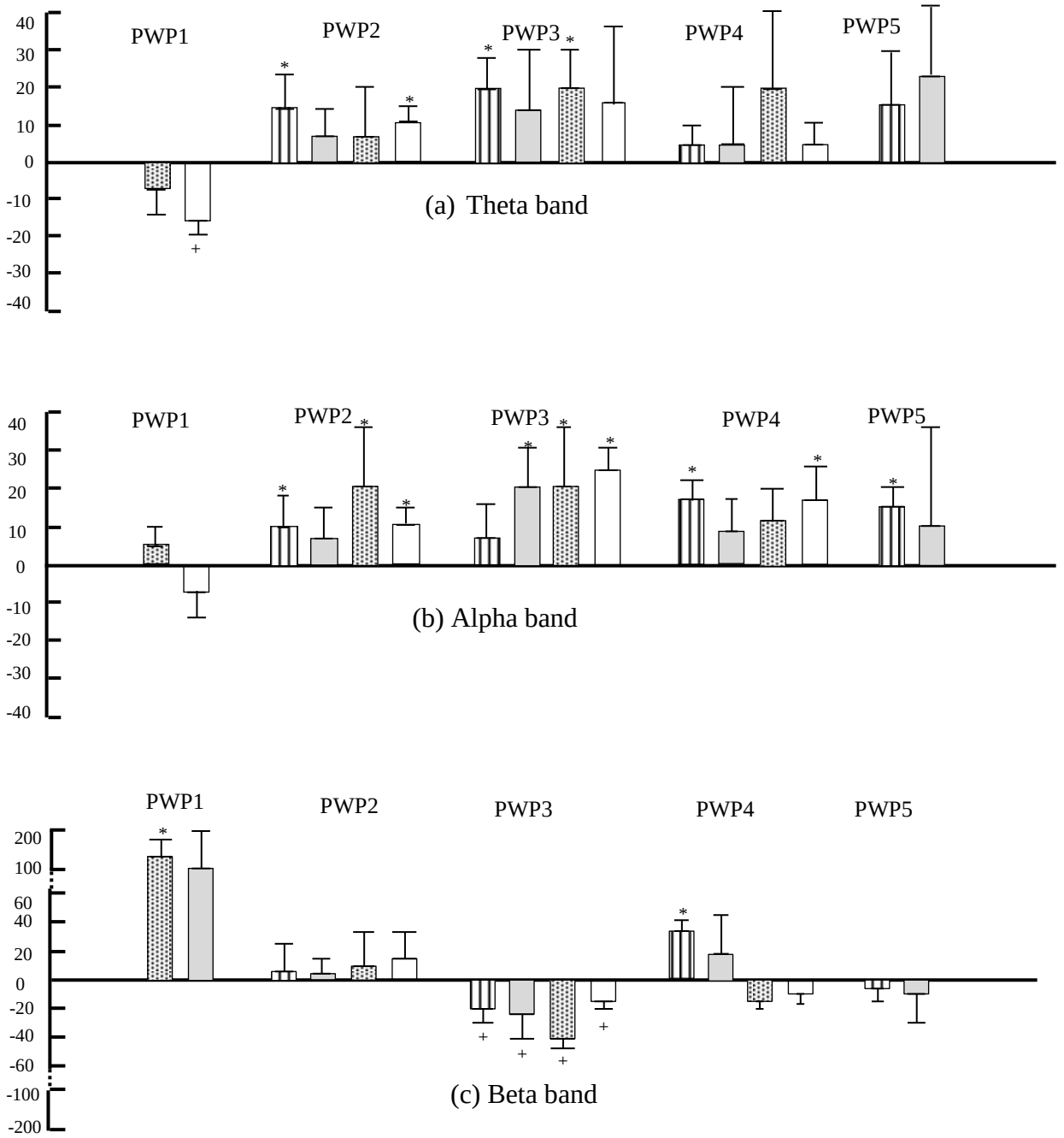


Figure 4.10: Relative change in PSD at C4 site over ten days (day1-day10; vertical lines bar, day11-day20; filled grey bars, 21-30; dotted bars, day 31-day40; white bars) in: (a) theta band, (b) alpha band, and (c) beta band for each patient. The Protocol 4 was used for training. Significant increase in PSD is shown with *, while significant decrease in PSD is shown with +. The results for PWP1 for first twenty training days are not shown because this PWP1 received training with Protocol 4 for last 15 training days. PWP5 received twenty training sessions only.

In the theta band (subfigure ‘a’), only PWP1 showed decrease in PSD, while other patients showed increase in PSD over all training days. This decrease in PSD is significant only for last training days, while the increase in PSD is significant in two patients (PWP2 and PWP3) for 50 % training days.

In the alpha band (subfigure ‘b’), only PWP1 showed decrease in PSD, while other patients showed increase in PSD over all training days. This increased alpha PSD is significant for 75% days in PWP2 and PWP3 (last thirty days) and for only 50% of days in PWP4 (first ten and last ten days) and PWP5 (first ten days).

In the beta band (subfigure ‘c’), two patients (PWP1 and PWP2) showed increase in PSD, while two patients (PWP3 and PWP5) showed decrease in PSD. PWP4 showed increased PSD for first 50% of training days, while decrease in PSD for last 50% of training days. The increase in PSD is significant in PWP1 and PWP4 for first ten training days, while decrease in PSD is significant in PWP3 for all training days.

Averaging PSD over all training days: The relative change in PSD over all training days is shown for Cz, C3, and C4 sites in theta, alpha, and beta frequency bands.

Table 4.4 shows the effect of training on a relative change in PSD (during NF - Pre NF) at C4 site in three frequency bands averaged over all training days. The positive numbers shows increase in PSD during NF, while negative numbers shows a decrease in PSD. In the theta band, three patients (PWP2, PWP3 and PWP4) show a statistically significant increase in PSD, while only PWP1 shows a significant decrease in PSD. In the alpha band, three patients (PWP2, PWP3 and PWP4) show a statistically significant increase in PSD. In the beta band, two patients (PWP1 and PWP2) show a statistically significant increase

in PSD, while PWP3 shows a significant decrease in PSD. In conclusion, only PWP1 followed training rule in the theta band, two patients (PWP2 and PWP4) followed training rule in the alpha band, and PWP3 followed training rule in the alpha and beta bands. PWP5 non-significantly followed training rule in the alpha and beta bands.

Table 4.4: Relative change in PSD at training site (C4) in three frequency bands. A significant decrease in PSD is shown in bold and italic, while significant increase in PSD direction is shown in bold only. A Wilcoxon paired two tailed non-parametric test was applied.

Code	theta		alpha		beta	
	Change in PSD (%) Mean ± SD	P-value	Change in PSD (%) Mean ± SD	P-value	Change in PSD (%) Mean ± SD	P-value
PWP1	-9.3±4.9	***0.02***	-9±12.8	0.16	116±82	**0.02**
PWP2	9±9.8	**0.9e-4**	9.4±15	**0.4e-4**	6.5±16.6	**0.05**
PWP3	22±19	**0.4e-3**	12±13	**0.8e-3**	-27±19	***0.1e-3***
PWP4	6.8±11	**0.01**	10±17	**0.03**	17.6±34	0.06
PWP5	18.6±33.6	0.07	12.5±21.5	0.08	-9.5±19	0.5

Table 4.5 shows the relative change in PSD (during NF - Pre NF) at C3 site in three frequency bands averaged over all training days. The results for PWP1 at C3 are not presented because C3 location was measured for three training days only. A significant decrease in PSD is shown by a single patient (PWP4) in the theta band and a single patient (PWP3) in the beta band, while a significant increase in PSD in the alpha band can be seen in three patients (PWP2, PWP3 and PWP4). PWP5 shows a non-significant change in PSD in all three frequency bands.

Table 4.5: Relative change in PSD at C3 site in three frequency bands. A significant decrease in PSD is shown in bold and italic while significant increase in PSD shown in bold only (Wilcoxon paired two tailed non-parametric test).

	theta		alpha		beta	
Code	Change in PSD (%) Mean ± SD	P-value	Change in PSD (%) Mean ± SD	P-value	Change in PSD (%) Mean ± SD	P-value
PWP1	NA	NA	NA	NA	NA	NA
PWP2	-18±19.8	0.09	79.6±60.4	**0.03**	10±16.6	0.22
PWP3	-2.3±28	0.85	116±47.7	**0.5e-3**	-28.2±21	***0.003***
PWP4	-28.8±9.5	***0.2e-3***	30.4±9.5	**0.2e-3**	1.9±18.5	0.74
PWP5	-13.9±48.4	0.11	5.6±26.9	0.62	-13.4±26.8	0.18

Table 4.6 shows the relative change in PSD (during NF - Pre NF) at Cz site averaged over all training days. A significant decrease in PSD is shown in bold and italic while significant increase in PSD shown in bold only. A significant increase in PSD is shown by two patients (PWP2 and PWP3) in the theta band and a single patient in the alpha (PWP4) and beta (PWP1) bands, while a significant decrease in PSD is observed in PWP3 in the beta band. PWP5 shows a non-significant change in PSD in all three frequency bands.

Table 4.6: Relative change in PSD at Cz site in three frequency bands. A significant decrease in PSD is shown in bold and italic while significant increase in PSD shown in bold only (Wilcoxon paired two tailed non-parametric test).

	theta		alpha		beta	
Code	Change in PSD (%) Mean ± SD	P-value	Change in PSD (%) Mean ± SD	P-value	Change in PSD (%) Mean ± SD	P-value
PWP1	-2.8±4.2	0.08	-2.7±9.2	0.7	59±44	**0.02**
PWP2	10.6±10	**0.4e-4**	0.9±12.5	0.7	7.2±16.7	0.06
PWP3	20.4±24	**0.2e-3**	6.2±13.8	0.7	-23.4±19	***0.9e-4***
PWP4	6.8±11	**0.01**	12.5±21	**0.03**	9.3±26	0.12
PWP5	25±58	0.07	-1±21	0.7	-1.7±28	0.76

ii. Change in Baseline PSD before NF Training

Table 4.7 shows slope direction, r and p values for change in baseline PSD at C4 site in Pre NF state only. A statistically significant decrease in baseline PSD is observed only in PWP1 in the theta band, while statistically increase in baseline PSD is noticed in two patients (PWP1: beta band, PWP2: alpha band). In conclusion, a statistically significant change in baseline PSD in the direction of training protocol (expected direction) is noticed in two patients (PWP1: theta decreased, PWP2: alpha increased), while a significant change in unexpected direction is noticed in PWP1 in the band only.

Table 4.8 shows slope direction, r and p values for change in baseline PSD at C3 site in Pre NF state only. Neither patient shows statistically significant change in slope direction.

Table 4.9 shows slope direction, r and p values for change in baseline PSD at Cz site in Pre NF state only. A statistically significant increase in baseline PSD is noticed in three patients (PWP1: beta, PWP2: alpha, PWP4: alpha), while significant decrease in baseline PSD is noticed in PWP1 only in the theta band.

Table 4.7: Shift in baseline PSD at C4 site**.** A statistically significant decrease in slope direction is shown in bold and italic, while a significant increase in slope direction is shown in bold only.

	theta			alpha			beta		
Code	slope	r	p	slope	r	p	slope	r	p
PWP1	**-**	0.64	***0.009***	-	0.15	0.3	**+**	0.55	**0.02**
PWP2	-	0.01	0.56	**+**	0.16	**0.02**	+	0.014	0.57
PWP3	+	0.003	0.78	**-**	0.2	0.12	-	0.14	0.27
PWP4	+	0.02	0.46	+	0.13	0.06	**+**	0.216	0.15
PWP5	+	0.06	0.36	-	0.009	0.71	-	0.083	0.26

Table 4.8: Shift in baseline PSD at C3 site.

	theta			alpha			beta		
Code	slope	r	p	slope	r	p	slope	r	p
PWP1	NA	NA	NA	NA	NA	NA	NA	NA	NA
PWP2	-	0.43	0.28	-	0.34	0.4	+	0.02	0.76
PWP3	-	0.05	0.86	-	0.27	0.3	+	0.0002	0.92
PWP4	+	0.2	0.4	+	0.06	0.28	+	0.004	0.99
PWP5	+	0.2	0.4	-	0.28	0.3	-	0.02	0.95

Table 4.9: Shift in baseline PSD at Cz site. A statistically significant decrease in slope direction is shown in bold and italic while significant increase in slope direction is shown in bold only.

	theta			alpha			beta		
Code	slope	r	p	slope	r	p	slope	r	p
PWP1	-	0.7	***0.03***	-	0.09	0.8	+	0.8	**0.01**
PWP2	-	0.13	0.5	+	0.4	**0.03**	+	0.12	0.5
PWP3	+	0.05	0.8	-	0.2	0.1	+	0.0004	0.9
PWP4	+	0.08	0.6	+	0.79	**0.009**	+	0.42	0.13
PWP5	+	0.37	0.2	-	0.5	0.07	-	0.04	0.86

4.4.4. Effect of Training on Dominant Frequency

The effect of training on dominant frequency at training site (C4), contralateral (C3) and adjacent to the training sites (Cz) is presented in three ways: (i) change in dominant frequency over all training days, (ii) immediate and short-term effect of training on dominant frequency, and (iii) changes in baseline dominant frequency on each day before NF training.

i. Change in Dominant Frequency over all Training Days

Table 4.10 shows change in dominant frequency over all training days. Only PWP5 shows significant increase in dominant frequency at C3 and C4 sites. Three patients (PWP1, PWP2 and PWP4) show non-significant increase in dominant peak frequency. PWP3 shows non-significant decrease in dominant frequency.

ii. Immediate and Short-Term Effect of Training on Dominant Frequency

Figure 4.11 shows immediate and short-term change in dominant frequency of PWP5 at training (C4) site. The figure represents PSD in three states (Pre NF, During NF and Post NF). The patient shows shift in dominant frequency towards higher frequency during NF (immediate effect) which was sustained in Post NF state (short-term effect), though not to the same level as during NF.

Table 4.10: Change in dominant frequency over all training days at Cz, C3 and C4 sites. A significant decrease in dominant frequency is shown in bold and italic, while significant increase is shown in bold only (Wilcoxon paired non-parametric test).

Code	C3			Cz			C4		
	Dominant Frequency (Hz)			Dominant Frequency (Hz)			Dominant Frequency (Hz)		
	Pre NF mean ± SD	NF mean ± SD	p-value	Pre NF mean±SD	NF mean±SD	p-value	Pre NF mean±SD	NF mean±SD	p-value
PWP1	NA	NA	NA	8.2±0.76	8.5±0.45	0.12	8.7±0.24	8.82±0.13	0.26
PWP2	7.5±0.4	7.6±0.4	0.44	7.64±0.59	7.47±0.29	0.14	7.6±0.15	7.6±0.32	0.78
PWP3	8.19±0.5	8±0.32	0.06	8±0.67	7.6±0.37	0.061	8.3±0.94	7.8±0.43	0.13
PWP4	9.64±1.08	9.63±0.54	0.71	9.24±1.12	9.4±0.5	0.21	9.57±1.14	9.83±0.44	0.13
PWP5	9.42±0.58	10±0.3	**0.0008**	9.4±0.35	9.3±0.71	0.75	9.65±0.62	10.13±0.3	**0.004**

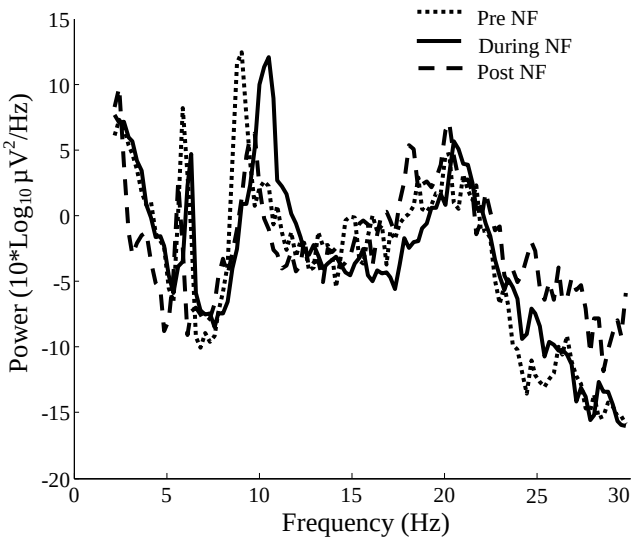


Figure 4.11: Full spectrum PSD showing change in dominant frequency in three states: Pre NF (Dashed line), During NF (solid line) and Post NF (Dotted line). This PSD spectrum is of PWP5.

iii. Change in baseline dominant frequency

Table 4.11 shows slope direction, r and p values for change in baseline dominant frequency at three sites in Pre NF state only. Each patient shows non-significant positive slope for dominant frequency calculated at C4 site.

Table 4.11: Shift in baseline dominant frequency at Cz, C3 and C4 sites.

	C3			Cz			C4		
Code	slope	r	p	slope	r	p	slope	r	p
PWP1				-	0.01	0.8	+	0.03	0.63
PWP2	+	0.01	0.84	+	0.1	0.21	+	0.001	0.97
PWP3	-	0.05	0.41	-	0.02	0.53	+	0.003	0.93
PWP4	-	0.04	0.43	+	0.11	0.86	+	0.04	0.33
PWP5	+	0.01	0.79	+	0.07	0.29	+	0.003	0.95

4.4.5. Effect of Training on Total Time Patients Achieved Threshold

Table 4.12 shows percentage of time patients followed the rule (during NF - Pre NF) over all training days. A significant increase in time-percentage can be seen for all patients except PWP5. Patients showed a significant increase in time following training rules is in the same frequency band in which PSD was significantly modulated in the desired direction.

Table 4.12: Relative change in total time (percentage) patients' followed the training rules. A significant decrease in percentage of time patients following the rules is shown in bold and italic, while significant increase is shown in bold only (Wilcoxon paired two tailed non-parametric test).

	theta		alpha		beta	
	Change in time-percentage (%) Mean ± SD	P-value	Change in time-percentage (%) Mean ± SD	P-value	Change in time-percentage (%) Mean ± SD	P-value
PWP1	10±7.8	**0.03**	-10±15.3	0.11	-44.5±23.3	***0.03***
PWP2	-9.6±15.8	***0.5e-3***	16.3±28.6	**0.3e-3**	-5.6±18.2	0.1
PWP3	-23.5±17	***0.1e-3***	4±26	0.2	45±24.5	**0.5e-4**
PWP4	-6.5±11.6	***0.01***	12.5±22.8	**0.052**	-16.6±20.6	***0.002***
PWP5	-17.3±29	0.07	12.8±26	0.2	15.1±28	0.13

4.4.6. Global Effect of Training

The global effect represents the effect of training with Protocol 4 on PSD and coherence over whole head when a sixteen channels experimental protocol was used for NF training.

i. Global Change in PSD

The PSD scalp maps in Pre NF and during NF states for each patient in three frequency bands are shown in Figure 4.12.

The global effect of training on PSD in the inhibit theta band is shown in Figure 4.12 (a). It can be noticed that apart from PWP1 and PWP3, other patients did not regulate theta band PSD in the desired direction (reduce theta) at C4 site. However, a global reduction in frontal theta PSD can be seen for all patients.

The global effect of training on PSD in the reward alpha band is shown in Figure 4.12 (b). The alpha power is increased in four out of the five patients at the C4 site but the global increase in power is noticed in all patients including PWP1 who showed reduced alpha power at training site. Furthermore, the increased alpha power is more prominent at the adjacent sites of the training site. In two patients, the maximum power is shifted to the central region from the frontal (PWP5) and parietal (PWP3) cortices.

The global effect of training on PSD in the inhibit beta band is shown in Figure 4.12 (c). The PSD in beta band at C4 site is increased in PWP1 and PWP3, while decreased in other patients. The increased beta band PSD in PWP1 is global; mainly in the frontal region which might be due to increased concentration [109]. For the other four patients, the frontal beta ipsilateral to the training site is decreased.

ii. Global Change in Coherence among Each Pair of Channels

For each patient, electrode pairs showing statistically significant difference of coherence between two states (NF-Pre NF) in three frequency bands (theta, alpha, and beta bands) are presented in Figure 4.13.

The global effect of training on coherence in the inhibit theta band is shown in Figure 4.13 (a). A statistically significant decrease in coherence is noticed in three patients (PWP3, PWP4 and PWP5), while increase in coherence is found in PWP1 only. The

decrease in coherence is global in PWP3. For PWP4, a reduced coherence is noticed between temporal and frontal region. For PWP5 reduced coherence is noticed among occipital sites. In PWP1, Pz and P3 sites show increased coherence with Fz site.

The global effect of training on coherence in the reward alpha band is shown in Figure 4.13 (b). Increased coherence is noticed between the occipital and other regions of the brain for PWP1 and PWP4. For PWP5 decreased coherence is noticed between the occipital and parietal region and increased coherence between Cz site and the frontal region of the brain.

The global effect of training on coherence in the inhibit beta band is shown in (Figure 4.13 (c)). The coherence between the central and frontal regions is increased in three patients (PWP1, PWP3 and PWP5), and decreased in other two patients (PWP2 and PWP4). The coherence among posterior region, and between posterior and frontal regions is decreased in three patients (PWP2, PWP4 and PWP5), while increased in PWP1.

In conclusion, the frontal and occipital areas showed the largest change in coherence with other regions of the brain in all frequency bands; mainly in the beta band. The direction of change in coherence was not consistent in each patient for each frequency band. Furthermore, the change in coherence was independent of change in PSD. This global change in coherence may cause reduction of pain intensity.

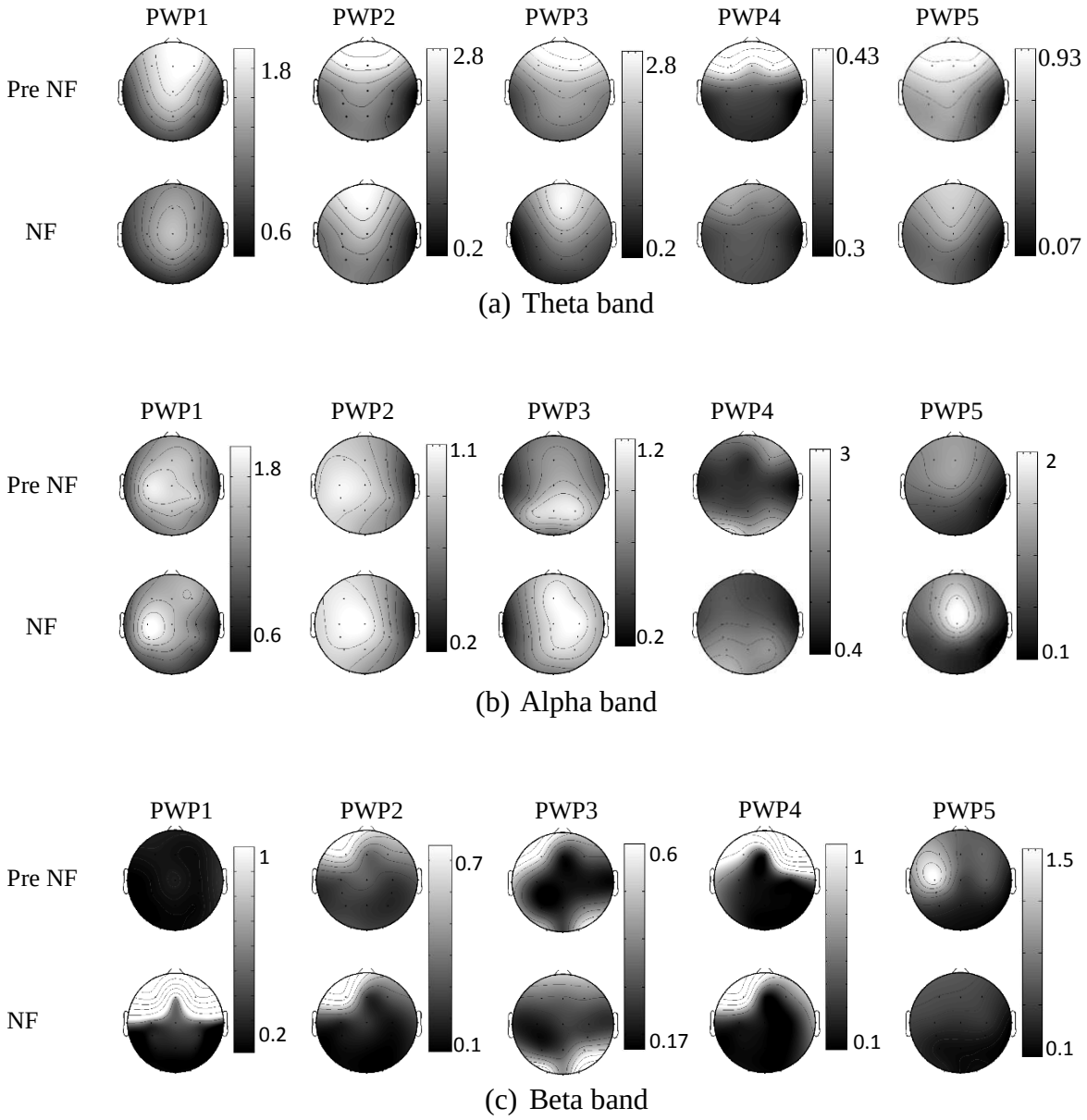


Figure 4.12: Immediate global effect of NF training on PSD (16 channels). PSD scalp maps in in three frequency bands: (a) theta, (b) alpha, and (c) beta bands. For each subfigure, first row represents PSD scalp maps in Pre NF and second row represents PSD scalp maps during NF state for each patient (PWP1; column 1, PWP2; column 2, PWP3; column 3, PWP4; column 4, PWP5; column 5). For each patient, a scale bar is shown on the right side of the scalp map for each frequency band.

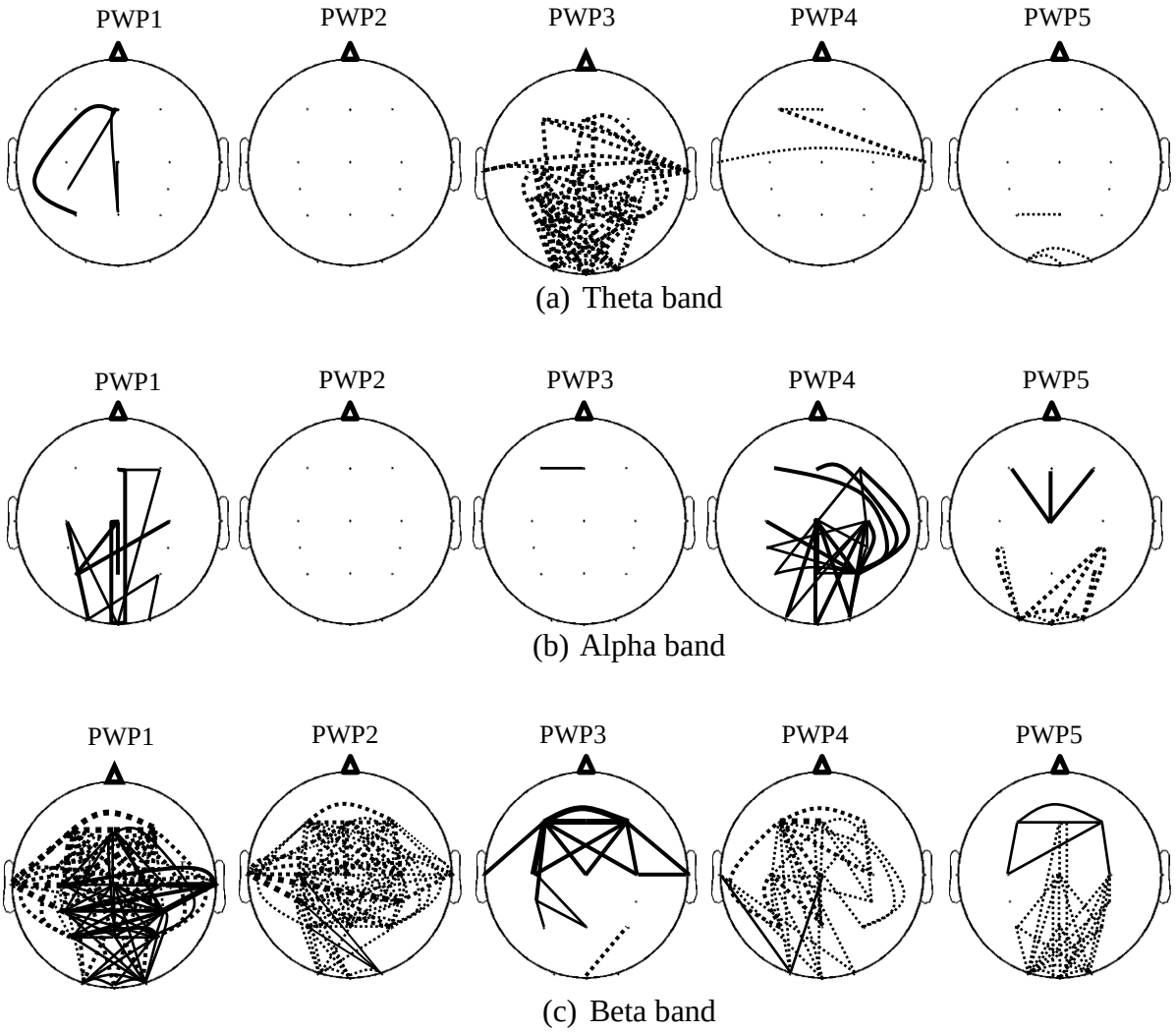


Figure 4.13: Immediate global effect of NF training on coherence. Scalp maps showing statistically significant (corrected for multiple comparison) change in coherence among 16 scalp sites during NF compared to Pre NF (NF-Pre) for each patient in three frequency bands. Solid lines show increase in coherence value and dotted lines show decrease coherence during NF compared to Pre NF. The thickness of line shows strength of change in coherence (thin line: 0 to 0.1, medium line: 0.1 to 0.2, thick line: 0.2 to onwards).

4.4.7. NF Modulation of Wide Spread and/ or Local Sources

To find whether patients modulate local activity or widespread sources, EEG PSD with Protocol 4 (monopolar derivation) feedback was compared with EEG PSD of laplacian

derivation feedback. Figure 4.14 shows PSD of each patient at C4 site in Pre NF and during NF states for both Protocol 4 and laplacian montage feedback performed on the same training day.

It can be noticed from Figure 4.14 that four patients modulated both widespread and local alpha activity while PWP3 modulated only widespread alpha. In the theta band, three patients (PWP2, PWP4 and PWP5) modulated only local theta, PWP1 modulated only widespread theta, and PWP3 modulated both local and widespread theta activity. Each patient, except PWP2, modulated both local and widespread beta sources.

4.4.8. Comparing PSD between NF and Mental Task

Table 4.13 compares change in PSD in alpha band during three states (NF, reading and math tasks) with respect to Pre NF state on the same training day.

Each patient shows increased PSD during NF and decreased PSD during the mental task compared to PSD in Pre NF state. The increased PSD during NF is significant in four patients (except PWP1), while the decreased PSD during the mental tasks is significant in three patients (PWP2, PWP3 and PWP4).

Figure 4.15 compares the effect of actual NF training with mental task in PWP3 (reading task; subfigure ‘a’) and PWP4 (math task; subfigure ‘b’). Compared to Pre NF, the PSD during NF in the alpha band is increased while PSD during the mental tasks (reading/ maths) reading is decreased. The decreased PSD during mental tasks in the alpha band indicates that increased PSD during NF is not by chance but an effect of voluntarily modulation of brain waves.

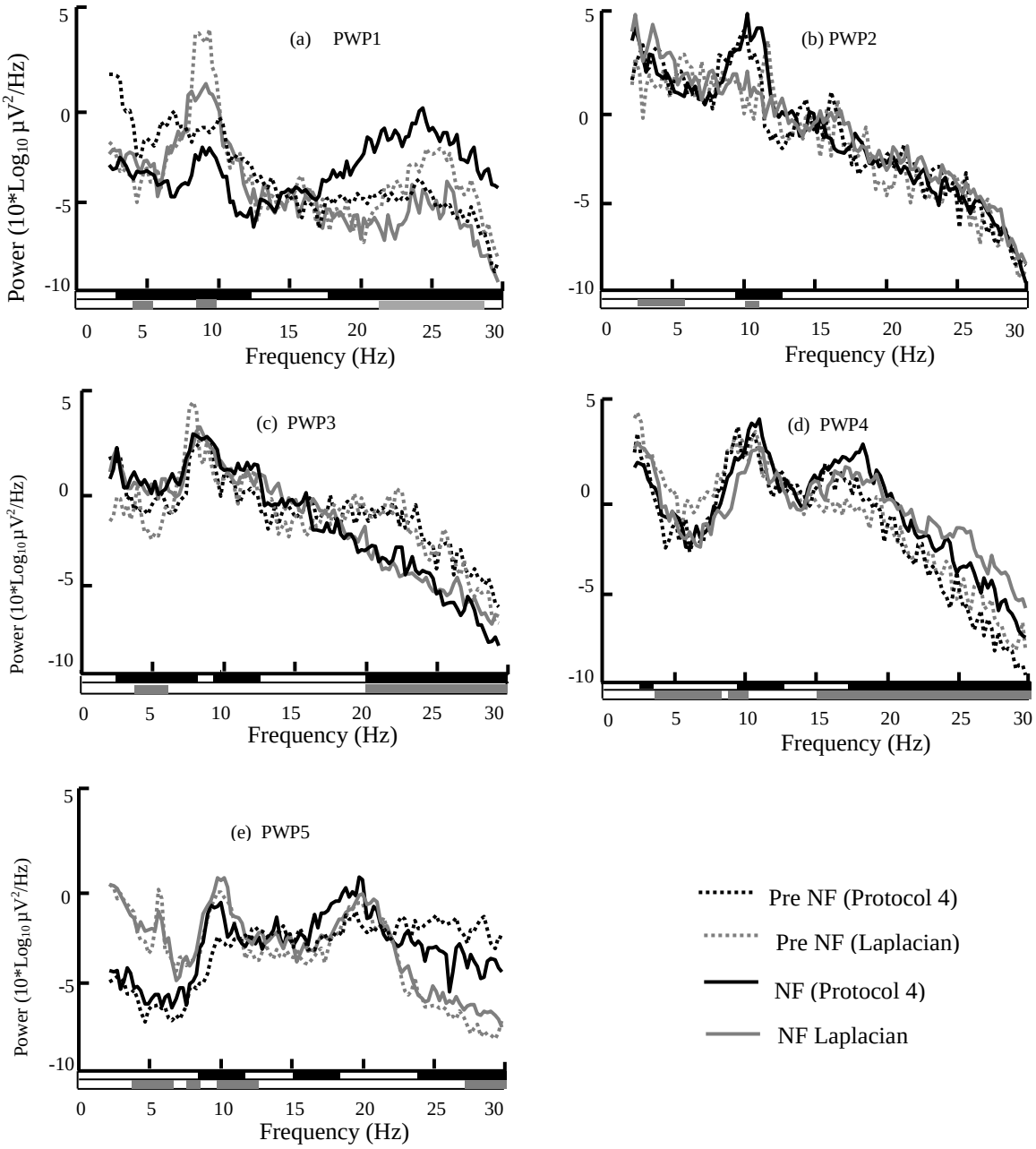


Figure 4.14: Comparison of PSD modulation in laplacian and monopolar derivatives with feedback from the C4 site. PSDs during NF is shown with solid lines (black line: monopolar, grey line: laplacian) and PSD in Pre NF is shown with dotted lines (black line: monopolar, grey line: laplacian). The subfigure 'a' is for PWP1, subfigure 'b' is for PWP2, subfigure 'c' is for PWP3, subfigure'd' is for PWP4 and subfigure 'e' is for PWP5. The significant change in PSD with Protocol 4 is shown with thick black line and significant change in PSD with Laplacian feedback is shown with grey thick line above x-axis.

Table 4.13: Percentage change in PSD during NF, reading and math tasks compared to PSD in Pre NF. A statistically significant decrease in PSD is shown in bold and italic, while increase in PSD is shown in bold only. A parametric unpaired ttest was applied.

	Actual NF (Change in PSD)		**Reading Task (Change in PSD)**		**Math Task (Change in PSD)**	
	Mean (%)	P-value	Mean (%)	P-value	Mean (%)	P-value
PWP1	12	0.3	-10	0.3	-15	0.2
PWP2	18	**0.05**	-11	0.2	-34	***0.02***
PWP3	32	**0.02**	-16	***0.03***	-36	***0.001***
PWP4	23	**0.01**	-13	0.5	-61	***1e^{-9}***
PWP5	37	**0.03**	-5	0.8	14	0.3

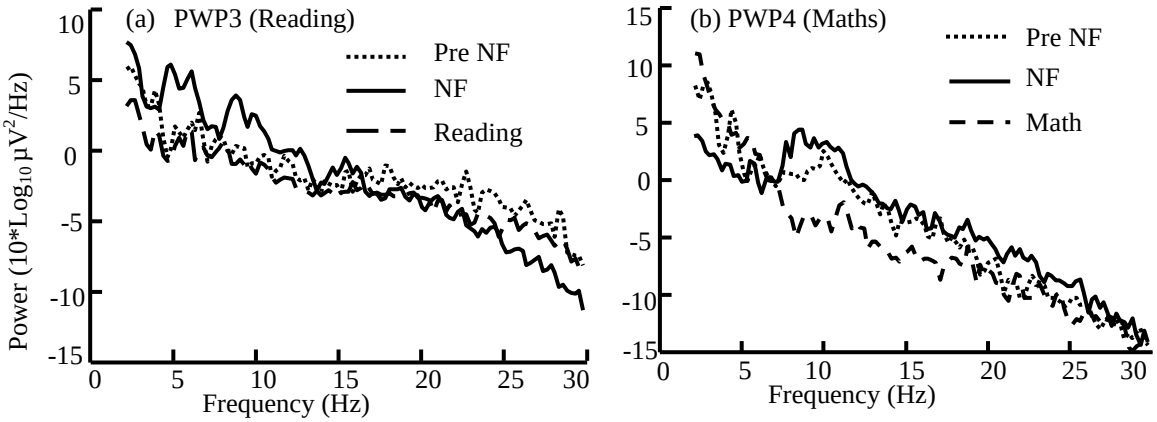


Figure 4.15: Comparison of modulation of PSD during NF and in mental tasks with respect to PSD in Pre NF state at C4 site. PSD during NF is shown with solid line, PSD in Pre NF is shown with dotted line, and PSD during mental task is shown with dashed line. (a) PSD of PWP3 during reading, (b) PSD of PWP4 during math task.

4.4.9. Effect of Placebo NF on Pain and EEG

Pre-recorded EEG Placebo: Figure 4.16 shows PSD of PWP5 in Pre NF (dotted line), during NF (solid line) and during feedback from Pre-recorded EEG or placebo (dashed

line). The PSD in the reward alpha and inhibit beta band is significantly changed in opposite direction during NF and placebo.

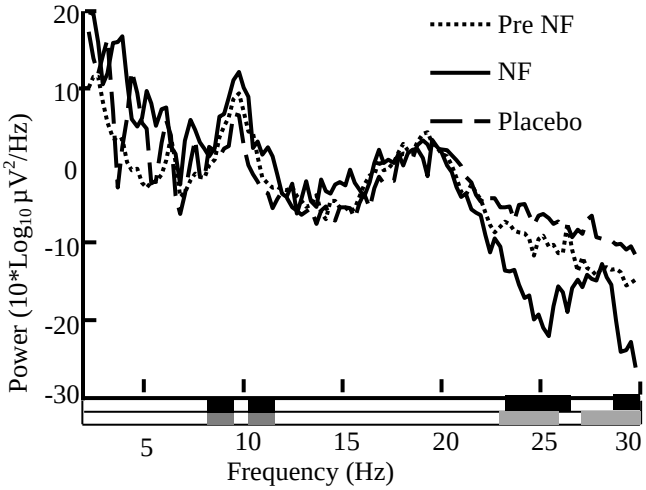


Figure 4.16: Change in EEG PSD during placebo feedback of pre-recorded EEG. PSD of PWP5 in Pre NF (dotted line), during NF (solid line) and placebo (dashed line). A significant change in PSD between NF and Pre NF states is shown with thick black line and significant change in PSD between placebo and Pre NF states is shown with thick grey thick line above x-axis.

Feedback from Occipital site in EO state: Figure 4.17 (a) shows PSD of PWP4 at electrode location Oz and C4 while receiving a visual feedback from Oz site as a placebo. It was mentioned in sections 4.4.1 and 4.4.3 that the main NF strategy of PWP4 was to modulate reward alpha, therefore, we will discuss only reward alpha band. During placebo training, PSD at C4 site in the alpha band was not changed while PSD at Oz (placebo feedback site) site was significantly decreased. This shows that feedback from the untrained site i.e. Oz site makes it hard for a patient to modulate the PSD in the desired direction.

Figure 4.17 (b) shows PSD at C4 site while using Protocol 4 as a feedback immediately after the placebo feedback from Oz site. The PSD is globally increased during NF compared to PSD in Pre NF. This shows that that change in EEG during NF is a consequence of patients learning strategy to modify or modulate brainwaves from C4 site.

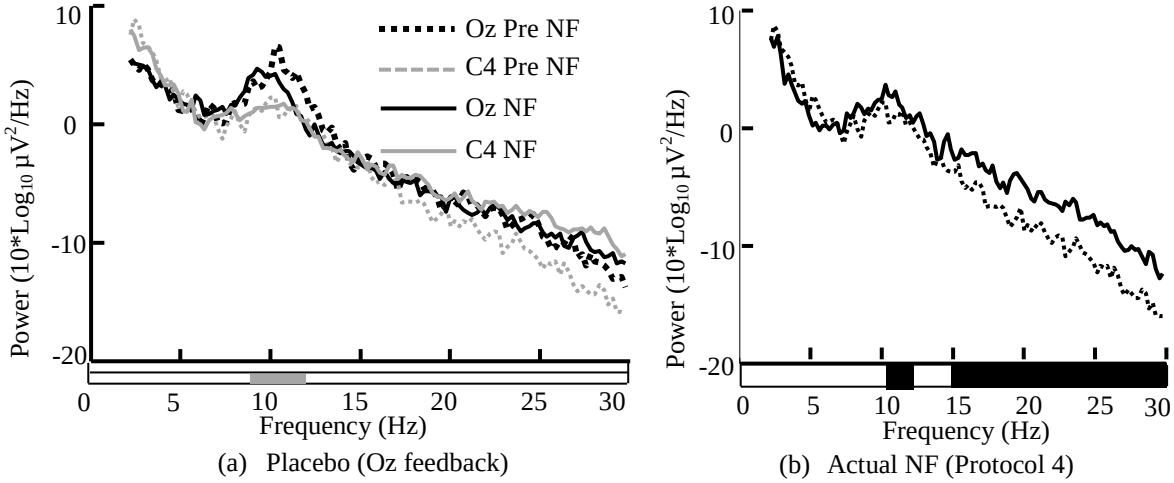


Figure 4.17: Placebo effect with feedback in EO state from the occipital site. For subfigure (a): solid lines show PSD during NF (gray line: C4 PSD, black line: Oz PSD) and dotted lines show PSD in Pre NF (gray line: C4 PSD, black line: Oz PSD). The significant change between Oz PSD is shown with black rectangle and significant change in C4 PSD is shown with grey rectangle. For subfigure (b): dotted line shows PSD in Pre NF and solid line shows PSD during NF with Protocol 4 immediately after placebo test.

Effect of Feedback in EC state from Occipital site: Figure 4.18 shows PSD scalp maps in Pre NF and during NF for sixteen channels experimental setup when patients received occipital 7-10 Hz activity as a feedback in EC state. During NF PSD is increased both at training site (occipital) and at C4 site, patient did not report reduction in pain.

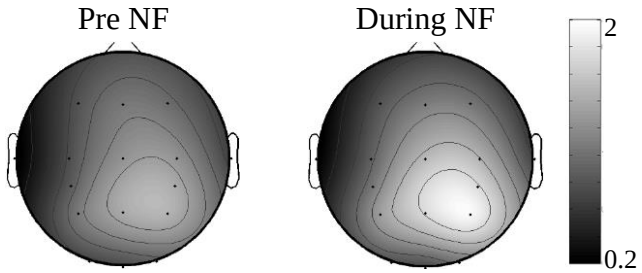


Figure 4.18: PSD scalp maps showing effect of placebo with feedback in EC state from occipital site in 7-10 Hz frequency band.

Effect of Protocol 1 on EEG PSD and Pain: As stated in section 4.4.1, a single patient (PWP4) who was able to modulate the PSD while receiving a feedback with Protocol 1 did

not report reduction in pain. This supports the finding that the reduction of pain following modulation of PSD with Protocol 4 might be an effect of training.

4.4.10. Learned Mental Strategy to Control Pain

Figure 4.19 shows PSD in Pre NF, during NF and during mental practise of NF (no feedback) for four patients at C4 site.

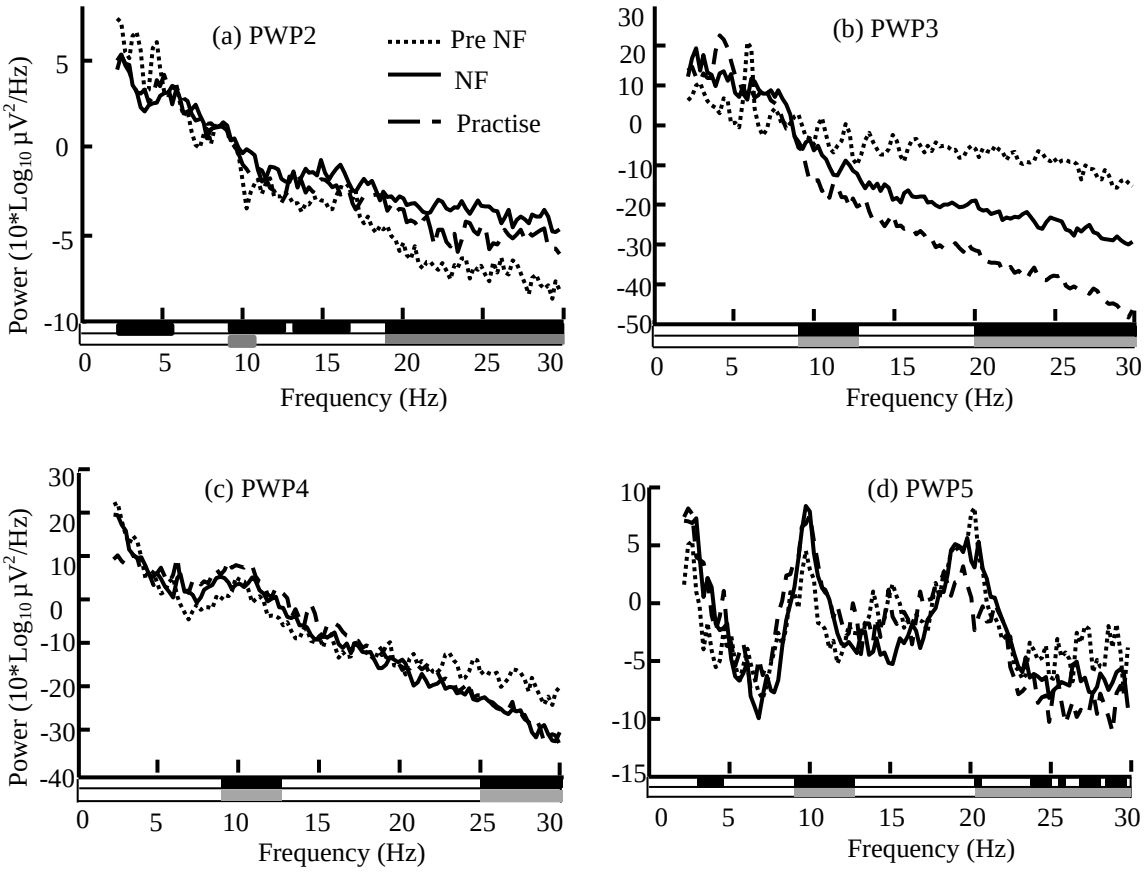


Figure 4.19: Comparison of modulation of PSD during NF and without feedback with PSD in Pre NF state at C4 site. PSD is shown in three states: Pre NF (dotted line), during NF (solid line) and during mental practise (dashed line). (a) PWP2, (b) PWP3, (c) PWP4 and (d) PWP5. The significant change in PSD between NF and Pre NF states is shown with black thick line while significant change in PSD between mental practise and Pre NF is shown with grey thick line above the x-axis on each subfigure.

The analysis of whole PSD spectrum (Figure 4.19) shows that modulation of PSD without feedback is in the same direction and in the same frequency as during NF. The accompanying change in pain intensity in three states (Pre NF/ during NF/ Practising NF) is: (PWP2: 5/4/5, PWP3: 6/3/3, PWP4: 5/5/4, PWP5: 7/6/6). However, after several weeks patients self-reported a loss of this ability, indicating that they would benefit from occasional repeated NF treatment.

4.4.11. Learning Curve of NF Training

Figure 4.20 shows time-course of Power in Post NF state for all training days with Protocol 4 starting with a baseline power recorded on the first session when Protocol 4 was used. A non-parametric Wilcoxon unpaired test was used to compare EEG PSD in Post NF with the baseline EEG PSD, recorded on the first session.

In the theta band, the reduction in EEG PSD in Post NF state with respect to the baseline PSD was noticed in PWP1 only for all sessions but this reduction in PSD was non-significant. In other patients, the change in PSD was not consistent (increased for some sessions while decreased for other sessions).

In the alpha band, PSD in Post NF state as compared to the baseline PSD (First sessions with Protocol 4) was non-significantly increased in all patients except PWP1.

In the beta band, two patients (PWP3 and PWP5) showed decreased PSD in Post NF states compared to PSD in baseline, while other patients showed increase in PSD. This increases/ decreases in PSD were non-significant.

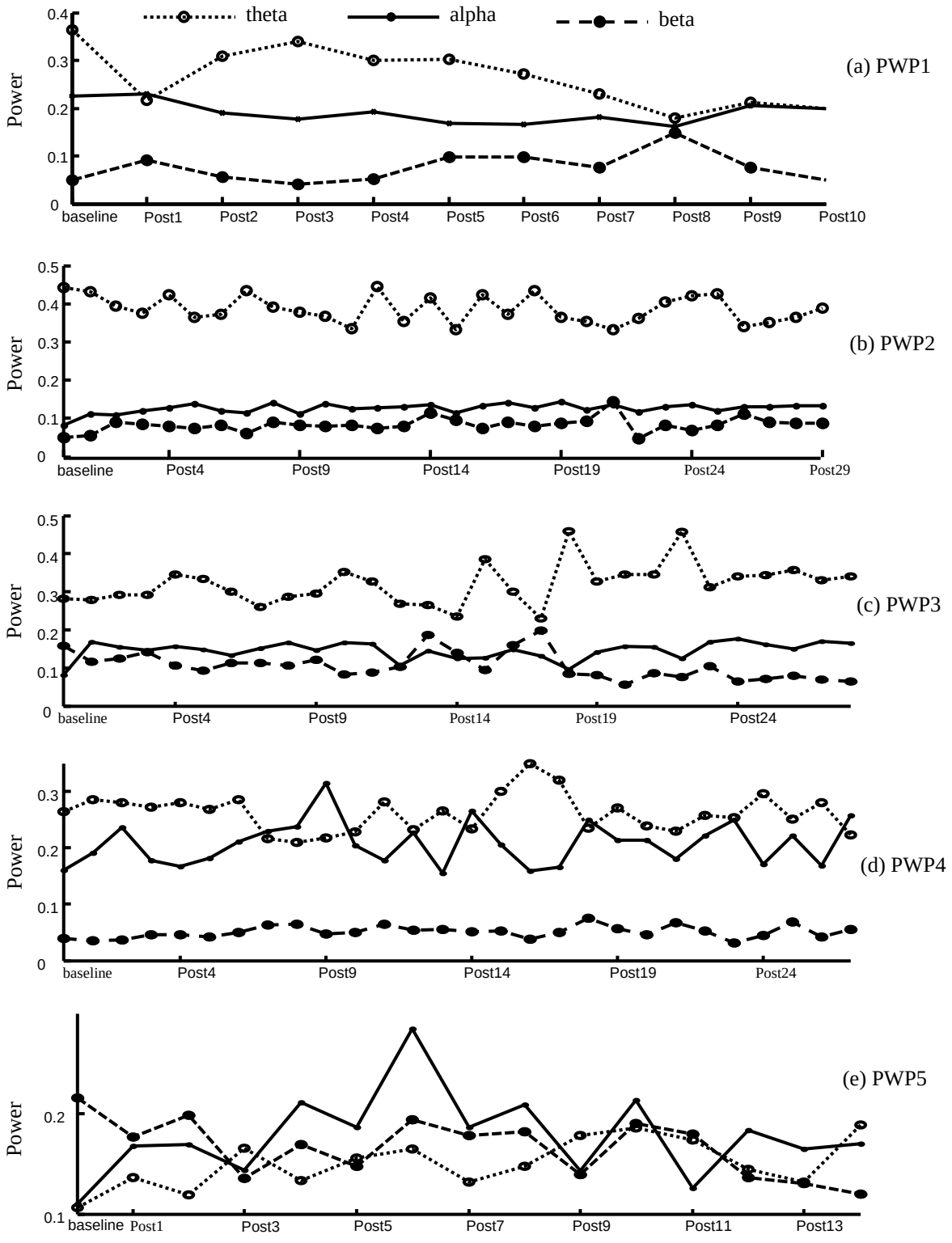


Figure 4.20: Time-course of Post NF power together with resting baseline for theta, alpha, and beta bands with Protocol 4 feedback.

4.4.12. Subjective Response of Each Patient with Each Protocol

PWP1 had complete injury (ASIA A) and pain in the lower limbs. Pain was developed in the same year when patient was injured; 7 years before receiving NF training. While receiving feedback with Protocol 1, this patient failed to modulate the EEG PSD, hence did not report reduction of pain. However, improved sleep was reported by this patient. With feedback from Protocol 4, this patient reported clinically non-significant reduction of pain (Table 4.3) following reduction of theta power. No side effect of the training was reported with any training protocol. This patient was tested neither for the placebo nor for the mental practising NF (without GUI). However, modulation of EEG PSD in EC state at the training site (Oz) and over the primary motor cortex (Cz, C3, and C4 sites) without reduction of pain demonstrate that reduction of pain with Protocol 4 might be real..

PWP2, similar to PWP1, had a complete injury and pain for seven years before receiving first NF training. This patient did not follow training rule while receiving feedback with Protocol 1 and Protocol 3, while reported reduction of pain following modulation of EEG with feedback using Protocol 2 and Protocol 4. However, large reduction of pain was reported with Protocol 4. In addition to reduction of pain, pleasant warmth sensation was reported over the body parts perceived as being painful; mainly on the feet. This patient was not tested for the placebo effect but reported smaller reduction of pain with Protocol 2 compared to Protocol 4. Also, modulation of EEG PSD in EC state at the training site (Oz) and over the primary motor cortex (Cz, C3, and C4 sites) without reduction of pain demonstrate that reduction of pain with Protocol 4 might be real. The patient modulated the PSD in the similar direction during NF and while practising NF (without GUI). This

demonstrates that patient learned the mental strategy to modulate the EEG PSD to control pain.

PWP3 had incomplete injury (ASIA B) and pain over the last three years. This patient did not follow training rule with Protocols 1 and 2, while modulated the EEG PSD with Protocols 3 and 4. The reduction of pain was reported with both protocols but strong spasms with Protocol 3 did not allow the patient to continue training with this protocol. With Protocol 4, patient reported improved dorsi-flexion of the foot, spasm-free while stretching a body at bed time, and pleasant warmth sensation that lasted for some hours after training. This patient was also not tested for placebo effect but modulation of EEG PSD in EC state at the training site (Oz) and over the primary motor cortex (Cz, C3, and C4 sites) without reduction of pain demonstrate that reduction of pain with Protocol 4 might be real.

PWP4 had incomplete injury (ASIA B) and pain over the past 24 years. This patient did not follow training rule with feedback from Protocol 2, while modulated the EEG PSD with Protocols 1, 3 and 4. The pain was not reduced with Protocol 1 but patient reported improved sleep. Pain intensity was reduced with Protocol 3 but strong spasm was noticed. However, pleasant warmth sensation was reported followed by reduction of pain with Protocol 4. Furthermore, patient reported being spasms-free for the rest of the training day. This patient was tested for the placebo effect in which feedback was provided in EO state from the occipital site. It was noticed that patient failed to modulate the EEG PSD in the desired direction at the training site (Oz) and at the C4 site. However, immediately after the placebo test patient successfully modulated the EEG in the required direction with feedback from Protocol 4. This demonstrates that patient learned the strategy to modulate

the EEG PSD with Protocol 4 (C4 site). This was further confirmed while patient was asked to modulate the EEG PSD without feedback information (no GUI). Furthermore, modulation of EEG PSD in EC state at the training site (Oz) and over the primary motor cortex (Cz, C3, and C4 sites) without reduction of pain demonstrate that reduction of pain with Protocol 4 might be real.

PWP5 had incomplete injury (ASIA B) and pain over the past 11 years. This patient did not follow training rule with feedback from Protocol 1, while modulated the EEG PSD with Protocols 2, 3 and 4. The reduction of pain was reported with each protocol but strong spasms were also noticed with Protocol 3. The reduction of pain was largest with Protocol 4. Also, patient reported spasm-free and pleasant warmth sensation over the body parts perceived as being painful. During pre-recorded EEG placebo, EEG of this patient was changed in the opposite direction as compared to EEG during NF. Patient learned the mental strategy to modulate the EEG PSD in the desired direction without feedback information (no GUI). Furthermore, modulation of EEG PSD in EC state at the training site (Oz) and over the primary motor cortex (Cz, C3, and C4 sites) without reduction of pain demonstrate that reduction of pain with Protocol 4 might be real.

4.5. Discussion

The two main objectives of the Phase 2 of the study were to test different NF protocols for the treatment of CNP in paraplegics, and to find the immediate global (topographically) effect of a NF training on PSD and coherence among each channel. The NF protocols were created based on the results of the study reported in Chapter 3, past neuroimaging studies defining the cortical areas involved in pain, and NF and neurostimulation studies for the

management of pain [243,248,249,346,368]. The modulation of PSD followed by a clinically and statistically significant reduction in pain showed that frequency dependent EEG based CNP signatures can be used to develop NF protocols (section 4.4.2, Table 4.2, and Table 4.3), although a study on the larger number of patients is required to further confirm the efficacy of NF training for the treatment of CNP.

Design of NF Protocols (section 4.3.5 Part ii): The rationale for both inhibit bands (theta and beta) came from results of Chapter 3 and from results of past neuroimaging studies showing theta and beta band overactivation in patients with chronic pain [257–260]. The theta and beta bands were also chosen as inhibit bands in previous NF studies on pain management [140–142]. The SMR reinforcement was chosen on the basis of pain management studies using NF [140,141,367,371]. The neuroimaging studies and results of Chapter 3 showed that a dominant alpha peak is shifted towards lower frequencies in patients with pain compared to those of able-bodied and SCI patients without pain [46,257–259,262]. Therefore, for the reward band we chose a slightly narrower the alpha band (9-12 Hz) without lowest frequencies, in order to shift the dominant alpha peak frequency towards the higher frequencies. The alpha reward band was chosen in two published NF studies for chronic pain management [142,368].

A NF in this study was provided from the central (C3, Cz and C4), parietal (P4) and centro-parietal (CP4) areas, though C4 site was used for most of training days. These electrodes are located over the primary sensory and the primary motor cortex. Sensory cortex is a part of a pain matrix recognised in the literature [27]. The primary sensory-motor cortex was chosen based on: (i) neuroimaging studies showing the overactivation of M1 in CNP[17,18], (ii) results of Chapter 3 showing stronger ERD during MI in PWP over the

sensory-motor cortex, and (iii) results of neurostimulation studies for treatment of CNP based in rTMS and tDCS achieving the best reduction of pain when targeting M1[19-21]. A single rTMS study in SCI-related NP suggested stimulation of cortical area corresponding to painful body area [336], and two NF studies [140,141] on fibromyalgia suggested Cz site. Patients in our study had paralyzed and painful lower limbs, therefore, feedback was first provided from the Cz site located over the primary motor cortex of the paralyzed painful limbs. Due to the nature of EEG recording reflecting the mixed activity of local and distant sources, electrode location Cz probably records the activity of both sensory and motor cortex.

The selection of C3 and C4 sites was based on rTMS and tDCS studies stimulating motor cortex areas adjacent to the somatotopic representation of the painful body part [334,344,345,349,420]. The rTMS study for pain management on SCI patients also suggested stimulation of cortical representation of the upper limbs because, unlike the lower limb, it is not expected to shrink due to disuse reorganisation and is closer to the scalp [335]. A case study of NF [368] and a tDCS study for treatment of CNP pain [347] also proposed targeting the left hemisphere (C3). Another tDCS study proposed stimulation of the ipsilateral hemisphere of the dominant hand [346] (C4 in our case). Therefore, feedback in this study was also provided from C3 and C4 sites.

The selection of CP4/ P4 was based on rTMS studies stimulating primary sensory cortex [325] and parietal cortex [327], and studies showing lateral effect of stimulation on non-stimulated cortices [324,330]. Another reason of selecting the primary sensory and parietal cortices came from a neuroimaging study showing parietal and centro-parietal cortices

projection towards DLPFC and thalamus regions in patients with pain following SCI compared to SCI patients without pain [87].

Effectiveness of Protocol 4: Although four different protocols (scalp locations on sensory-motor and parietal cortices) were tested, Protocol 4 (C4 site, inhibit theta 4-8 Hz and inhibit beta 20-30 Hz, and reward alpha 9-12 Hz) was most effective in reducing pain following significant modulation of PSD in a desired direction (section4.4.1). The strong training effect from C4 site (which corresponds to cortical representation of the left hand/arm) is in accordance with a tDCS study in which the stimulation was applied at the cortical presentation of the non-painful limb rather than painful limb [346]. Patients reported spasms while receiving a feedback from the cortical presentation of another non-painful limb i.e. C3 site (dominant hand). There is no certain reason for strong spasm.

*Band Specificity During NF Training***:** To date only few studies have shown full spectrum PSD during NF training to find the effect of training a single frequency band on the rest of the spectum[363,366,421]. These studies found that alpha desynchronization was positively correlated with theta and beta desynchronization. In our study (section 4.4.1), the full spectrum analysis also revealed that modulation of PSD in specific frequency band induced effect on full spectrum PSD. The global change in whole spectrum from theta band to beta band while modulating a PSD in specific frequency band was also reported in past NF studies [363,421].

The immediate change in PSD during NF, analysed for a single training day, was sustained for several minutes beyond the training (Post NF, short-term) with each protocol, except with Protocol 1. This indicates that short-term plasticity might cause long-term plasticity effect of NF training over the number of training days.

Relative Change of PSD During NF and Shift in Baseline PSD: The temporal change in baseline value has been reported in two NF studies [200,422]. The relative change in PSD at training site (Table 4.4) and shift in baseline PSD (Table 4.7 and Table 4.9) found in our study is in accordance with neuroimaging studies showing decrease of alpha and increase of theta and beta band power/ amplitude in patients with pain [257–260]. This shift in baseline PSD demonstrates that training might have a successful long-term effect.

Bilateral Effect of NF Training: The bilateral or lateralized effect of NF training has been reported in past NF studies [366,423–425]. It is worth noting that although patients in our study modulated relative EEG power at C4 the effect was more pronounced at C3 site (Table 4.5 and Table 4.6). The strong modulation of brain activity over the contra-lateral hemisphere was also reported by Barnea *et al* [424] while comparing the effect of feedback from C3 and C4 sites on other brain sites. Furthermore, it was assumed that activation of asymmetric hemispheric control circuits could modify distant hemispheric networks.

Global modulation of PSD and Coherence: In a sixteen channel NF experimental paradigm, the effect of NF training on brain activity was not restricted to the contra-lateral site only but was wide spread over the whole scalp (*section 4.4.6)*, which is similar to the effect of rTMS and tDCS [324,330].

To the best of our knowledge, the immediate wide spread effect of NF training has not been examined in previous NF studies. However, short-term (beyond the training, Post NF) and long-term (after a number of training sessions) wide spread effect of NF training has been reported [199,366,426,427]. Though patients received NF from C4 location, the effect of NF training was strong over the frontal region. This effect was observed in previous NF studies [199,366,426,427], where NF was used to study the connectivity changes and to enhance

cognitive performance in healthy adults and in patients with cognitive impairment. In general, the change in coherence was independent of change in PSD.

The frontal beta and frontal midline theta mainly increases with increased concentration on a task [109]. Therefore, increase in frontal PSD would be expected if it would reflect general concentration rather than NF training. The reduction in power at the frontal site during NF could be attributed to NF training rather than to general concentration on task. The global effect of NF training can be partially attributed to the nature of the EEG signal which reflects the activity of multiple sources; however patients were also able to modulate local sources as it was further confirmed by NF with laplacian derivative (see section 4.4.7). A widespread modulation of EEG power can also be attributed to changes in the connectivity as confirmed by the analysis of coherence (Figure 4.13).

Influence of NF training on the Intensity of Pain: All five patients who received 20 or more NF sessions achieved a statistically significant reduction of pain, with four patients reporting a clinically significant (>30%) reduction of pain (section 4.4.2). The reduction of pain in all patients was gradual and lasted for several weeks after termination of the therapy. In our study the percentage reduction in pain intensity is larger than in previous neurostimulation and NF studies [142,319,335,337,345,353], though there were only five patients.

A negative correlation between pain intensity and the number of NF sessions suggests that NF had a carry-over effect (*Table 4.2*), resulting in gradual decrease in baseline pain intensity. It also demonstrates that patients would benefit from larger numbers of treatment sessions because the effect of NF of the pain intensity was not saturated.

Placebo Effect: In this study, there was no separate control group similar to fMRI feedback study for management of pain [150,198]. Instead, patients were tested for placebo effect once they gained a skill to modulate EEG PSD in a desired direction.

Failure to modulate EEG while receiving EEG of pre-recorded session as a feedback demonstrates that modulation of EEG PSD during NF with Protocol 4 was real (Figure 4.16). A decrease in the alpha and increase in the beta band power during a single-blinded placebo (pre-recorded session for a feedback) might be due to increased concentration. Similarly, increases in the alpha PSD during NF and decreases in the alpha PSD during mental tasks (read and maths) further supports that modulation of EEG PSD during NF might be caused by a voluntary modulation of brainwaves rather than by a general engagement in a cognitively demanding task.

Failure to modulate the PSD at Oz site in EO state (placebo feedback site) might be due to visual input that reduces the occipital alpha (Figure 4.17). This phenomenon of occipital alpha to visual input together with patients learning ability with Protocol 4 might make it further difficult to modulate the PSD with placebo feedback from Oz site.

As discussed in results section that patients did not report reduction of pain following successful modulation of EEG PSD with EC training from Oz site (Figure 4.18) and with Protocol 1 (Figure 4.6). This demonstrates that reduction of pain with Protocol 4 training might be related to the modulation of PSD in the chosen frequencies and locations rather than an effect of placebo. The early NF study on pain management also found that modulation of occipital did not help to control pain [168].

Studies using fMRI showed that placebo intervention can also activate deeper cortical structure (ACC, IC) which are involved in processing of pain [428]. Thus in testing for a placebo treatment, one can only compare the reduction of pain between real treatment and placebo, rather than expecting that placebo treatment will not at all affect the intensity of pain. Based Watson *et al.*, we can suggest that modulation of PSD followed by reduction of pain with Protocol 2 can also be considered as an effect of placebo.

NF Training and Dominant Frequency: The increase in baseline dominant frequency (significant in PWP5 only) is in accordance with the results found in Chapter 3 and results of neuroimaging studies of pain showing decrease in dominant frequency [46,257–259,262,403] (section 4.4.4). This increment in baseline dominant frequency indicates that NF training might enhance cognitive performance [199,429].

Learned mental strategy and modulation of pain: As previously stated, one justification for the use of a long-term NF training was to train patients to modulate the PSD without feedback. This is a potential advantage of NF training over other neuromodulation treatments based on external stimuli to manage pain. Patients reported that self-induced modulation of PSD was accompanied with reduction of the intensity of pain.

4.6. Conclusion

The results of this pilot study demonstrate that NF training has a potential to manage CNP in paraplegic patients. However, a randomized double-blinded sham-controlled study is required to further confirm its effect on large numbers of patients.

Chapter 5. Long-Term Neurological Outcomes of Neurofeedback Training on Central Neuropathic Pain in Paraplegic Patients

5.1. Abstract

Objective: The aim of this chapter is to find whether long-term neurofeedback (NF) training induces changes in pain related surface and deep cortical areas.

Methods: Five paraplegic patients with Central Neuropathic Pain (CNP) from the Phase 2 of the study also participated in the Phase 3 of the study. Electroencephalogram (EEG) was recorded and compared in a relaxed state and during motor imagery (MI) before the first day of NF training and after the last NF training day. The changes at deep cortical structures are analysed using standardized low resolution brain electromagnetic tomography (sLORETA) with the emphasis on Brodmann areas (BAs) related to pain.

Results: In relaxed eyes open (EO) state, cortical activity in pain-related areas was increased in the theta (4-8 Hz) and alpha (9-12 Hz) bands, while it was decreased in the beta1 (12-15 Hz) and beta2 (20-30 Hz) bands. During MI tasks, the event-related desynchronization (ERD) of patients with CNP was reduced after NF and looks similar to ERD of paraplegic patients without pain and ERD of able-bodied in the theta (4-8 Hz), sensory-motor rhythm1 (SMR1; 8-12 Hz), and sensory-motor rhythm2 (SMR2; 16-24 Hz) bands.

Conclusion: NF training induced changes in brain activity both in the relaxed state and during MI tasks. This long-term change in the brain activity was noticed both at the surface and in the deep cortical areas related to pain matrix.

5.2. Introduction

Recently Jensen et. al [353] found that reduction of pain with hypnosis and meditation treatments was associated with increase in wide spread EEG amplitude in theta and alpha bands at the surface of the cortex, but did not analyse changes at the deeper cortical structures. However, Koberda et. al [374] reported reduction in power in theta and beta bands following reduction of pain with feedback from the deeper cortical structures. Saranthein et. al [258] found reduction in the theta band power of anterior cingulate cortex (ACC) following reduction of pain intensity with surgery of the thalamus. The above mentioned studies and other pain management studies (see section 2.2.2) did not provide long-term changes in the brain activity related to motor task.

The objective of this study was to provide long-term global effect of NF training on EEG activity in a relaxed state and during MI tasks.

5.3. Methods

5.3.1. Participants and EEG Recordings

Five paraplegic patients with CNP who completed NF training in the phase 2 of the study also participated in the phase 3 of the study. Similar to phase 1 (Chapter 3), EEG was

recorded with 61 channels in both spontaneous relaxed (EO and EC) state and during MI of the Feet (F) and upper limbs (Right hand: RH, Left hand: LH). The purpose of multichannel recording was to perform quantitative EEG analysis over the whole cortex in order to assess the long-term changes due to NF therapy.

5.3.2. EEG Processing and LORETA imaging

EEG data (spontaneous and MI) of five subjects recorded before and after the NF therapy were re-referenced to an average reference after removing artefacts (see Chapter 3) Due to a relatively small number of subjects, we performed group analysis and analysis of each subject individually before and after NF. Each subject was analysed separately because of variation in response to NF training in phase 2 of the study.

The average reference data for **spontaneous EEG** (EO and EC states) for each subject was split into 4 s long epochs. Each epoch was exported to sLORETA in order to compare changes in brain activation before and after NF at the surface and in deep cortical levels [430]. The current source density was calculated in four frequency bands (theta, alpha, beta1, and beta2 bands) for each epoch separately in order to compare frequency dependent changes in brain activation for each subject individually. In order to compare changes in spontaneous EEG activity on a group level, the current source density for each epoch was averaged for each patient. The above mentioned frequency bands were chosen based on protocols described in Chapter 4.

sLORETA analysis was also performed to find the differences between EC and EO activities (EC-EO) at cortical and deep cortical levels before the first and after the last day

of NF training (After NF-Before NF). This was calculated in five frequency bands (theta, alpha, beta1, beta2, and 2-30 Hz bands) for each patient individually and on a group level.

sLORETA software, which provides a solution to the EEG inverse problem [431], was used to estimate the cortical three dimensional distribution of EEGs current density [430]. The maps generated from the EEG using LORETA indicate the locations of the underlying source generators. The sLORETA implementation incorporates a realistic head model [432] using Montreal Neurological Institute (MNI) 152 template [433]. The electrode coordinates on MNI152 scalp for 10/20, 10/10 and 10/5 were based on Jurack et. al and Osstenveld [104,105]. sLORETA estimates sources in grey matter volume (6239 voxels) to 5mm grid resolution using a digitized MNI probability atlas registered to a recognized probabilistic talairach anatomical brain atlas [434]. Also, BAs are displayed using MNI space with correction/ conversion to talairach space [435].

sLORETA images were statistically compared between before NF and after NF through voxel by voxel using non-parametric t tests [436]. For individual subject, unpaired test was used and for a group level paired test was applied. A randomization procedure was applied to correct for multiple comparisons.

For **MI EEG data**, ERD/ERS was calculated before and after NF for each trial for each type of MI task for each subject. The calculation of ERD/ERS for each trial separately would allow us to apply statistics to compare ERD/ERS before and after NF for a single subject. In order to perform comparison on a group level (before vs after NF), the ERD/ERS for each trial was averaged for each subject. For statistical analysis, a non-parametric statistics based on permutation test was applied over each time and frequency

window to compare ERD/ERS before and after NF. A false discovery rate (FDR) was applied to correct for multiple comparison from multiple time-frequency windows.

Scalp maps were created based on ERD/ERS averaged over certain frequency bands (theta, SMR1, and SMR2; similar to Chapter 3) and short time windows (0.4 s). The comparison between scalp maps of each individual subject (before and after NF) and on a group level was performed based on a non-parametric permutation statistics (p=0.05) and FDR was applied to account for comparison from multiple electrode sites.

5.3.3. sLORETA Analysis on Selected BA's

Although sLORETA analysis provides information about the current density for the whole brain, we were primarily interested in the regions of the cortex related to pain. These areas include primary motor cortex (M1), premotor cortex (PMC), supplementary motor cortex (SMC), primary and secondary sensory cortices (S1 and S2), dorsolateral prefrontal cortex (DLPFC), posterior parietal cortex (PPC), anterior cingulate cortex (ACC), and insular cortex (IC). Therefore, we compared change in brain activity before and after NF in the following BAs (S1 (1, 2, 3), S2 (40, 43), M1 (4), PMC (6), SMC (8), DLPFC (9, 46), APFC (10, 11), PPC (5, 7), ACC (24, 32), PCC (23, 31), IC (13)) [258,437–440].

5.4. Results

5.4.1. Effect of NF Training on Relaxed State EO EEG Activity

Individual Subject Analysis: Table 5.1 shows relative number of voxels (in percentage) showing long-term statistically significant changes in the brain activity in the BAs' related

to the pain matrix in four frequency bands (theta, alpha, beta1 and beta2) in EO state for each patient. The significant value was set to $p<0.05$.

Table 5.1: Number of voxels (Percentage) showing change in activation in EO state for each patient in BA's related to pain

Bands	Areas / BA	S1 1,2,3	S2 40,43	M1 4	PMC 6	SMC 8	DLPFC 9,46	APFC 10,11	PPC 5,7	ACC 24,32	PCC 23,31	IC 13
Theta	PWP1	**2**	**NS**	**3**	**3**	**1**	**5**	**NS**	**2**	**NS**	**NS**	**NS**
	PWP2	NS	NS	NS	NS	NS	13	NS	NS	10	NS	NS
	PWP3	100	100	92	99	99	98	98	97	100	99	97
	PWP4	100	100	92	99	99	99	98	97	98	99	97
	PWP5	100	100	92	99	99	99	98	95	99	81	97
alpha	PWP1	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**5**	**NS**	**NS**	**NS**
	PWP2	16	14	3	9	14	13	15	21	4	4	30
	PWP3	**8**	**24**	**5**	**5**	**9**	**18**	**14**	**14**	**6**	**30**	**37**
	PWP4	100	85	86	93	87	85	88	88	95	77	65
	PWP5	100	92	85	87	94	96	69	97	99	97	97
beta1	PWP1	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**
	PWP2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
	PWP3	**2**	**5**	**3**	**25**	**27**	**36**	**34**	**10**	**46**	**NS**	**NS**
	PWP4	**100**	**100**	**92**	**99**	**99**	**99**	**99**	**97**	**100**	**100**	**97**
	PWP5	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**	**NS**
beta2	PWP1	***NS***	***NS***	***NS***	***NS***	***NS***	***10***	***NS***	***NS***	***NS***	***NS***	***30***
	PWP2	***19***	***12***	***26***	***39***	***39***	***32***	***16***	***54***	***79***	***98***	***41***
	PWP3	***94***	***83***	***80***	***94***	***92***	***93***	***92***	***88***	***99***	***99***	***96***
	PWP4	***NS***	***NS***	***NS***	***NS***	***NS***	***4***	***5***	***NS***	***NS***	***NS***	***NS***
	PWP5	***100***	***100***	***92***	***98***	***98***	***98***	***99***	***97***	***99***	***99***	***97***

Bold numbers show significant reduced activation, normal font numbers show significant increased activation, **NS= non-significant reduced activation,** NS=non-significant increased activation. BA: broadmann areas, EO: eyes open, S1: primary secondary sensory cortex, S2: secondary sensory cortex, M1: primary cortex, PMC: premotor cortex, SMC: supplementary motor cortex, DLPFC: dorsolateral prefrontal cortex, APFC: anterior prefrontal cortex, PPC: posterior parietal cortex, ACC: anterior cingulate cortex, PCC: posterior cingulate cortex, IC: insular cortex.

In the theta band, a statistically significant reduction of activation, over a limited number of voxels, was noticed only in PWP1. Three patients (PWP3, PWP4 and PWP5) showed statistically significant increase in activation and PWP2 showed non-significant (except over DLPFC) increase in activation.

In the alpha frequency band, a statistically significant increased activation was noticed in all pain related surfaces and deep cortical areas in three patients (PWP2, PWP4 and PWP5). The large number of voxels showing statistically significant increase in activation was noticed in PWP4 and PWP5. Other two patients (PWP1 and PWP3) showed reduced activation though it was statistically significant only in PWP3.

In the beta1 frequency band, two patients (PWP3 and PWP4) showed statistically significant reduction of activation while PWP1 and PWP5 showed non-significant reduction of activation. The increased non-significant activation was noticed only in PWP2.

In the beta2 frequency band each patient showed reduced activation; it was statistically significant over each pain related areas in three patients (PWP2, PWP3 and PWP5). Other two patients showed statistically significant reduction of activation over the frontal and insular cortices. The large number of voxels showing statistically significant reduction of activation was mainly noticed in PWP3 and PWP5.

Group Analysis: The group analysis showed that surface and deep cortical activities, related to pain areas was reduced in the beta1 and beta2 bands, and it was increased in the theta and alpha bands, though statistically significant change was noticed only in the beta2

band. Therefore, we will discuss only beta2 band further in the following text. The activation value was -0.94 for $p<0.05$.

Table 5.2 shows the number of voxels (percentage) and coordinates represent maximum significant reduction of activation in the beta2 band averaged over five subjects. Although the NF training was provided from the surface cortical areas, the number of voxels showing statistically significant reduction of activation is large in deep cortical areas related to pain matrix, such as ACC and IC. Also, patients received NF training from the right hemisphere (C4 site), but reduction of beta activity was strong on the left hemisphere.

Table 5.2: Number of voxels (percentage) showing reduced activation averaged over five subjects in the beta2 band in EO state

Cortical areas	BAs	Total voxels (Percentage)	Maximum change in activation	MNI coordinates with maximum value		
				X	Y	Z
S1	1, 2, 3	NS	-	-	-	-
S2	40, 43	NS	-	-	-	-
M1	4	NS	-	-	-	-
PMC	6	2	-0.97	-15	25	40
SMC	8	4	-0.96	-20	30	45
DLPFC	**9**, 46	30	-0.99	-15	40	25
APFC	**10**, 11	4	-0.96	-20	45	30
PPC	5, 7	NS	-	-	-	-
ACC	24, **32**	20	-0.99	-15	35	20
PCC	23, 31	NS	-	-	-	-
IC	13	24	-1.01	-30	15	15

BA: broadmann areas, EO: eyes open, MNI: Montreal Neurological Institute, NS: non-significant change in activation. The acronyms for cortical areas are presented in Table 5.1.

The negative value for maximum change in activation shows that brain activity is reduced after NF training in beta2 frequency band.

Figure 5.1 shows long-term changes in surface and deep cortical activity in beta2 band averaged over five patients. The subfigure ‘a’ shows a surface cortical activity over 3D cortical map (four views: Frontal, Top, Left and Right). A reduced activation can be noticed over the whole cortex though it was stronger over the left part of the sensory-motor and frontal cortices.

A change in activation in deep cortical structures, such as cingulate and insular cortices in the beta2 band is presented with MNI slice views. A subfigure (b) shows reduced activation at **BA13** (MNI coordinate: -30 15 15, activation=-1.01) representing a left part of the IC. A subfigure (c) shows reduced activation at **BA32** (MNI coordinate: -15 35 20, activation=-0.99) representing a left dorsal part of the ACC. A subfigure (d) shows reduced activation at **BA24** (MNI coordinate: -5 25 15, activation=-0.99) representing a left ventral part of the ACC.

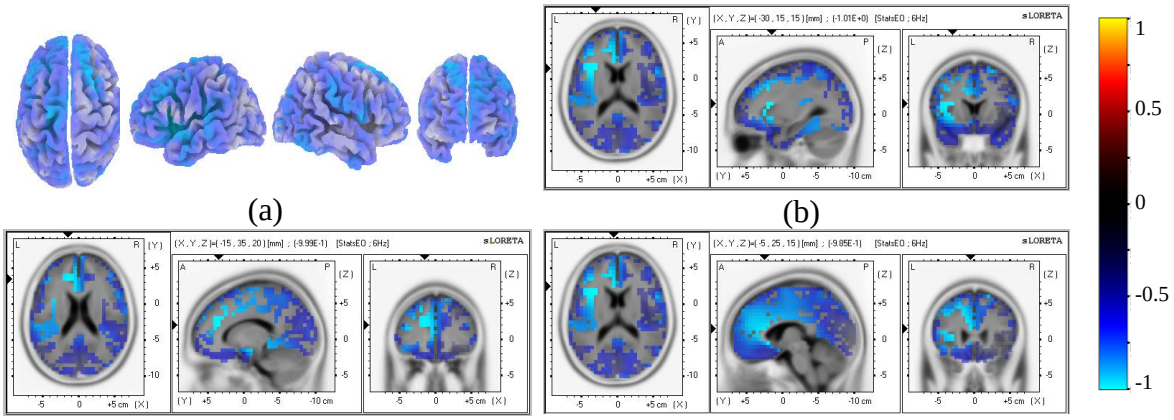


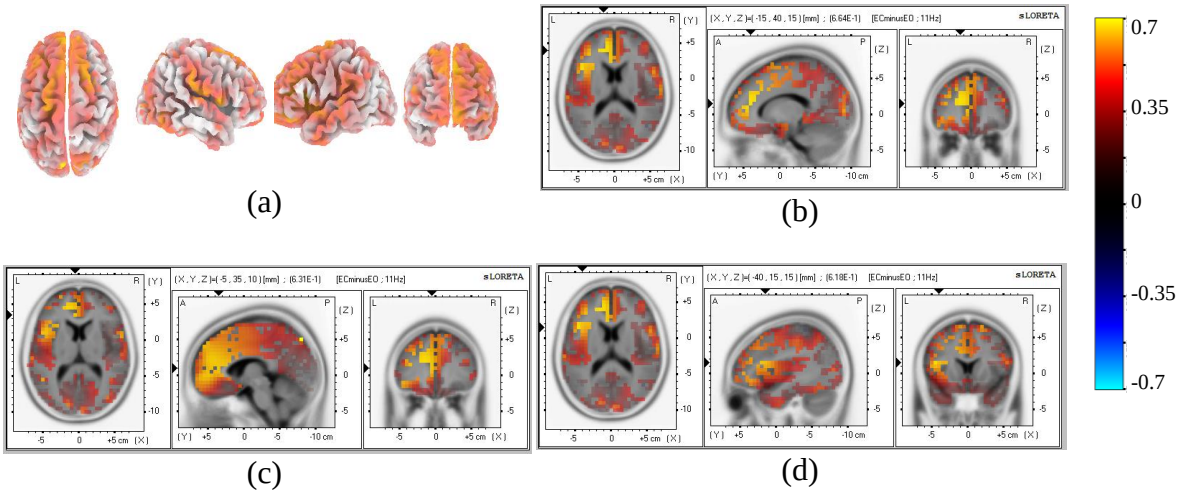
Figure 5.1: Change in activity in EO state in the beta2 band before the first and after the last NF training day (After-Before) averaged over five patietns band showing lateral views and MNI slices. (a) Lateral Views (top, left, right and frontal), (b) BA 13 [MNI coordinate: -30 15 15, t=-1.01], (c) BA32 [MNI coordinate: -15 35 20, t=-0.99], (d) BA 24 [MNI coordinate: -5 25 15, t=-0.99]. Blue aeras correspond to reduced activity after NF.

5.4.2. Effect of NF Training on Difference between EC and EO Activity

A group analysis showed that a difference in the EC and EO (EC-EO) cortical activity at the surface and deep cortical activity related to painful areas decreased in the theta band, while increased in the beta1, beta2 and 2-30 Hz bands. In the alpha band, the difference in EC and EO activity was reduced in the frontal cortex and at the ACC, while it increased in the other regions. In beta2 band, a statistically significant change in activity was noticed only over a single voxel representing ACC [MNI 5 35 15, activation=3.4, BA 32]. The statistically significant threshold was 3.4 for $p < 0.05$. The analysis will be presented in only 2-30 Hz band, though non-significant, based on results of Chapter 3 and Boord study [262] showing reduced EC/EO activity in patients with pain over that frequency band.

Figure 5.2 (a) shows long-term changes in the difference between EC and EO activation before and after NF treatment, over 3D cortical map in 2-30Hz frequency band averaged over five patients. The increased difference between EC and EO activity can be noticed over the whole surface 3D scalp.

A change in activation in deep cortical structures, such as cingulate and insular cortices in beta 2-30 Hz frequency band is presented on MNI slice views (Figure 5.2, subfigures (b-d)). Increased difference between EC and EO activity following a long-term NF training can be noticed over the BA32 [MNI: -15 40 15, activation=0.66] representing the left dorsal ACC, BA24 [MNI: -5 35 10, activation=0.63] representing the left ventral ACC, and BA13 [MNI: -40 15 15, activation=0.62] representing the left IC.



(a) (b) (c) (d)

Figure 5.2: Change in difference between EC and EO activity (EC-EO) in 2-30 Hz at surface and deep cortical levels before the first and after the last day of NF training (After NF – Before NF) showing lateral views and MNI slices: (a) Lateral Views (top, left, right and frontal), (b) BA 32 [MNI coordinate: -15 40 15, t=0.66], (c) BA24 [MNI coordinate: -5 35 10, t=0.63], (d) BA 13 [MNI coordinate: -40 15 15, t=0.62]. Red areas correspond to increased activity after NF.

5.4.3. Effect of NF Training on Dynamic Activation of Sensory-Motor Cortex

An ERD/ERS for three electrodes, Cz, C3 and C4, was analysed during MI of the corresponding limbs (feet for Cz, right hand for C3, and left hand for C4) before the first and after the last day of NF training. These areas are chosen to analyse how NF training influences the brain response during MI of a paralyzed painful limb and of a non-paralyzed non-painful limb. The effect of NF training on dynamic activation of sensory-motor will be presented for individual patients and averaged over five patients before the first and after the last day of NF training. Furthermore, dynamic activation of the sensory-motor of PWP group before and after NF training is also compared with the activation of the sensory-motor cortex of paraplegic patients with no pain (PNP) and able-bodied (AB) groups during MI of paralyzed painful (F) and non-paralyzed non-painful (RH and LH) limbs.

Figure 5.3 shows ERD/ERS during MI of the paralyzed lower limb at electrode location Cz that corresponds to the primary motor cortex of the F. Compared to ERD/ERS before NF, each patient shows a reduced activation after NF. Over the whole time range, the reduced activation was statistically significant in theta and SMR1 bands in PWP1 and in both SMR and theta bands in PWP5. Three patients show significantly reduced activation over particular time and frequency windows.

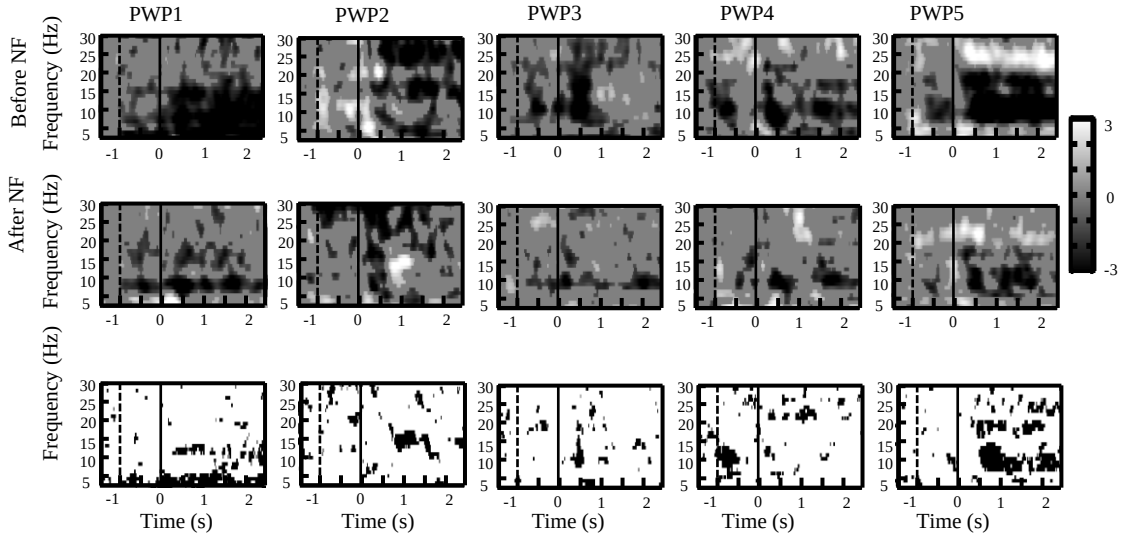


Figure 5.3: ERD/ERS time frequency map at Cz site for each patient before and after NF during MI of F. Figures below show area of statistically significant ($p<0.05$) difference in ERD/ ERS before and after NF. The moment when a warning cue was presented is shown with a dashed line (t=-1 s) and the moment when an execution cue was presented is shown with a solid vertical line (t=0 s).

Figure 5.4 shows ERD/ERS during MI of the upper dominant right limb at electrode location C3 that corresponds to the cortical presentation of RH. Each patient except PWP4 shows significantly reduced ERD; the statistically significant reduction of ERD is time- and frequency- specific for each patient. The PWP4 shows wide spread ERD after NF but

difference in ERD/ ERS (After and Before NF) is significant only around 0.7 s in a frequency range of SMR1 band.

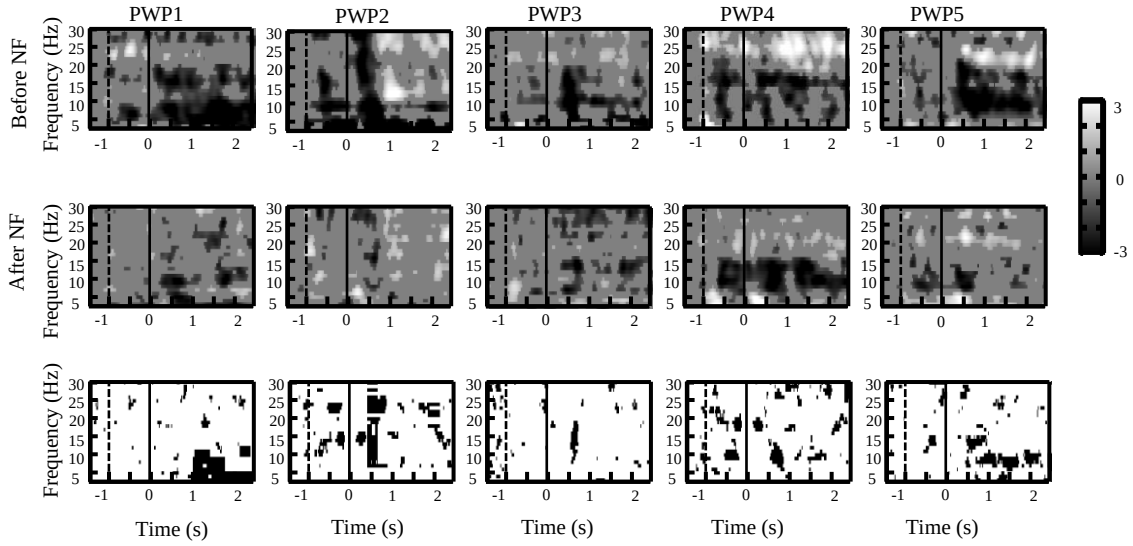


Figure 5.4: ERD/ERS time frequency map at C3 site for each patient before and after NF during MI of RH. Figures below show area of statistically significant ($p<0.05$) difference in ERD/ ERS before and after NF. The moment when a warning cue was presented is shown with a dashed line (t=-1 s) and the moment when an execution cue was presented is shown with a solid vertical line (t=0 s).

Figure 5.5 shows ERD/ ERS during MI of the upper non-dominant left limb at electrode location C4 that corresponds to the cortical representation of the left hand. In PWP4, the significant reduction of ERD is noticed in the SMR1 band only, while in PWP5 the significant reduction of ERD is noticed in SMR1 and SMR2 bands. In PWP2, the significant reduction of ERD is noticed in frequencies above 20 Hz, while in PWP1 and PWP3 the significant reduction of ERD is noticed in the theta band.

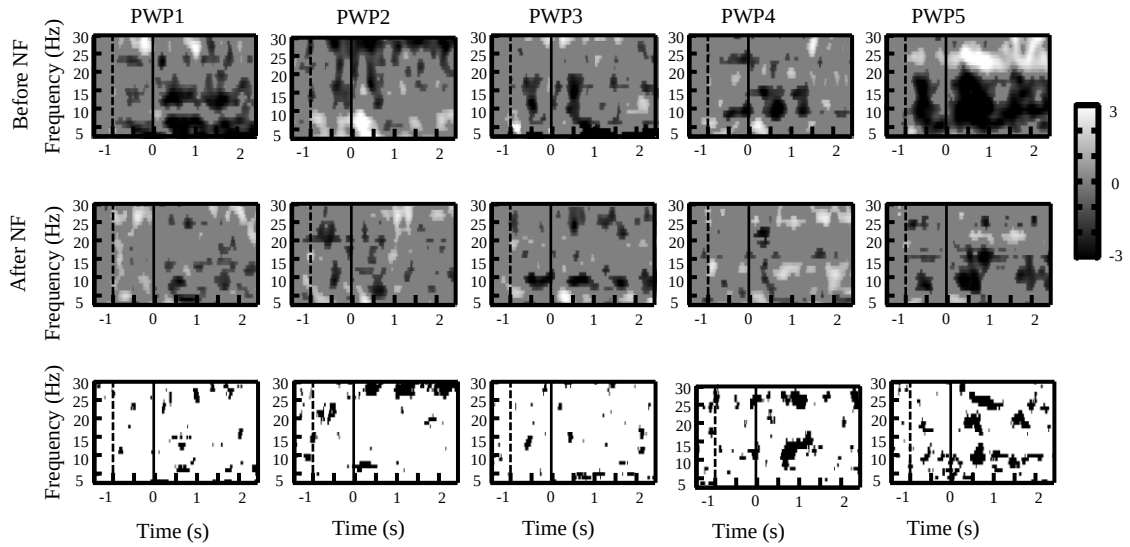


Figure 5.5: ERD/ERS time frequency map at C4 site for each patient before and after NF during MI of LH. Figures below show area of statistically significant ($p<0.05$) difference in ERD/ERS before and after NF. The moment when a warning cue was presented is shown with a dashed line (t=-1 s) and the moment when an execution cue was presented is shown with a solid vertical line (t=0 s).

Figure 5.6 (a) shows ERD/ERS time frequency map of four groups (AB, PNP, PWP_before and PWP_NF) at Cz, C3 and C4 sites during MI of their corresponding limbs (Cz during F, C3 during RH, and C4 during LH). Figure 5.6 (b) shows comparison of ERD/ERS of each two group (AB and PWP_ before, AB and PWP_NF, PNP and PWP_ before, PNP and PWP_NF, AB and PWP_ before, PWP_ before and PWP_NF) during MI of corresponding limbs (Cz, during F; C3 during RH; and C4 during LH).

During MI of F, over the cortical representation of lower limbs (Cz site), the ERD of PWP before NF is significantly stronger than ERD of AB group in theta and SMR2 bands; and also stronger than ERD of PNP group in theta, SMR1, and SMR2 bands. After NF, the ERD of PWP group is comparable to ERD of PNP group in SMR2 band, while it is

comparable to ERD of AB group in the theta and SMR1 bands. Comparing ERD/ERS of PWP group before and after NF, the ERD is significantly reduced after NF in theta, SMR1 and SMR2 bands.

During MI of RH, over the cortical representation of dominant right upper limb (C3 site), the ERD of PWP before NF is significantly stronger than ERD of AB group in theta band; and ERD of PNP group in theta, SMR1 and SMR2 bands. After NF the ERD of PWP is comparable to ERD of AB and PNP groups in theta band, while ERD of PWP group after NF is still stronger than ERD of PNP in SMR1 and SMR2 bands. Comparing ERD/ERS of PWP group before and after NF, the ERD is significantly reduced after NF in theta band, while comparable in SMR1 and SMR2 bands.

During MI of LH, over the cortical representation of non-dominant left upper limb (C4 site), the ERD of PWP before and after NF is significantly stronger than ERD of AB and ERD of PNP groups in theta, SMR1, and SMR bands. Comparing ERD/ERS of PWP group before and after NF, the ERD is not changed in all three frequency bands of interest (theta, SMR1, and SMR2).

In conclusion, during MI of F, the ERD of PWP after NF looks similar to ERD of AB in theta, and SMR1 bands; and ERD of PNP in SMR2 band over the cortical representation of F. The ERD of PWP was reduced after NF in all three frequency bands of interest (theta, SMR1, and SMR2). During MI of RH, the ERD of PWP after NF looks similar to ERD of AB and ERD of PNP in theta band over the cortical presentation of RH. The ERD of PWP after NF was reduced in theta band. During MI of LH, the ERD of PWP after NF was not changed at the cortical representation of LH.

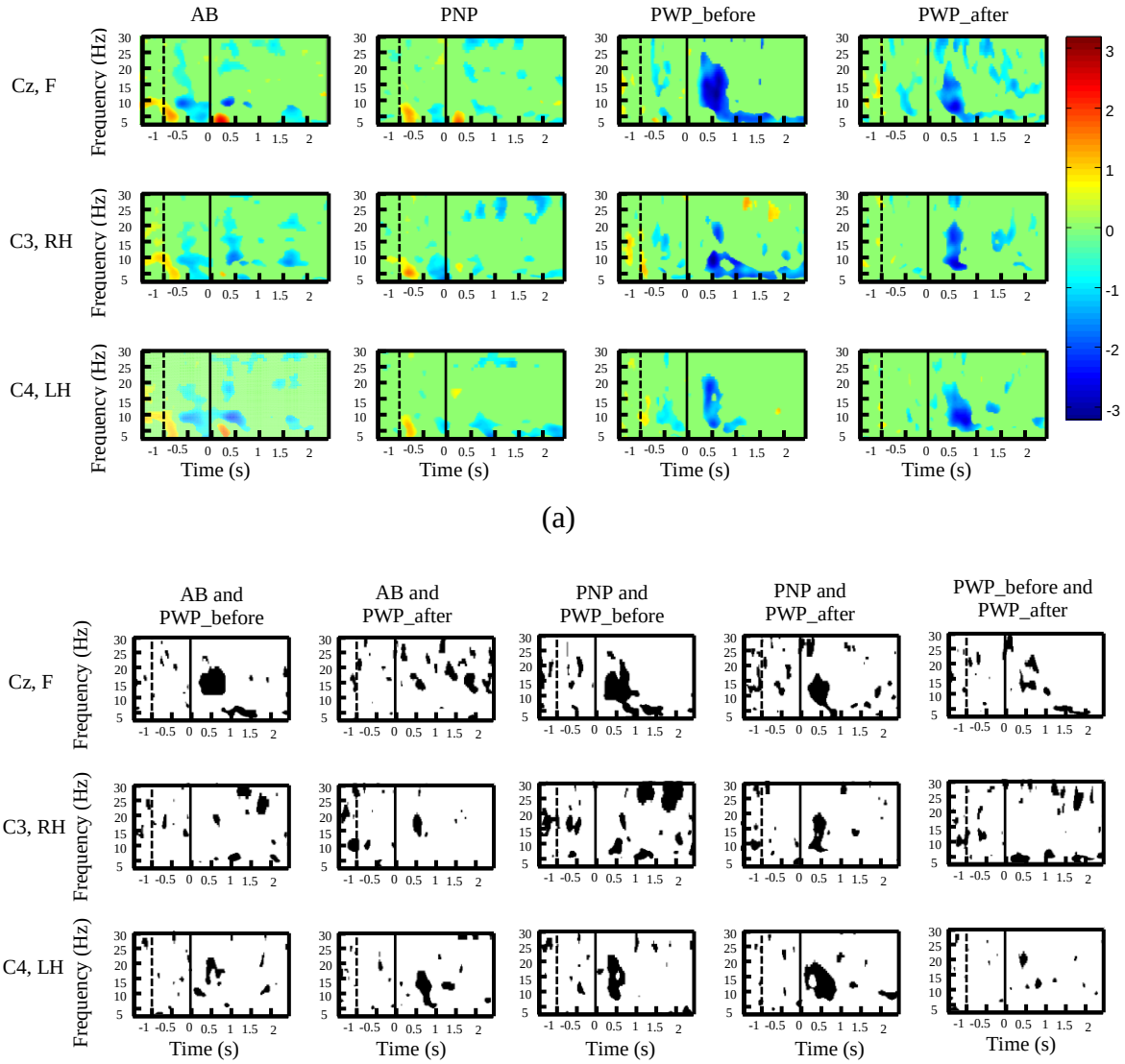


Figure 5.6: (a) ERD/ERS time frequency maps of four groups (AB: column1, PNP: column2, PWP before NF: column3, and PWP after NF: column4) during MI of F at Cz site: first row, during MI of RH at C3 site: second row, and during MI of LH at C4 site: third row. (b) Comparison of ERSP time frequency maps of four groups (AB and PWP before NF: column1, AB and PWP after NF: column2, PNP and PWP before NF: column3, PNP and PWP after NF: column4, PWP before and after NF: column5) during MI of F at Cz site: first row, during MI of RH at C3 site: second row, and during MI of LH at C4 site: third row.

5.4.4. Effect of NF Training on Dynamic Cortical Activation over Whole Cortex

Cortical activation in the theta, SMR1 and SMR2 frequency bands during MI of F, RH, and LH (for a post-cue period t=0.4 –0.8 s) is analysed over the whole cortex before the first and after the last day of NF training.

Figure 5.7 (a) shows ERD/ERS scalp maps averaged over theta band and over the post-cue period t=0.4-0.8 s during MI of RH. In each patient, except PWP4, ERD was reduced mainly over the central and frontal regions. In PWP2 and PWP5 the reduced ERD is wide spread. The reduction in average ERD over five patients is also restricted to the central and frontal regions.

Figure 5.7 (b) shows ERD/ERS scalp maps averaged over theta band and over the post-cue period t=0.4-0.8 s during MI of F. The ERD in two patients (PWP1 and PWP4) was significantly reduced over the whole scalp while ERD of PWP3 was significantly reduced over the frontal area. The change in ERD in PWP2 and PWP5 was non-significant. The reduction in average ERD over five patients is also restricted to the frontal region. The reduction in ERD at the sensory-motor area during MI of the paralysed lower limb was not significant.

Figure 5.7 (c) shows ERD/ERS scalp maps averaged over theta band and over the post-cue period t=0.4-0.8 s during MI of LH. The ERD is significantly reduced only in two patients (PWP1 and PWP5). The reduction in ERD is wide spread in PWP1 while it is restricted to the central and frontal areas in PWP5. The reduction in average ERD over five patients is not significant.

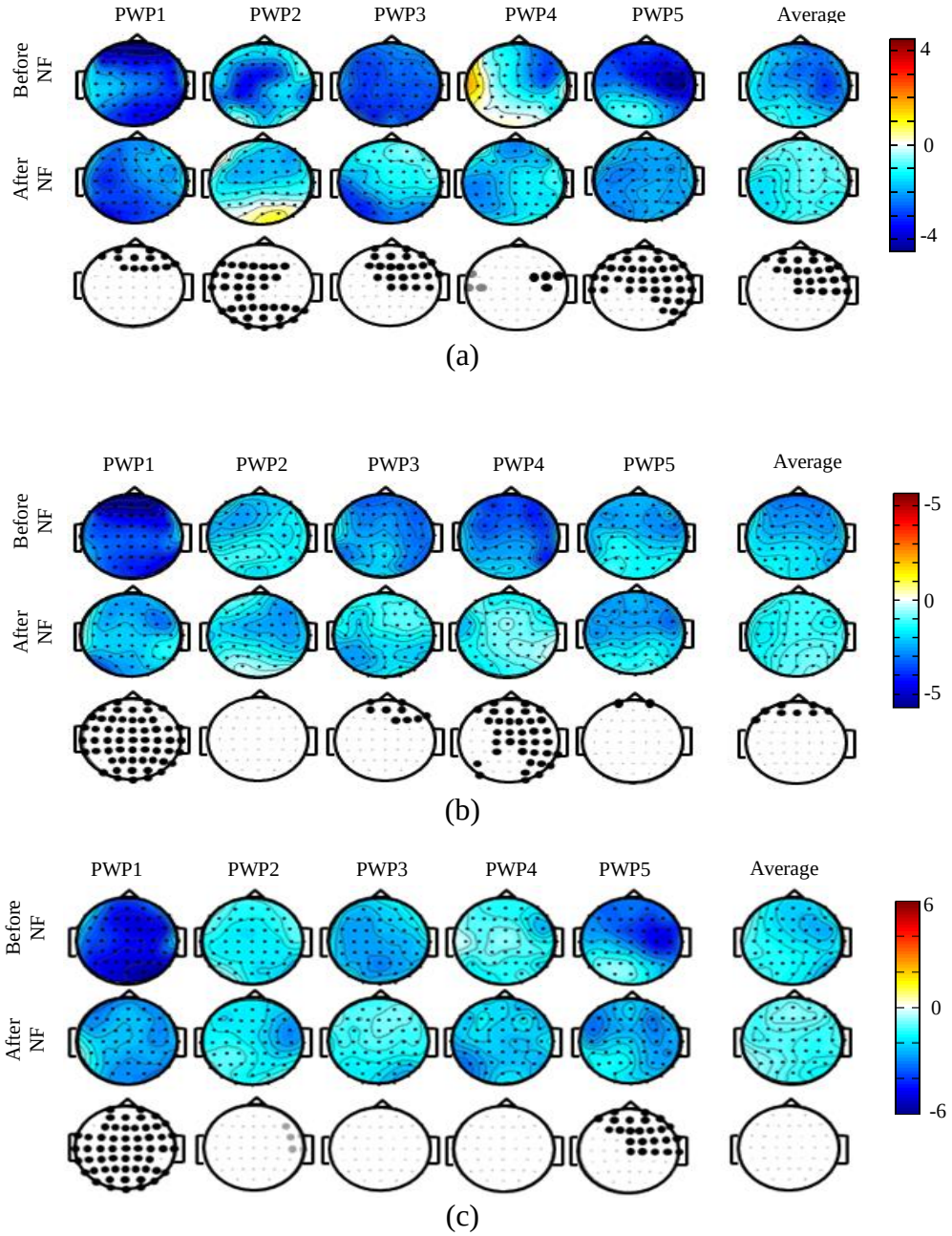


Figure 5.7: ERD/ERS over whole scalp for t=0.4-0.8 s in the theta band for each patient individually and averaged over five patients for different types of MI tasks (MI of RH, subfigure ‘a’; MI of F, subfigure ‘b’; MI of LH, subfigure ‘c’). In each figure, upper row represents ERD/ERS maps before NF, middle row presents maps after NF. Last row on each subfigure shows the areas of statistically significant differences (p=0.05) between scalp maps before NF and after NF. A significant reduction in ERD is shown with filled black circles and significantly increased ERD is shown with grey filled circles.

Figure 5.8 (a) shows ERD/ERS scalp maps averaged over SMR1 band and over the post-cue period t=0.4-0.8 s during MI of RH. After NF, the ERD is significantly reduced in two patients (PWP3 and PWP5) over the sensory-motor and frontal areas, while ERD in PWP2 is significantly reduced over the central and posterior regions of the scalp. PWP1 shows ERS over the occipital area while PWP4 shows ERS over the lateral frontal area. The group average reduction in ERD over five patients after NF compared to ERD before NF is non-significant.

Figure 5.8 (b) shows ERD/ERS scalp maps averaged over the SMR1 band and over the post-cue period t= 0.4-0.8 s during MI of F. After NF, the ERD of PWP5 is significantly reduced over whole head. The ERD of two patients (PWP3 and PWP5) is significantly reduced over the central and frontal regions while ERD of PWP2 is significantly reduced over the frontal region. The reduction in ERD in PWP4 is non-significant. The group average ERD is significantly reduced over the frontal region.

Figure 5.8 (c) shows ERD/ ERS scalp maps averaged over the SMR1 band and over the post-cue period t=0.4-0.8 s during MI of LH. After NF, the ERD of PWP5 is significantly reduced over the whole scalp. The ERD of PWP1 is significantly reduced over the frontal region, while the ERD of PWP3 is significantly reduced over the left lateral hemisphere. The reduction in ERD of PWP2 is non-significant. The ERD of PWP4 is significantly increased over the central and frontal areas. The group averaged ERD is significantly reduced over the central and frontal regions.

The largest change in ERD was noticed over the central and frontal regions during MI of paralyzed lower limb i.e. F and non-paralysed non-dominant hands (LH).

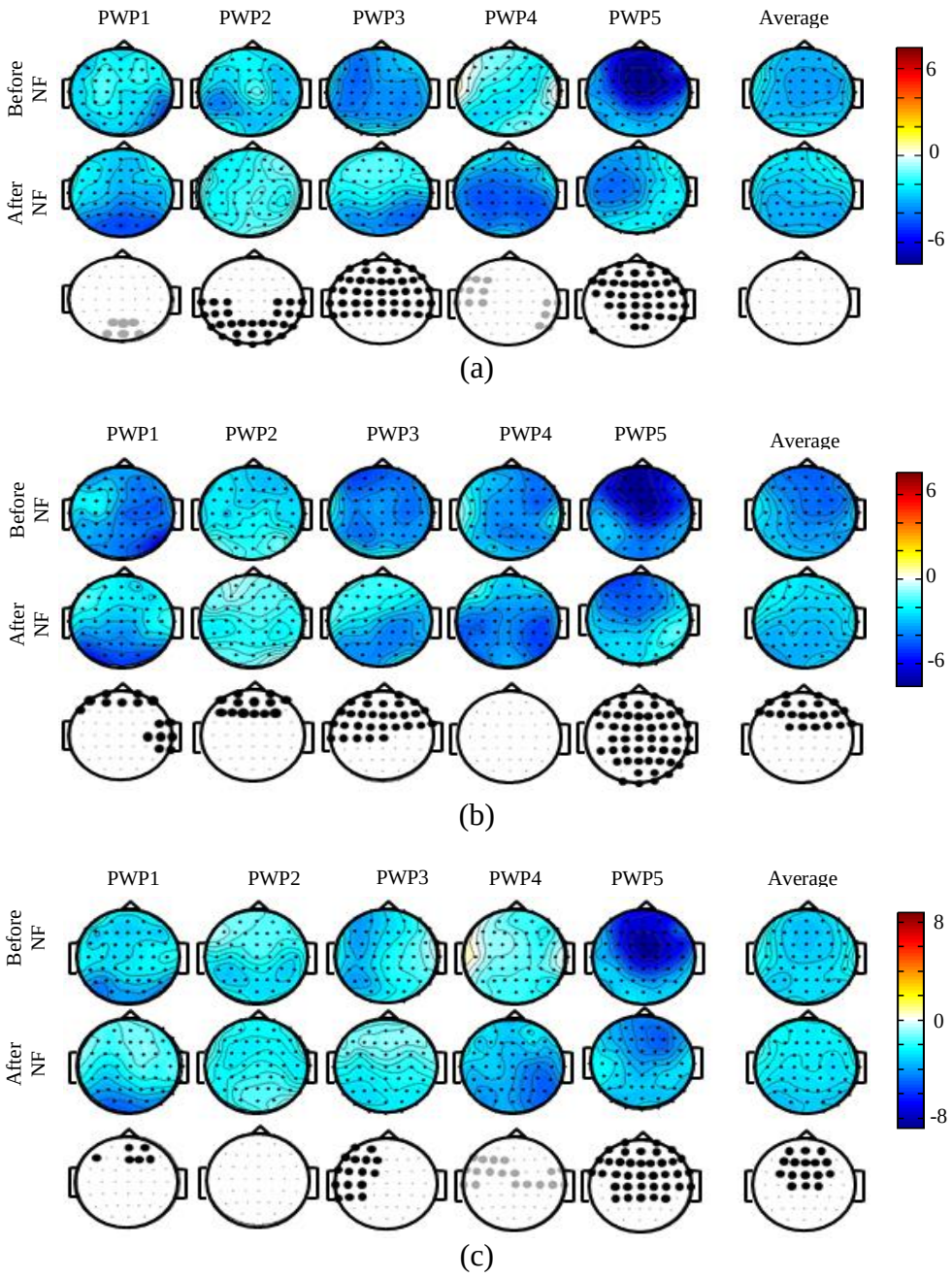


Figure 5.8: ERD/ERS over whole scalp for t=0.4-0.8 s in the SMR1 band for each patient individually and averaged over five patients for different types of MI tasks (MI of RH, subfigure ‘a’; MI of F, subfigure ‘b’; MI of LH, subfigure ‘c’). In each figure, upper row represents ERD/ERS maps before NF, middle row presents maps after NF. Last row on each subfigure shows the areas of statistically significant differences (p=0.05) between scalp maps before NF and after NF. A significant reduction in ERD is shown with filled black circles and significantly increased ERD is shown with grey filled circles.

Figure 5.9 (a) shows ERD/ ERS scalp maps averaged over the SMR2 band and over the post-cue period t=0.4-0.8 s during MI of RH. The ERD after NF as compared to before NF is significantly reduced in three patients (PWP2, PWP3 and PWP5), non-significantly reduced in other two patients (PWP1 and PWP4). The significant reduction in ERD in PWP3 and PWP5 is spread from the centro-parietal to the frontal region, while in PWP2 is restricted to the left frontal area. The reduction in ERD averaged over five patients is non-significant.

Figure 5.9 (b) shows ERD/ ERS scalp maps averaged over the SMR2 band and over the post-cue period t=0.4-0.8 s during MI of F. After NF, the ERD is significantly reduced over the whole scalp in PWP5. The reduction of ERD is significant over the posterior region in PWP3, while it is significant over the central and frontal regions in PWP4. The change in ERD in two patients (PWP1 and PWP2) is not significant. The group averaged ERD is significantly reduced over the frontal and the left central region.

Figure 5.9 (c) shows ERD/ ERS scalp maps averaged over the SMR2 band and over the post-cue period t=0.4-0.8 s during MI of LH. After NF, the ERD was significantly reduced over the fronto-lateral part of right hemisphere in PWP2 and over the fronto-lateral left hemisphere in PWP3. The ERD in PWP5 is significantly reduced over the central and frontal regions. There is no change in ERD in PWP4 while ERD after NF increased in the occipital cortex in PWP1. The average ERD was significantly reduced over the fronto-lateral part of the right hemisphere.

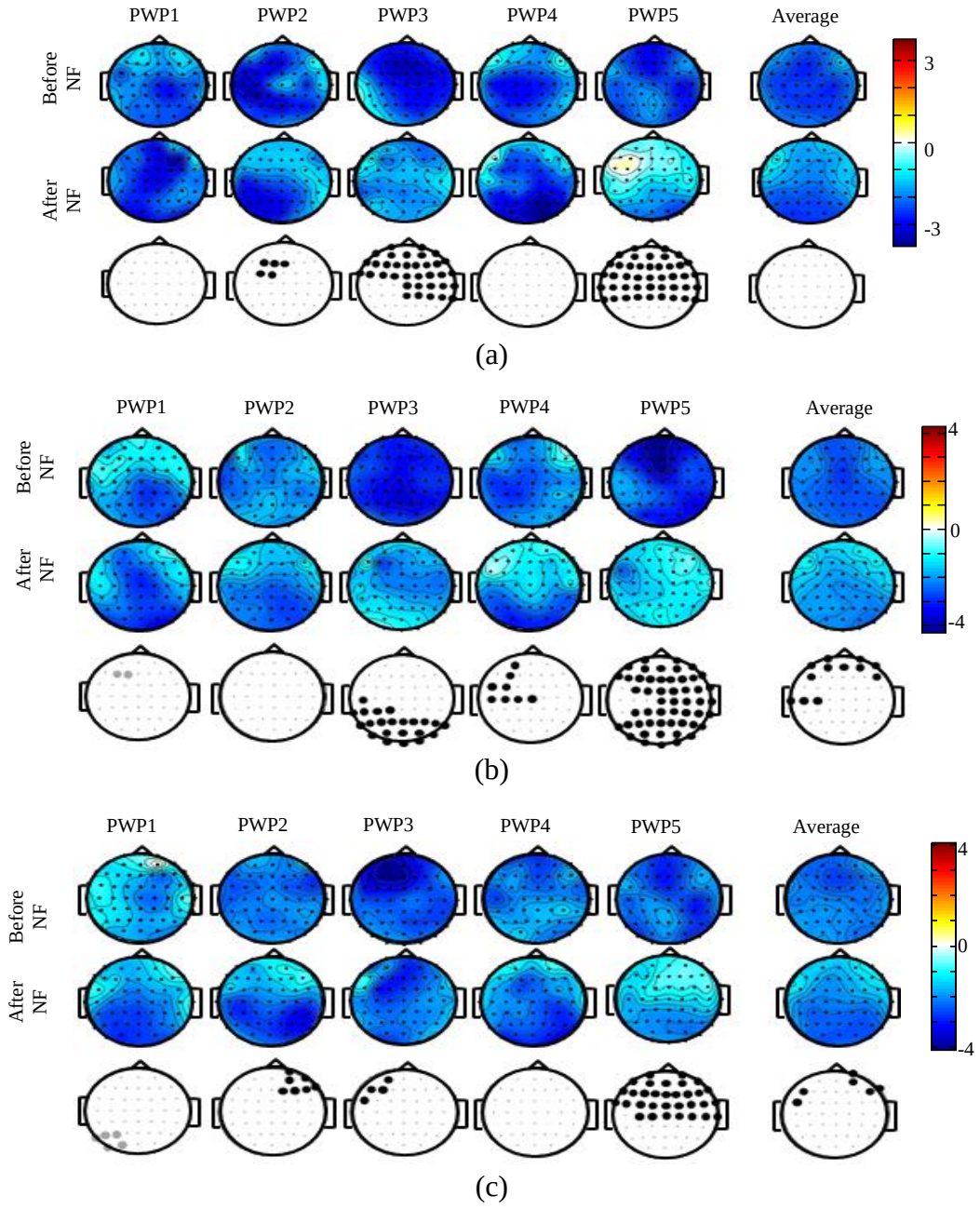


Figure 5.9: ERD/ERS over whole scalp for t=0.4-0.8 s in the SMR2 band for each patient individually and averaged over five patients for different types of MI tasks (MI of RH, subfigure ‘a’; MI of F, subfigure ‘b’; MI of LH, subfigure ‘c’). In each figure, upper row represents ERD/ERS maps before NF, middle row presents maps after NF. Last row on each subfigure shows the areas of statistically significant differences (p=0.05) between scalp maps before NF and after NF. A significant reduction in ERD is shown with filled black circles and significantly increased ERD is shown with grey filled circles.

In conclusion, the intensity of ERD was reduced over the whole scalp but significant reduction of ERD was noticed in central and frontal regions of the scalp. In theta band, this significant reduction of ERD was noticed during MI of RH and F, while in SMR1 and SMR2 bands this reduction of ERD was noticed during MI of F and LH. Common to all, the reduction of ERD was noticed in three frequency bands of interest (theta, SMR1 and SMR2) during MI of paralyzed painful lower limb i.e. F.

5.4.5. Global Effect of NF Training on Cortical Activation over Whole Time

Figure 5.10 shows frequency-specific spatio-temporal changes in ERD following NF treatment over the post-cue period t= 0.4-0.2 s averaged over 0.4 s time windows in three frequency bands (theta, SMR1 and SMR2) during MI of paralyzed lower and non-paralyzed upper limbs.

A change in ERD in the theta band for each type of MI tasks is shown in Figure 5.10 (a). During MI of RH, the ERD is significantly reduced over the central and frontal region for the period t=0.4-0.8 s and for t>1.2 s. In the period t=0.8-1.2 s, the ERD is similar before and after NF. During MI of F, the ERD is significantly reduced over the frontal and centro-frontal regions in the period t=0.4-0.8 s. For t> 1.2 s, the reduction in ERD is wide spread; posterior to anterior region mainly over the right hemisphere. During MI of LH, a significant reduction in ERD could be noticed over some electrode locations around the central cortex. In summary, the spatio-temporal reduction in ERD in theta band can be noticed dominantly during MI of RH and F. This reduction in ERD is widespread during MI of RH while restricted to central and frontal regions during MI of F.

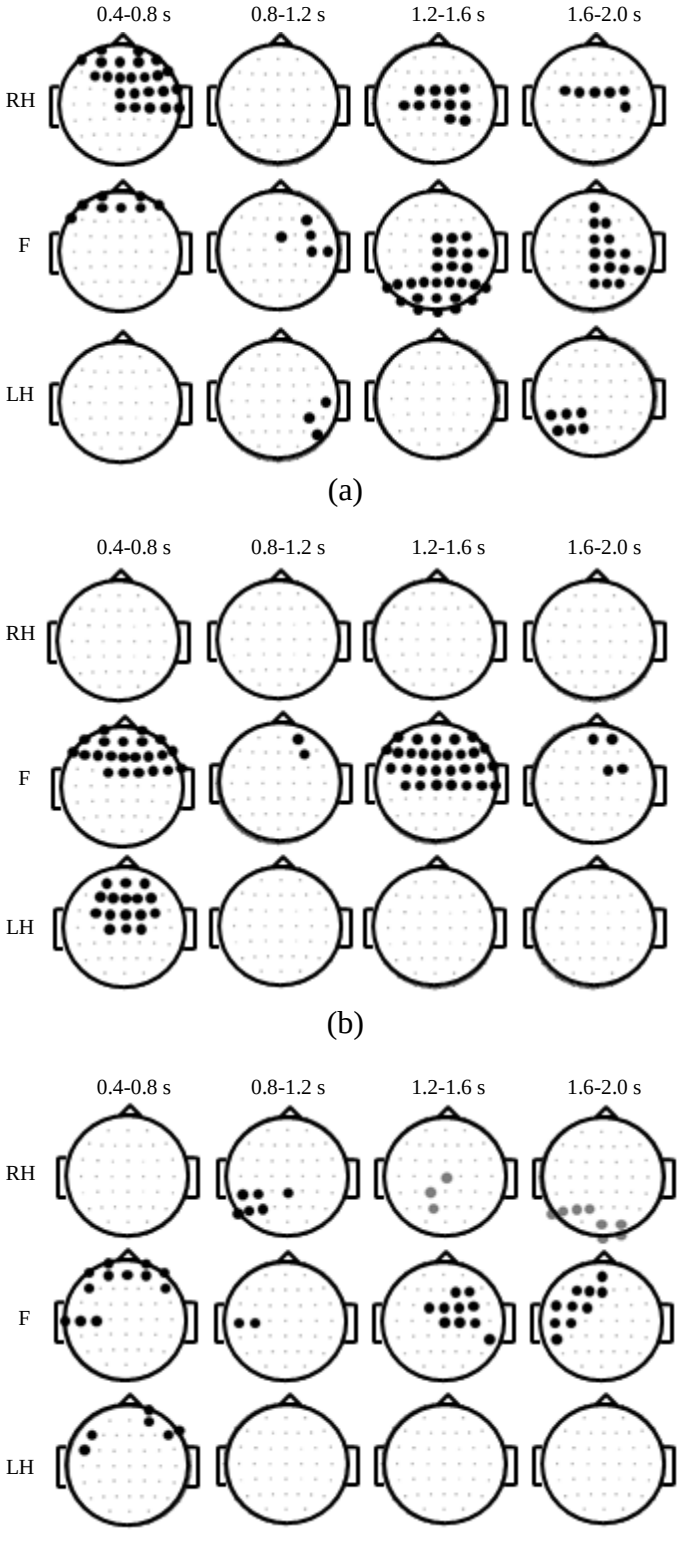


Figure 5.10: Comparison of spatio-temporal change in ERD/ERS of PWP group before the first and after the last day of NF training. Averaged group scalp maps showing statistically significant ERS/ERD between 'Before NF' and 'After NF' conditions in three frequency bands (theta, subfigure 'a'; SMR1, subfigure 'b'; SMR2, subfigure 'c') over four different time windows (0.4-0.8 s; column 1, 0.8-1.2 s; column 2, 1.2-1.6 s; column 3, 1.6-2.0 s; column 4) for three types of motor imagination tasks (RH; right hand, F; foot, LH; left hand). The black filled circles represent significantly reduced ERD, grey filled circles represent increased ERD, and dots represent non-significant change in ERD/ ERS.

A change in ERD in SMR1 during each type of MI tasks is shown in Figure 5.10 (b). During MI of RH, the ERD is similar before and after NF for all time period of interest. During MI of F, the reduction in ERD is significant over the central and frontal regions; mainly for t=0.4-0.8 s and t=1.2-1.6 s. During MI of LH, the significant reduction in ERD can be noticed over the central and frontal regions for a time-period t=0.4-0.8 s. In summary, the significant reduction in ERD is restricted to the central and frontal regions during MI of F for a whole time period of interest and only for t=0.4-0.8 s during MI of LH.

The change in ERD in SMR2 during each type of MI tasks is shown in Figure 5.10 (c). During MI of RH, significant reduction of ERD can be noticed for t=0.4-0.8 s followed by a significant increase in ERD for t>0.8 s in parieto-occipital areas. During MI of LH, the significant reduction in ERD over the frontal part can be noticed only for t=0.4-0.8 s. During MI of F, the ERD is significantly reduced over the central and frontal regions for all time range.

In conclusion, the reduction in ERD over time was noticed during each type of movement for each frequency band. In the theta band, the reduced ERD was pronounced during MI of F and RH; it is mainly over the central and frontal regions. In SMR1 and SMR2 bands, the significant reduction in ERD over all time range was noticed during MI of F and only for t=0.4 to 0.8 s during MI of LH; it is mainly over the central and frontal areas.

5.5. Discussion

The aim of this Chapter was to find changes in spontaneous and evoked EEG activity after long-term NF training. The results confirm that NF training induced changes in the EEG activity at the surface and in deep cortical levels related to pain matrix. In this study, sLORETA analysis was performed on spontaneous EEG data, while cue-based EEG was analysed at the surface of the cortex. The sLORETA in addition to providing spatial information about deeper cortical structures also provided information on frequency content [258].

Influence of NF Training on Spontaneous EEG in EO State: The sLORETA analysis showed that NF training from the surface of the cortex induced changes in relaxed state EEG both at the surface and deeper cortical structures. These cortical areas include S1 and S2 cortices which are involved in the sensory-discriminative evaluation of pain [27], and areas that function in the emotional/affective component of pain, such as the PFC, ACC and IC [29–31], as well as higher-order sensory structures involved in sensory vigilance processing, including the PCC. The reduced activation was noticed in beta1 and beta2 bands, while increased activation was noticed in theta and alpha bands. Statistically significant changes were noticed only in the beta2 band. The non-significant changes in brain activation on group analysis might be due to changes in brain activity in different frequency bands in each subject. In theta band, only a single patient showed statistically significant reduced activity while three patients (PWP3, PWP4 and PWP5) showed statistically significant increased activity. PWP2 showed statistically non-significant increased activity. In alpha band, three patients (PWP2, PWP4 and PWP5) showed statistically significant increased activity, while PWP3 showed significantly reduced

activity at the surface and in deep cortical levels. The PWP1 showed statistically non-significant reduction in activity. In beta1 band, three patients showed non-significant change in brain activity. PWP3 and PWP4 showed statistically significant reduced activity. In beta 2 band, the reduction of activity was statistically significant in three patients over all pain related areas while the reduction was significant over the frontal and insular cortices in PWP1 and PWP4. The changes in brain activity in deeper cortical areas correspond to results of fMRI and PET studies showing cortical areas affected by pain [87,245,247 254,255]. Increased alpha power on the surface of the cortex has also been reported in a recent NF study for pain management in SCI population [142] and in other pain management studies such as hypnosis and meditation [353]. A reduced beta band power after pain management has been reported only in one NF study [374]. Increase in the alpha power in open-eyes state might be associated with decrease in CSE demonstrated in TMS and NF study of Ros et al [423]. The increase in theta band power has been reported after reduction of pain with hypnosis treatment [353]. This increased theta band power might be associated with the analgesic effect of NF training similar to antiepileptic, antidepressants and antispastic drugs which also increased activity of theta band [274,412,413].

Difference in EC and EO Activity: The difference in EC and EO activity after NF was increased in beta1, beta2 and in 2-30 Hz bands, though significant increase was noticed only over a single voxel (BA 32) in beta2 band. In the alpha band, the difference in EC and EO activity was increased after NF over all regions except the frontal cortex and ACC. In theta band, the difference in EC and EO activity after NF was non-significantly reduced.

Comparing Effect of Scalp EEG NF with sLORETA and fMRI Feedback: Pain management studies based on fMRI and sLORETA feedback mainly focussed on

modulating the activity of the rostral part of the ACC (BA 24), DLPFC (BA 9) and IC (BA 13) [150,198,372–374]. In our study, NF training resulted in reduced activation in BA 24, BA 9 and BA 13; mainly in 20-30 Hz and 12-15 Hz bands. This demonstrates that scalp EEG based NF training with a single channel produced effects similar to that reported in 19 channels sLORETA and expensive time-delayed fMRI feedback.

Influence of NF on Dynamic Cortical Activity: NF training did not only induce effect on spontaneous EEG but also changes evoked EEG activity. The reduced ERD after NF was not restricted to the cortical areas from which patients received NF training (Chapter 4) and to the cortical areas corresponding to the MI tasks (Cz for F MI, C3 for RH MI, and C4 for LH MI) but was spread over the whole scalp; the significant reduction was mainly observed in the frontal and central regions. This significant reduction was noticed over all time range in all three frequency bands (theta, SMR1, and SMR2) during MI of F (paralyzed and painful lower limb). During MI of RH, the reduced ERD over all time was noticed only in theta band, while this reduced ERD during MI of LH was restricted to only t=0.4-0.8 s in SMR1 and SMR2 bands. The reduced dynamic activation over the whole scalp following reduction of pain is an expected phenomenon, as shown in results of Chapter 3 that PWP group before receiving NF training had stronger ERD than both AB and PNP groups. This demonstrates that reduced brain activity (reduced ERD) after NF might be associated with reduction in pain intensity or vice versa.

5.6. Conclusion

NF training induced long-term changes in the brain activity in relaxed state and during MI of non-painful limbs and limb perceived as being painful. In relaxed state, a statistically

significant reduction of activity was noticed at the surface and deep cortical areas known to be ‘pain matrix’. In task-related EEG, the reduced ERD was noticed during MI of painful and non-painful limbs; mainly during MI of lower limb (F) perceived as being painful.

Chapter 6. General Discussion

This study reported about changes in the relaxed (state) and dynamic brain activity in paraplegic patients following reduction of chronic central neuropathic pain (CNP) with long-term neurofeedback (NF) training. This study was divided into three phases: Phase 1 (Diagnostic phase, Chapter 3), Phase 2 (Treatment phase, Chapter 4), and Phase 3 (Neurological outcomes, Chapter 5).

The objective of Phase 1 (Diagnostic phase) was to detect frequency dependant dynamic oscillatory signatures of CNP in paraplegic patients. This objective was achieved by comparing electroencephalogram (EEG) of three matched groups (able-bodied: AB, paraplegic patients with CNP: PWP, and paraplegic patients without pain: PNP). To date, EEG studies that aimed to compare the brain activity of paraplegic patients with pain with the brain activity of the able-bodied population are limited to task-unrelated eyes open (EO) and eyes closed (EC) relaxed states [46,257–259,262]. Therefore, these studies only provides frequency information, failing to provide time-dynamics information. To the best of our knowledge, this was the first EEG study that compared not only spontaneous state EEG activity, but also compared the task-related EEG activity of three groups (AB, PNP and PWP). The results showed that the presence of CNP leads to frequency-specific EEG signatures both in a relaxed state and during motor imagery (MI) tasks. Spinal cord injury (SCI) patients with and without CNP showed significantly different signatures of spontaneous and evoked EEG activity. In the relaxed state, CNP is characterised by an increase in power in the theta and alpha bands and a shift in the dominant alpha frequency towards lower values. During MI, CNP is characterised by a dynamic, frequency

dependant, increase in event-related desynchronization (ERD) over the sensory-motor and parietal cortex, which is not somatotopically restricted to painful parts of the body. The spatially distributive strong ERD of the PWP group was not limited to a certain time period, but was spread over the period after the imagination onset.

There were two objectives of Phase 2 of the study. The first objective was to test large numbers of training sessions of different NF protocols (Protocol 1 to Protocol 4) for the treatment of CNP in paraplegics. The second objective was to find the immediate global effect of NF training on the power spectral density (PSD) and coherence among each channel. The NF protocols were created based on the results found in Chapter 3, past neuroimaging studies defining the cortical areas involved in pain, and NF and neurostimulation studies for the management of pain [243,248,249,346,368]. Five out of seven patients received 20 or more NF sessions. All five patients achieved a statistically significant reduction of pain and four patients (except PWP1) reported a clinically significant (>30 %) reduction of pain. The modulation of PSD followed by clinically and statistically significant reductions in pain showed that frequency dependent EEG based CNP signatures can be used to develop NF protocols. However, a study which will recruit a larger number of patients is required to further confirm the efficacy of NF training for the treatment of CNP. Out of four tested protocols, Protocol 4 was the most effective in reducing pain following modulation of PSD. The modulation of PSD and coherence over the whole cortex, in a sixteen channel NF system, demonstrated the NF training induced global effect. Furthermore, patients learned the mental strategy to modulate the PSD without feedback. The decrease in the alpha band PSD during mental task (maths and reading) and increase in alpha PSD during NF demonstrates that modulation of PSD may be an effect of voluntarily modulation of EEG PSD. This was further confirmed by placebo

sessions in which EEG of a pre-recorded session was shown as a feedback. The modulation of PSD in EC state and modulation of PSD with Protocol 1 demonstrates that the reduction of pain may be real rather than effect of placebo.

The objective of Phase 3 (Chapter 5, objective 4, neurological outcomes) was to find long-term changes in the EEG activity in pain related cortical presentations following NF training. This was achieved by comparing the EEG of patients with CNP (PWP) before the first and after the last session of NF training. EEG was recorded in relaxed EO and EC states, and during MI of paralyzed painful limb (F) and non-paralyzed non-painful (right hand: RH, and left hand: LH) limbs. Spontaneous EEG activity was analysed both at the surface of the cortex and at the deeper cortical structures, while evoked EEG was analysed on the surface of the cortex only. The results showed that NF training modulates brain activity not only in the relaxed state, but also during MI of upper and lower limbs. The reduced EEG activation in the EO state was noticed in beta1 and beta2 bands, while increased activation was noticed in the theta and alpha bands. Statistically significant changes were noticed only in the beta2 band. The reduction in ERD was topographically distributed, mainly over the sensory-motor and frontal regions of the brain. A significant reduction in ERD was noticed in all three frequency bands (theta, SMR1 and SMR2) over the whole time range during MI of paralyzed painful lower limb i.e. F. This significant reduction in ERD was noticed in the theta band only over whole period of MI of RH, while for early times (t=0.4-0.8 s) only in SMR1 band during MI of LH. After NF, the ERD of PWP was similar to the ERD of AB in the theta band during MI of F and RH, and in SMR1 band during MI of F. The ERD of PWP was also similar to the ERD of the PNP group in the theta band during MI of RH and in SMR2 band during MI of F.

6.1. Suggestions for Further Improvements of NF Protocols

Alpha/theta feedback in EO state: In the Phase 2 of the study, alpha was selected as a reward band in order to shift peak frequency from lower frequencies to high frequencies. In addition, the theta band was suppressed due to increased theta power in PWP compared to the PNP group. This suggests that patients can be trained to increase the alpha / theta ratio rather than to modulate theta and alpha activities simultaneously. However, results of NF training showed that patients did not necessarily follow a rule in both the theta and alpha band simultaneously. This demonstrates that it may be difficult to follow rules if the ratio of both bands is shown as a feedback. Another approach is to show peak frequency as a feedback and ask patients to move the peak frequency towards higher values similar to the study of Angelakis et al. [429].

Feedback from the Frontal Site: Analysis of 16 channels PSD during NF training showed that the effect of NF training was strong in the frontal sites. Also, the reduced ERD after NF training was strong in the frontal site which suggests providing feedback from the frontal site.

Neurofeedback from Deep Cortical Structures: Though we trained patients over the right hemisphere (C4 site) for most training days, the reduced activation after NF was strong on the left hemisphere in the beta band. This reduced activation was noticed mainly in the deep cortical areas related to pain, emotional and sensory vigilance processing. This suggests to standardized low resolution brain electromagnetic tomography (sLORETA) feedback studies on pain management to select beta as an inhibit band and provide feedback from the voxels over the left side of the limbic lobe. The effect of scalp EEG-based NF training up to the deeper cortical structures could also assist functional magnetic

resonance imaging (fMRI) NF studies to specifically target brain areas that are shown to change cortical activation after reduction of pain with NF training.

Connectivity-based Feedback: Although, the analysis was not performed to find the connectivity changes before the first and after the last day of NF training (long-term change in connectivity). The coherence analysis performed for sixteen channels experimental paradigm suggested to create NF protocols based on the connectivity strength/ weakness using both scalp EEG and LORETA feedback; mainly targeting the pain related surface and deep cortical areas. In an analysis of 16 EEG channels during NF training, the largest changes in connectivity were noticed in the beta2 band. This change in coherence was patient and electrode site specific. The connectivity changes may allow better understanding of the effect of NF training on structural changes in the brain in patients with pain.

6.2. Suggestion for NF Placebo of Pain Treatment

A sham protocol in repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) studies is introduced by changing the position of the coil and intensity of current. The effect of rTMS or tDCS can be noticed from the first session. Therefore, the sham group does not need to attend many sessions to test its influence on pain. EEG based NF training is based on voluntarily effort to learn to control brain activity in order to manage pain; it requires a large number of sessions to learn to modulate brain activity. The number of sessions is based on patients' learning ability. It would not be ethical to ask patients to attend these large number of NF sessions for a sham treatment.

Also failure to reduce pain might discourage patients in the sham group to continue training.

Placebo effect in NF training can be performed in three ways: (i) by providing NF from the cortical location and/or frequency bands which are neither a part of the 'treatment NF protocol' nor a part of the 'pain matrix', (ii) by providing NF from a the cortical location and/or frequency bands which are part of the 'treatment NF protocol' but not a part of the 'pain matrix', (iii) by providing pre-recorded NF session as a feedback.

In the former case, the effect of NF training might fail for two reasons: a trainee might not be able to modulate the EEG from the novel, untrained site or a trainee could modulate EEG by using 'placebo' protocol but the desired effect of training would fail. If a trainee cannot modulate EEG using the 'placebo' protocol, then one can only compare the effect of voluntary modulation of EEG versus no voluntary modulation of EEG, but cannot ascertain if a 'treatment' NF protocol is optimal. If one can prove that a trainee can modulate EEG during 'placebo', but the desired effect of training is lacking, then this can provide evidence that NF training protocol used for 'real' treatment is more effective than the 'placebo' protocol. To prove this, patients have to be trained to modulate the PSD at this site. In this study, with placebo feedback from the occipital (Oz) site in EO state, patient did not report reduction of pain and was not able to modulate the PSD in a desired direction. However, immediately after the placebo test, patient report reduction of pain with Protocol 4 feedback. Therefore, with this placebo test, it can be shown that voluntary modulation of PSD with Protocol 4 is an effect of patients learning ability to modulate the PSD and is related to reduction of pain, but it cannot provide information whether C4 was better site than Oz for training.

In the second case, the modulation of PSD without reduction of pain can provide evidence that NF training protocols that are designed to target the 'pain matrix' for the reduction of pain are more effective than protocols that do not target 'pain matrix'. In this study, patients did not report reduction of pain following modulation of PSD in the desired direction with feedback from the occipital site in EC state on all training days. However, immediately after EC feedback, patients reported reduction of pain with Protocol 4 feedback. Therefore, this placebo test can provide information that C4 site (Protocol 4) compared to Oz site (feedback in EC state) is more effective in reducing pain.

In the case of a pre-recorded NF session, a trainee cannot voluntarily modulate EEG; this protocol is only testing whether the voluntary modulation of brain activity really produces a desired effect. In a case that trainee already learned NF strategy and can apply it even without a feedback, a placebo test using a pre-recorded session might not be effective.

6.3. Proposed Mechanisms of NF for Pain Management

NF and Corticospinal Excitability (CSE): The ERD is associated with a decrease in neuronal synchrony, and is believed to be generated by the thalamo-cortical and/ or cortico-cortical loop [406,441]. Increased corticospinal excitability (CSE) and reduced intracortical inhibition (ICI) in pain and thalamic lesion [442,443] are associated with an increased ERD [444–446]. Therefore, in our study, the reduced ERD after NF may be associated with reduced CSE and increased ICI. Furthermore, the reduced hyper excitability (reduced ERD), increased ICI and reduced CSE may be linked to increased activity of g-amino butyric acid, which is mainly reduced in chronic pain [76,77]. In other

words, it can be hypothesised that NF training may reduce central sensitization in patients with CNP.

NF and Thermoregulatory Function: All patients frequently reported a pleasant sensation of warmth in the areas of the body perceived as 'painful' that preceded pain relief and lasted for several hours following NF treatment. As some patients had a complete SCI and could not possibly feel real changes in temperature, this sensation was most likely being generated in the brain. The central disinhibition due to reduced activity of the posterior part of the ventral medial nucleus of the thalamus caused thermo-sensory loss, thus contributing towards development of pain [76,81]. The pleasant warm sensation followed by reduction of pain and reduced cortical activity indicates that NF training may activate VMpo (thalamic nuclei responsible central integration of pain and temperature [42]), thus reducing thermo-sensory loss and central disinhibition. In other words, it can be hypothesised that NF training may have an effect on thermoregulatory function which supports the belief that pain is not only a feeling but also a behavioural drive that signals a homeostatic imbalance [42].

NF and Thalamo-Cortical Dysrhythmia (TCD): The shift in dominant frequency towards higher frequencies and a reduction of pain following NF training is in accordance with EEG studies showing slowing-down of theta-alpha peak frequency [46,257–259,262]. The increased difference between EC and EO (EC-EO) activity in the relaxed state, following a reduction in pain intensity, is in accordance with EEG studies showing reduced activity between EC and EO state in SCI patients with pain compared to SCI patients without pain and able-bodied groups [46,257–259,262]. TCD is characterized by a shift in dominant frequency towards lower frequencies [83,84] and reduced EEG activity between EC and EO state [262].

Following NF training, the shift in dominant frequency towards higher values and increased difference between EC and EO EEG activity demonstrates that NF training may also influence TCD.

ERD is associated with an enhanced thalamocortical transfer (sensory gate to the cortex) [441]. The results of our study (Phase 3) showing reduced ERD after NF together with Lopes [441] findings demonstrate that NF training may also modulate (reduce) activity of thalamo-cortico-thalamic circuits, which may also reduce hyperactivity of the thalamic neurons. Hence, it can be assumed that after NF training thalamic integrative circuits could not amplify nociceptive signals at the same rate and slowed down the amount of low threshold calcium spike burst which also controls TCD [82].

It has been shown that surgery of the central lateral nucleus of the thalamus control TCD reduced pain and activity in anterior cingulate cortex (ACC) [258,447]. In our study, reduced activity has been noticed in ACC which further supports a hypothesis that NF regulates TCD.

NF and Long-term Potentiation (LTP): It has been reported that patients with pain show reduced widespread connectivity mainly in the default mode and attentional networks [448,449]. Based on findings of the NF study, which showed a positive relation of default mode netork connectivity and resting alpha [366], and results of our study showing the immediate effect of NF training on connectivity changes among 16 channels, we expect that NF training may induce long-term connectivity changes. This should be confirmed by analysing changes in connectivity of resting state multichannel EEG before the first and after the last day of NF which is outside the scope of this thesis. The knowledge of

connectivity changes may allow greater understanding of the pain mechanism at supraspinal level in terms of LTP.

6.4. Limitation of the Study

Ideally, Phase 1 of the study should include another group of patients with CNP without paralysis or amputation to assess the separate effect of pain as the paralysis and amputation itself affect EEG. Furthermore, we restricted our analysis to the surface cortical areas only, defined by the 10-10 system. Because of the nature of EEG measurement, we could only record the activity of surface cortical areas involved in the processing of chronic pain, such as the sensory-motor cortex and to an extent the frontal cortex. The source localisation techniques could be used to estimate ERD of deeper structures, such as ACC and insular cortex (IC) [258]. Analysis of deeper cortical structures could also provide spatial information about areas of strongest theta, alpha and beta activity and could test whether the sources of different brain rhythms have spatially different locations. Surface cortical areas correspond to the areas which were typically targeted by non-invasive neuromodulatory treatments of pain.

Phase 2 was a pilot study, therefore tested on only five patients without a control group. Therefore, it is necessary to test the effects of NF training on a larger population with chronic NP in both SCI and non-SCI patients.

The custom made NF system developed in this study was tested on four healthy people as a part of an MSc thesis by another student [450]. These results are not presented in this thesis, however, subjects were able to modulate the PSD in all three frequency bands; although

they followed a protocol in the theta band for most of the training day. In this study and study on healthy population (MSc project), the performance of system was not tested with different window size for all training protocols. It was found with PWP2 that the small window size made it hard for a patient to follow the change in PSD in real time with Protocol 4.

Patients were not examined using standard clinical sensory tests for neuropathic pain, such as allodynia, hyperalgesia or quantitative sensory testing to determine thermal detection and pain thresholds or pinprick and light touch scores. Furthermore, we did not measure spasticity before and after treatment, though patients verbally reported reduced spasms.

Based on increased dominant frequency, we proposed that NF training may enhance cognitive functions [429]. Therefore, it is necessary to test patients with a Go/ No-Go task before and after the treatment to confirm whether NF training enhances cognitive performance in PWP.

Mechanisms of NF in pain management (section 6.3) should be explained by taking into account changes in the activity of the surface and deeper cortical level. Although we propose some mechanisms of action, we did not test functions of CSE and ICI using TMS when investigating the effect of NF training on central sensitization. Similarly, we did not assess changes in the thalamus when investigating the effect of NF training on TCD and thermo-regulatory functions. Furthermore, we did not find connectivity changes in the pain related surface and deep cortical areas while investigating the phenomena of NF training and LTP. Our conclusions were therefore mostly based on drawing a parallel between the effect of reduced pain following NF training and the known effect which CNP has on

modulation of the activity of the cortex. We also looked at the effect of other interventions (e.g. surgery) for the reduction of CNP and their hypothesised mechanism of action, and tried to correlate previously reported changes in surface cortical EEG with the results of our study.

6.5. Recommendations for Future Work

EEG based BCI is often designed for the SCI population to control the external environment based on the ERD. The strong and spatially distributed ERD noticed in pain group patients in Phase 1 of the study inform that MI based BCI performance may be better in PWP compared to PNP. However, similar to the study of Gustin et al. [87], two SCI patients with pain in Phase 1 of this study reported increased pain when performing MI.

Neuromodulatory approaches aim to modulate brain activity and typically target sites in the motor cortex, indirectly influencing cortical areas involved in the pain matrix [361]. However, the choice of stimulation site and frequency of stimulation is still a matter of debate. The frequency-specific dynamic oscillatory signatures of CNP (Chapter 3) can assist in designing more effective rTMS, tDCS, and NF treatment interventions for the treatment of CNP. We hypothesise that the areas of largest ERD, i.e. most active during motor imagery may be the most responsive to neuromodulatory treatments. Due to the nature of EEG recording we cannot be certain of the contribution of different cortical areas to the recorded ERD. However, theta, alpha and beta ERD showed a distinctive spatial distribution which indicates that for different stimulation frequencies of rTMS there may be distinctive optimal cortical areas. Finally, our results indicate that in paralyzed patients,

location of the most reactive cortical area may not be the same as in the other patient groups suffering from CNP due to a posterior shift of strongest ERD.

The results of the Chapter 4 provide evidences that protocols for NF training for the management of pain can be designed. However, controlled and crossover studies with a large number of patients should be performed to further confirm the efficacy of NF for pain management. In a controlled study, the effect of NF training can be compared with other interventions, or patients in that study can be split into different groups receiving feedback with different protocols and receiving feedback of other subjects EEG. In a crossover study, different NF protocols can be tested on all subjects as performed in Phase 2 of this study. However, the number of sessions and order for each protocol should be in a defined manner. These controlled and crossover studies can also help to better understand the placebo effect of NF training on reduction of pain.

A study by Jensen et al.[29] reported the effect of a single session of several neuromodulation techniques, including hypnosis, meditation, tDCS and NF. They found a very moderate effect of NF on reduction of pain and suggested hypnosis as a preferred neuromodulation technique for the treatment of CNP. It would be worthwhile to compare the influence of NF, tDCS and rTMS to reduce pain in a single study. This would further confirm the mechanism of neuromodulation techniques for pain management. For this kind of large study, we suggest to have more treatment sessions for the NF group than tDCS and rTMS groups.

Although the effect of different protocols in Chapter 4 (Phase 2) on pain intensity was assessed, the results of this chapter demand to test more protocols (section 6.4). We could assess the effect of our NF system and protocols on heterogeneous pain population. In the

SCI population, it is necessary to test the effect of NF training separately for complete and incomplete SCI patients because some patients reported a pleasant warm sensation. A NF study on complete patients only would exclude the effect of sensory pathways on this sensation.

All patients in this study were paraplegics with chronic pain; it should be expected that a similar effect could be achieved in tetraplegic patients with CNP. All patients in this study had CNP for several years. It has been shown that when comparing to acute pain, chronic pain produces anatomical structural changes [86,451] and involves additional cortical structures. Applying NF with patients who experiences this pain for a shorter period of time may reveal different EEG responses and may require a smaller number of NF sessions. In this study, we provided NF from sensory areas which are involved in the processing of both acute and chronic pain, so we believe that similar training sites would be effective in patients who experienced pain for a shorter period of time. The only limitation to this study would be that it is typically required that patients experience pain from 3-6 months before it can be classified as chronic and reliably identified as a CNP.

Previous studies on chronic pain showed that it influences general concentration. To find the effect of NF training on cognitive task, a GO/ NO-GO task, or some other test measuring concentration, could be introduced before and after the training [429].

We proposed mechanisms of NF for pain management based on reduction in ERD and changes in the relaxed state EEG. Therefore, the evidence for the proposed mechanism can be provided by establishing studies aimed to examine changes in the brain activity at sub-cortical structures such as the thalamus. The assumption that reduced ERD is associated

with reduced CSE and increased ICI can be confirmed by designing studies investigating these factors using TMS.

Further studies are needed to assess the effect of NF on spasm, achieved by applying some of standard test such as Modified Ashworth scale [452] or by measurement of H-reflex [453]. As we noticed that NF training reduced ERD in pain patients, this suggests that designing a protocol in a direction that increased ERD may help to improve MI based BCI performance of SCI patients without pain.

Regarding the data processing of the current data set, it would be worthwhile to define the deep cortical structures involved in pain. Furthermore, analysis of coherence among three groups (able-bodied, PWP and PNP) could beuseful in creating a NF protocol based on strengthening/weakening connections between different areas of the cortex. Also, we try to find changes in default mode network connectivity during NF (immediate effect) and before the first and after the last day of NF training (long-term). We will also try to find the effect of NF training on changes in the flow of information in short- and long- term. We also plan to study inter-frequency relation using bicoherence which help to better understand changes in activation of inhibitory cortical neurons at different frequencies.

6.6. Contribution to the Literature

- Previous studies lack frequency-specific dynamic information of the brain while assessing brain activity of patients with CNP. This study overcomes the above mentioned drawback in previous research and provides evidence that presence of CNP leads to EEG signatures in a relaxed state and during MI (dynamic oscillatory activity).

The results of the Phase 1 of this thesis inform why similar effects have been observed from rTMS and tDCS while stimulating different cortical areas. It could assist in designing more effective protocols for the treatment of pain with rTMS, tDCS, and NF.

- This is the first study showing the effect of different NF protocols on CNP and provides evidence that numbers of training sessions are negatively correlated with reduction of pain.

- This study shows an immediate global effect of NF training on feedback parameter i.e. PSD and untrained parameter i.e. coherence. The comparison between monopolar and laplacian feedback derivatives provides evidence that global change in EEG activity is an effect of NF training. Furthermore, it is shown that patients modulate both local and widespread alpha activity.

- The immediate and short-term effect of NF training on whole EEG PSD spectrum is shown for a single representative day. The study also changes in baseline EEG PSD over all training days. Also, the effect of training on dominant frequency is shown for a single training day and over consecutive training days.

- The evidence of patients learning ability to modulate the EEG PSD without feedback is also shown in this thesis. It is noticed that patients modulate the PSD in the same direction as with feedback.

- Although, there is no separate control group, the study provides overview of testing placebo effect in terms of modulation of EEG only and in terms of effect of EEG modulation on reduction of pain.

- This is the first NF study of pain management showing long-term post training effects on task-related and task-unrelated EEG activity at the surface and at deep cortical levels. The study also provides evidence of change in ratio of EC and EO activity (EC/EO) at the deep cortical level following long-term NF training.

Appendix

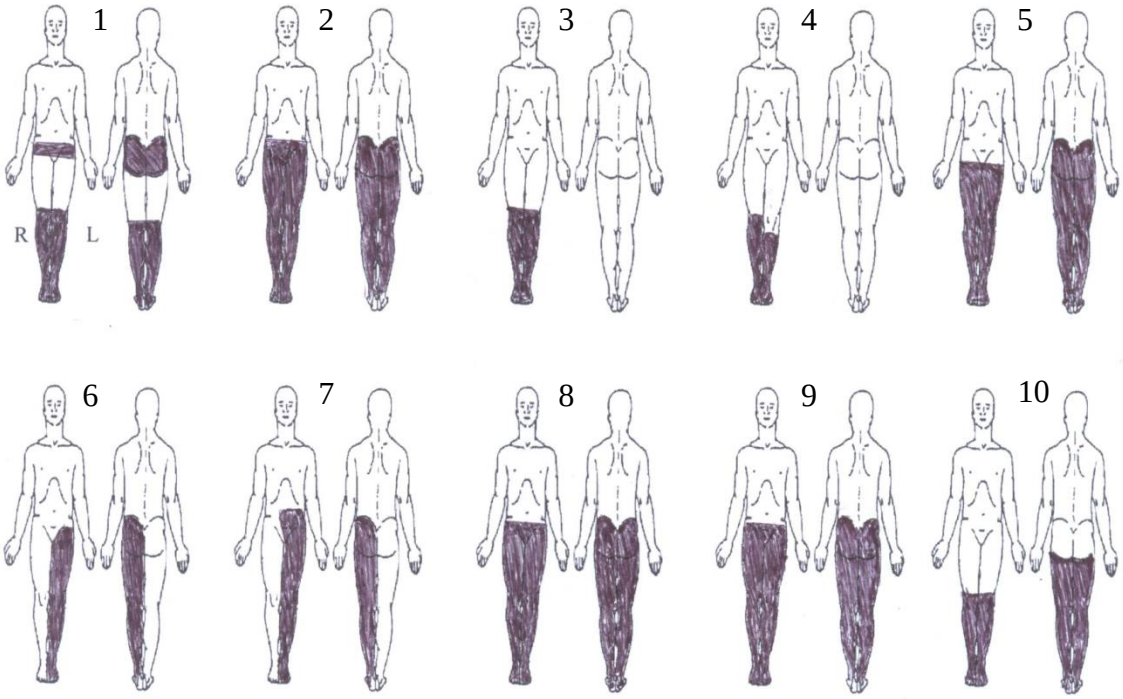


Figure A.1: Regions of the body perceived as being painful

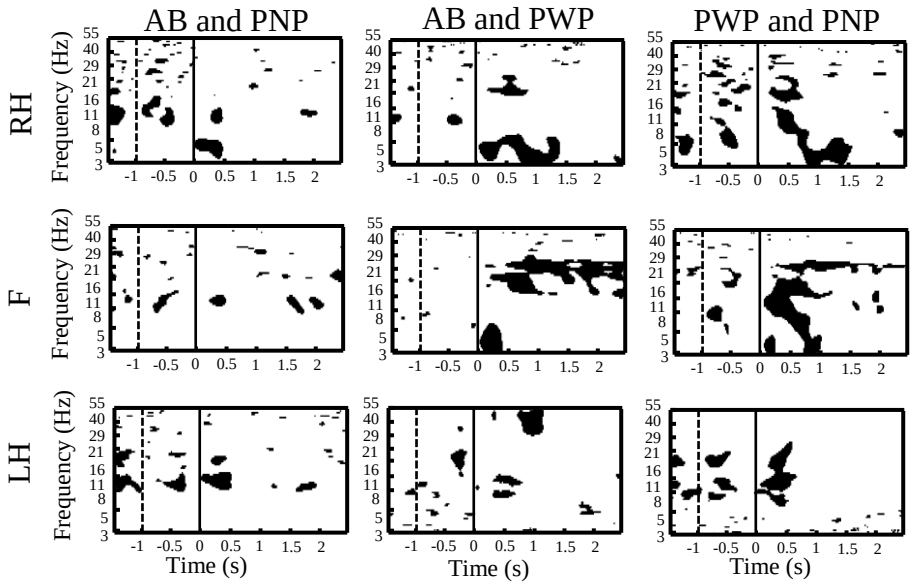


Figure A.2: ERD/ ERS comparison of each two group at Cz site for all three motor imagery (MI) tasks. Groups (AB= able-bodied, PNP= patient with no pain, PWP= patient with pain), Conditions (RH= right hand, F= foot, LH= left hand). At t=-1 s (dashed line), a warning cross was appeared. Participants were asked to start with motor imagery when a cue was appeared at t=0s (solid line) and to continue with motor imagination until t=3 s. ERD/ERS map shows a time period starting at t=-2 s before the cue and ending at t=2.5 s after the cue in a frequency range 3-55 Hz.

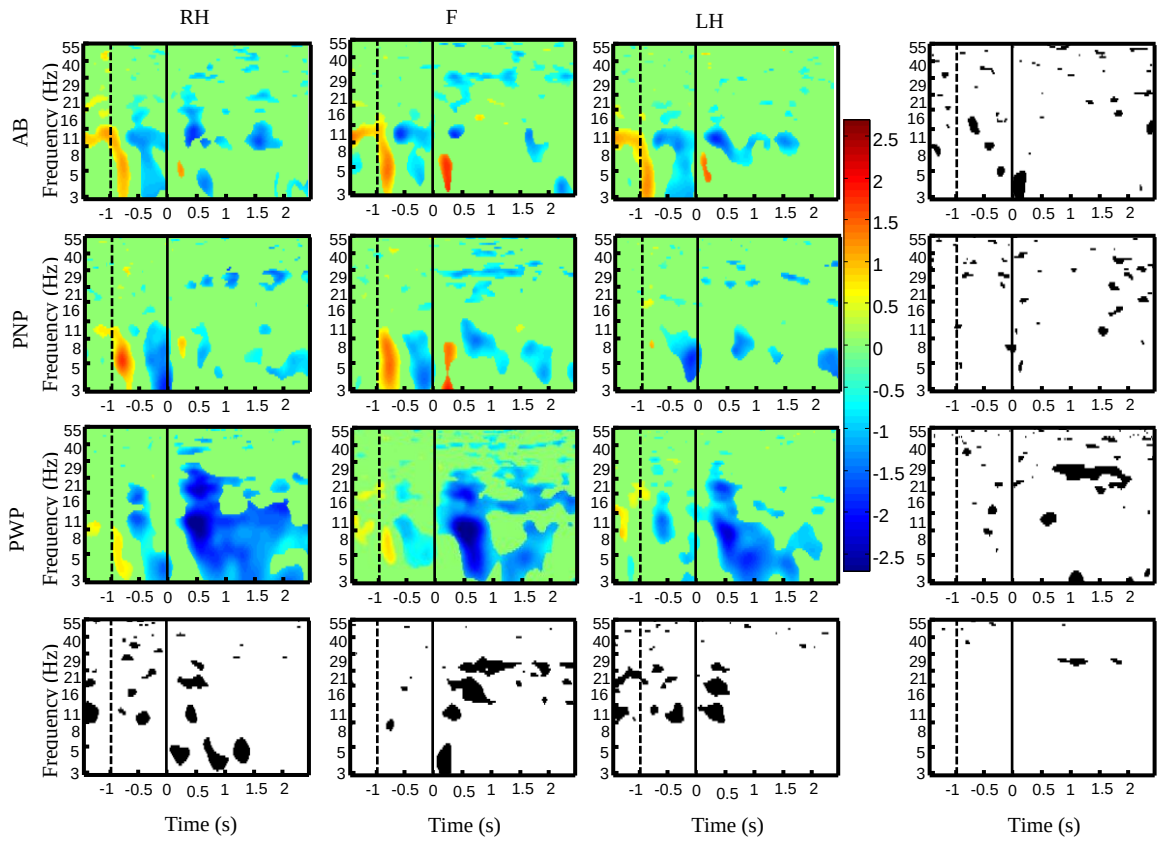


Figure A.3: ERD/ERS time frequency map at C3 site for all three groups (AB: able bodied, PWP patients with pain, PNP patients with no pain) and for all three motor imagery (MI) tasks (RH: right hand MI, F: feet MI, LH: left hand MI. Figures far right show areas of statistically significant differences among three MI tasks, while figures at the bottom row show areas of statistically significant differences among three groups (p=0.05) with FDR correction for multiple comparison. At t=-1 s (dashed line), a warning cross was appeared. Participants were asked to start with motor imagery when a cue was appeared at t=0s (solid line) and to continue with motor imagination until t=3 s. ERD/ERS map shows a time period starting at t=-2 s before the cue and ending at t=2.5 s after the cue in a frequency range 3-55 Hz.

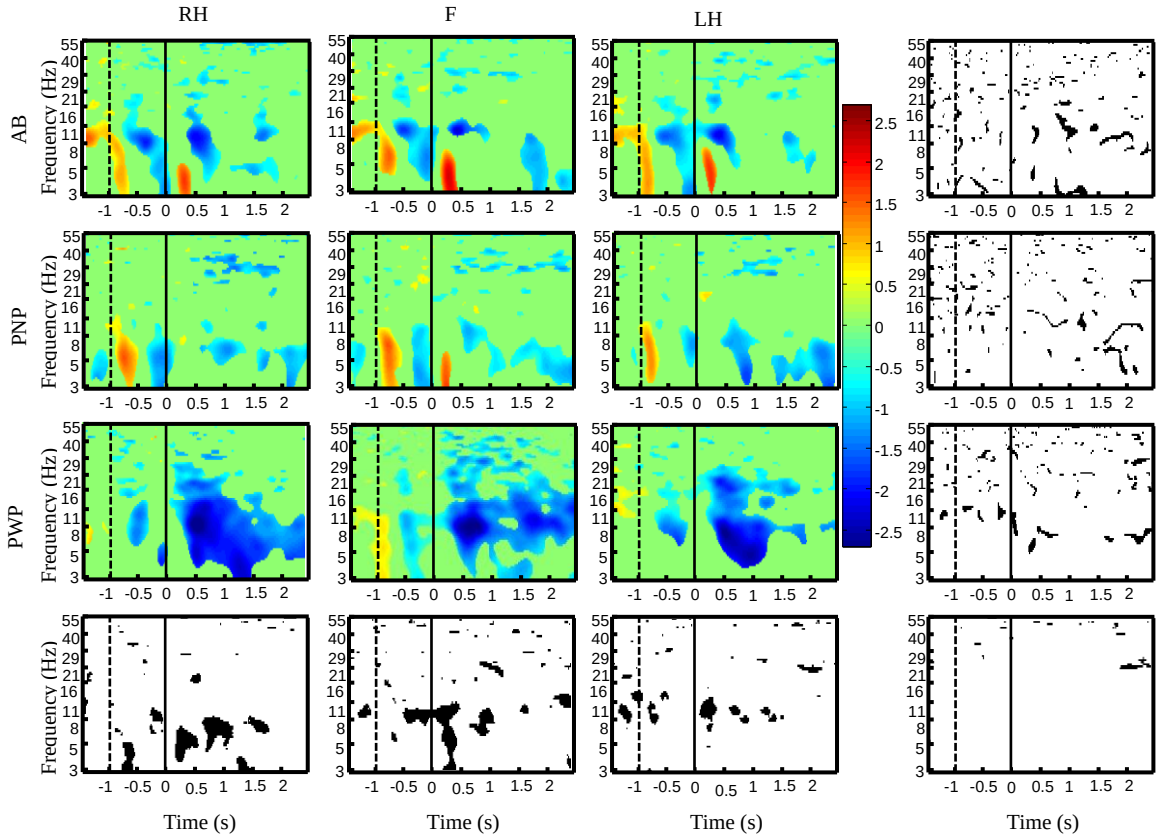


Figure A.4: ERD/ERS time frequency map at C4 site for all three groups (AB: able bodied, PWP patients with pain, PNP patients with no pain) and for all three motor imagery (MI) tasks (RH: right hand MI, F: feet MI, LH: left hand MI. Figures far right show areas of statistically significant differences among three MI tasks, while figures at the bottom row show areas of statistically significant differences among three groups (p=0.05) with FDR correction for multiple comparison. At t=-1 s (dashed line), a warning cross was appeared. Participants were asked to start with motor imagery when a cue was appeared at t=0s (solid line) and to continue with motor imagination until t=3 s. ERD/ERS map shows a time period starting at t=-2 s before the cue and ending at t=2.5 s after the cue in a frequency range 3-55 Hz.

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