Spatial distribution and temporal evolution of EEG alpha rhythms related to sensory-motor tasks during Mirror Visual Feedback illusion

Rizzo, Marco

DOI (link to publication from Publisher):
10.54337/aau510573583

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

SPATIAL DISTRIBUTION AND TEMPORAL EVOLUTION OF EEG ALPHA RHYTHMS RELATED TO SENSORY-MOTOR TASKS DURING MIRROR VISUAL FEEDBACK ILLUSION

BY
MARCO RIZZO

DISSERTATION SUBMITTED 2022

AALBORG UNIVERSITY
DENMARK

SPATIAL DISTRIBUTION AND TEMPORAL EVOLUTION OF EEG ALPHA RHYTHMS RELATED TO SENSORY-MOTOR TASKS DURING MIRROR VISUAL FEEDBACK ILLUSION

by

Marco Rizzo

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2022

Dissertation submitted: September 2022

PhD supervisor: Associate Prof. Lars Arendt-Nielsen, dr. med. Sci., Ph.D., Health Science and Technology Department, Aalborg University (DK)

PhD co-supervisor: Associate Prof. Laura Petrini, Ph.D., Health Science and Technology Department, Aalborg University (DK)

PhD committee: Professor Strahinja Dosen (chair)
Aalborg University, Denmark

Senior Lecturer Elia Valentini
University of Essex, United Kingdom

Assistant Professor Elisa Carlino
University of Turin, Italy

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Health Science and Technology

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-830-4

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Stibo Complete, 2022

CV

MARCO RIZZO

Marco obtained his B.Sc. in Psychology (2015) and M.Sc. in Cognitive Neuroscience and Neuropsychological Rehabilitation (2017) from the Psychology Department at La Sapienza University of Rome, Italy. After graduation, he worked as a research assistant at the Department of Physiology and Pharmacology (La Sapienza University of Rome) under the supervision of Prof. Claudio Babiloni. Here, he developed his interest in the electroencephalographic (EEG) investigation in patients affected by neurodegenerative diseases.

In 2018, Marco enrolled as a Marie Curie PhD Fellow at the Center for Neuroplasticity and Pain (CNAP), Health Science and Technology Department, Aalborg University (Denmark) in the context of the FRESCO@CNAP programme. Under the main supervision of Prof. Lars Arendt-Nielsen and co-supervision of Prof. Laura Petrini, he investigated the EEG brain cortical features during sensory-motor interaction tasks in neurologically healthy individuals. From July to September 2021, research activities were performed at the Department of Physiology and Pharmacology of La Sapienza University of Rome as part of a collaboration with Prof. Claudio Babiloni's group. Marco disseminated the results of his PhD project through poster presentations at the Congress of the European Pain Federation (EFIC) in 2019 and the IASP world congress on pain (2021).

PREFACE

The work that you are about to read provides a summary of the research conducted in the period between 2018 and 2022 at the Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Aalborg University, Denmark. The project was carried out in collaboration with the Department of Physiology and Pharmacology at Sapienza University, Rome, Italy. The project was cofounded by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 754465 and by the Danish National Research Foundation (DNRF121).

The PhD project aims to investigate the mirror visual feedback illusion and its effects on pain perception. In this respect, the current PhD dissertation contributes to the understanding of the neurophysiological mechanism underlying the illusion and sensory-motor interaction to improve the knowledge about cost-effective therapies based on the utilization of a mirror. Three scientific papers and two conference abstracts resulted from the proposed PhD work.

Within the thesis, the argument is discussed in five chapters. The first chapter introduces the relevant topics that led to the conceptualization of the idea behind this project. The second chapter treats the spatial and temporal dynamics related to the mirror visual feedback illusory phenomenon. Here, the results from the first two studies are discussed relative to the relevant literature in the field of neurophysiology. The third chapter concerns the effects of mirror visual feedback illusion on pain perception. The results are then discussed in the framework of attentional and nociceptive neurophysiological processes. Chapter 4 discusses the main methodological limitations of the studies. Finally, the thesis is concluded in Chapter 5 with a brief overview of the clinical implication and future perspectives.

Marco Rizzo

Aalborg University, September 2022

ENGLISH SUMMARY

Chronic pain and motor impairment are common clinical problems which harm the quality of life of the affected patients. In several conditions, such as phantom limb pain, complex regional pain syndrome, or post-stroke paralysis, the mismatch between motor commands and reafferent sensory feedback may lead to maladaptive neuroplasticity. Placing a mirror perpendicularly to the subject's view, unilateral movements produce the illusion of the opposite limb moving synchronously. This Mirror Visual Feedback (MVF) illusion has been proposed to restore the visual correspondence between the motor output and sensory input and promote cortical reorganization. However, the cortical areas and the mechanisms related to this illusory phenomenon are poorly understood.

The present PhD thesis synthesizes the results of three studies aimed at investigating the neurophysiological mechanisms underlying the MVF-induced illusion of finger movements and its effects on nociceptive processes in healthy individuals. The project was based on pioneering studies probing the electroencephalographic (EEG) oscillations of the alpha rhythm (alpha ERD/ERS) to understand the cortical mechanism underpinning the anticipation and experience of sensory-motor events. Furthermore, the interaction between sensory and motor events reduced the alpha ERD (less cortical activity) and the relative subjective pain perception. In line with this evidence, the following studies were designed.

The first study traced the spatial distribution and temporal evolution of the EEG alpha ERD/ERS in response to MVF illusion. Here, unilateral triggered movements of the index finger were associated with a bi-hemispheric activity (alpha ERD) of the centroparietal and frontal sensory-motor cortical areas (MVF condition). Notably, in the control condition without MVF the same cortical activity was observed only on the hemisphere contralateral to the moving finger. The second study confirmed these results. Moreover, the cortical source estimation of the EEG alpha ERD/ERS unveiled the involvement of the premotor, prefrontal, and posterior parietal associative cortical areas as responsible for visuomotor transformation during MVF illusion.

The project culminated in the third study, where the sensory-motor interaction between MVF-induced illusory movements and electrical stimulations was investigated through the estimation of the alpha ERD/ERS cortical sources. Electrical stimulations at individually-fixed intensity produced painful and non-painful sensations. Results indicated that the inhibition (reduced alpha ERD) of the midline limbic regions is associated with individual lower perception of the stimulation intensity.

In conclusion, the MVF-induced illusion of unilateral movements may induce sensory-motor cortical activation as strong as the one produced by real movements.

Moreover, MVF illusory movements involve cortical frontoparietal and posterior visuomotor transformation processes. As a core result, the illusion may interfere with the afferent sensory stimulations reducing the activity within the midline structures of the limbic system. Throughout this thesis, the neurophysiological model underlying these illusory and interactive mechanisms will be proposed, as reflected by the oscillations of the EEG alpha rhythm. A better understanding of these mechanisms might be relevant to developing individualized therapies for those patients with unilateral limb impairment.

DANSK RESUMÉ

Kroniske smerter og motorisk svækkelse er almindelige kliniske problemer, som skader patienters livskvalitet. Under flere tilstande, såsom fantomsmerter, komplekst regionalt smertesyndrom eller lammelse efter slagtilfælde, kan misforholdet mellem motoriske kommandoer og afferent sensorisk feedback føre til at neuroplasticiteten ikke tilpasses korrekt. Ved at placere et spejl vinkelret på en forsøgspersons syn, frembringer ensidige bevægelser illusionen af, at den modsatte legemsdel bevæger sig synkront. Denne Mirror Visual Feedback (MVF) illusion er blevet foreslået for at genoprette den visuelle overensstemmelse mellem det motoriske output og sensoriske input og fremme kortikal reorganisering. Imidlertid er de kortikale områder, som mekanismen dette illusoriske fænomen er relaterede til, ikke ordentligt forstået.

Denne ph.d.-afhandling syntetiserer resultaterne af tre studier, der sigter efter at undersøge de neurofysiologiske mekanismer, der ligger til grund for den MVF-inducerede illusion af fingerbevægelser og dens virkninger på nociceptive processer hos raske individer. Projektet var baseret på banebrydende undersøgelser, der undersøgte de elektroencefalografiske (EEG) oscillationer af alfa-rytmen (alfa ERD/ERS) for at forstå den kortikale mekanisme, der understøtter forventningen om og oplevelsen af sansemotoriske hændelser. Ydermere viste tidligere studier at interaktionen mellem sensoriske og motoriske hændelser alfa ERD (mindre kortikal aktivitet) og den relative subjektive smerteopfattelse var reduceret. I overensstemmelse med denne evidens blev følgende undersøgelser designet.

Den første undersøgelse sporede den spatielle fordeling og temporale udvikling af EEG-alfa ERD/ERS som følge af MVF-illusion. Her var ensidigt udløste bevægelser af pegefingeren forbundet med en bi-hemisfærisk aktivitet (alfa ERD) af de centroparietale og frontale sensorisk-motoriske kortikale områder (MVF). Navnligt i kontroltilstanden uden MVF blev den samme kortikale aktivitet kun observeret på hjernehalvdelen kontralateralt til den bevægede finger. Den anden undersøgelse bekræftede disse resultater. Desuden påviste den kortikale oprindelsesestimering af EEG-alfa ERD/ERS involvering af de præmotoriske, præfrontale og posteriore parietale associative kortikale områder som ansvarlige for visuomotorisk transformation under MVF-illusion.

Projektet kulminerede i det tredje studie, hvor den sensorisk-motoriske interaktion mellem MVF-inducerede illusoriske bevægelser og elektriske stimulationer blev undersøgt gennem estimering af alfa ERD/ERS kortikale oprindelser. Elektriske stimulationer med individuelt kalibreret intensitet frembragte smertefulde og ikke-smertefulde følelser. Resultater indikerede, at hæmning (reduceret alfa ERD) af de limbiske midterlinjeområder er forbundet med individuelt lavere opfattelse af stimuleringsintensiteten.

Som konklusion kan den MVF-inducerede illusion af ensidige bevægelser inducere sensorisk-motorisk kortikal aktivering lige så stærk som den, der frembringes af frivillige bevægelser. Desuden involverer MVF illusoriske bevægelser kortikale frontoparietale og posteriore visuomotoriske transformationsprocesser. Som et kerneresultat kan illusionen forstyrre afferente sansestimuleringer, hvilket reducerer aktiviteten i det limbiske system. I afhandlingen vil den neurofysiologiske model, der ligger til grund for disse illusoriske og interaktive mekanismer blive foreslået, som resultat af de viste oscillationer i EEG-alfa-rytmen. En bedre forståelse af disse mekanismer kan være relevant for at udvikle skræddersyede terapier til patienter med ensidig svækkelse af motorisk funktion.

ACKNOWLEDGEMENTS

The realization of this PhD project has been possible thanks to a number of people to whom I owe my acknowledgement. I would like to thank my supervisor Prof. Lars Arendt-Nielsen, who allowed me to start the PhD fellowship at CNAP and has been always helpful with his sharp and wise comments. I am immensely grateful to my co-supervisor Prof. Laura Petrini, from whom I received a warm welcome on my very first day and continuous support throughout these years. You have been always available to listen to any idea, change of mind, and complaint. Thanks! I am thankful to the entire CNAP group, including Prof. Thomas Graven Nielsen and any other person in the team who contributed to building this fantastic and inspiring environment, where I could find room for scientific and informal discussions. I sincerely thank all my colleagues for the time you spent with me in the laboratory or at my desk as well as for the laughs and the good moments spent together.

An enormous thank goes to Prof. Claudio Babiloni and the group from Rome. All of this would have not been possible without your constant scientific and technical support. Thanks for keeping my motivation always high.

I also wish to express my gratitude to all the people who crossed my way during this journey. Thanks to the Italian crew, you made Denmark a warmer place for me. Thanks to all my international friends. I am fortunate for having developed such solid friendships all over the world.

Finally, I would like to thank my parents Andrea and Elena and my sisters Nelly and Angela. Despite the distance and the hectic moment, you always unconditionally supported me.

TABLE OF CONTENTS

ABBREVIATIONS

ACC	Anterior cingulate cortex
CMS	Central midline structures
CRPS	Complex regional pain syndrome
DLPFC	Dorsolateral prefrontal cortex
DMN	Default Mode Network
ECN	Executive Control Network
EEG	Electroencephalography
ERD	Event-related desynchronization
ERS	Event-related synchronization
fMRI	Functional magnetic resonance imaging
IFG	Inferior frontal gyrus
IHI	Interhemispheric inhibition
IPL	Inferior parietal lobule
M1	Primary motor cortex
MBT	Mirror box therapy
MEG	Magnetoencephalography
MVF	Mirror visual feedback
PCC	Posterior cingulate cortex
PLP	Phantom limb pain
PPC	Posterior parietal cortex
S1	Primary somatosensory cortex
SN	Salience Network
TMS	Transcranial magnetic stimulation

CHAPTER 1. INTRODUCTION

Throughout history, optical illusions have been used to correct and achieve specific spatial perspectives in the architecture field, for aesthetic appreciation in the art field, and to drive the customers' attention in the world of advertising. Moreover, they have been often adopted by neuroscientists to investigate the neurobiological features of the visual system. Indeed, an optical illusion may be defined as a different perception from an event that would be typically expected based on physical or sensory predictions[1]. In other words, what we perceive is often shaped by what we expect and believe, and in some cases, the brain is deceived by the superimposition of the visual system over the other perceptive systems. Nonetheless, albeit optical illusions seem to fool the human brain, they might have beneficial effects for individuals experiencing chronic pain and motor impairment. For instance, while treating subjects with phantom limb pain (PLP) – a condition wherein amputees perceive persistent somatic feelings belonging to the missing limb – Ramachandran and Rogers-Ramachandran[2] noted that the congruent visual feedback of the missing limb obtained by means of a mirror alleviated the PLP-related symptoms. Since then, several studies applied mirror illusion in the experimental context to investigate the therapeutical effect of this deceptive phenomenon and enhance the knowledge of the brain's visual and sensory-motor system. In this regard, electroencephalography (EEG) is a technique that can probe the scalp's electrical activity in response to real or simulated movements and sensory events.

To better understand the scientific framework and the idea behind the present dissertation, this introduction allows the reader to familiarize themself with the concepts of (i) Mirror Visual Feedback (MVF) illusion and its clinical applications, (ii) the EEG cortical activity related to MVF and sensory-motor events, and (iii) the neurophysiological model of cortical sensory-motor interaction.

1.1. THEORETICAL FRAMEWORK OF MIRROR VISUAL FEEDBACK (MVF)

Several conditions of the central and peripheral nervous system, such as post-stroke hemiparesis, complex regional pain syndrome (CRPS), or the loss of one limb due to an amputation, may cause chronic pain symptoms and significant reduction of the motor function of the affected limb, with consequent maladaptive neuroplasticity in the corresponding body representation over the sensory-motor cortex[3–12]. In those patients, the mismatch between motor commands and reafferent body feedback may also lead to "*learned paralysis or nonuse*" and motor deterioration[13–15].

Intending to restore the correspondence between motor intention and visual feedback (efference-afference loops) in amputees with PLP, Ramachandran and Rogers-Ramachandran introduced the mirror box therapy (MBT), a technique that induces the illusion of bilateral movements during actual unilateral movements, observing a significant reduction of painful symptoms and the related aching sensations[2]. However, the involved brain areas and the mechanisms underpinning this therapeutic procedure are still a matter of discussion.

1.1.1. REHABILITATIVE UTILIZATION OF MVF

MBT is an MVF-based technique and consists of placing a mirror in the observer's body midline in order to produce the reflection of one limb (typically used for arms or legs) in the visual space of the opposite limb[2,16]. In its typical approach, the view of one limb moving reflected in the mirror produces the illusion of the contralateral limb moving synchronously[2,17,18]. Importantly, MVF-based therapies are believed not only to relieve painful symptoms but also to promote sensory-motor neuroplasticity and restore motor functions[19–27]. Two recent Cochrane Reviews based on 62 studies (1982 participants) compared mirror therapy with other control interventions (e.g., no-mirror, muscular or cortical electrostimulation, traditional occupational physiotherapy, etc.) in post-stroke motor impaired patients, enlightening moderate evidence that mirror therapy has positive effects on motor functions recovery and low evidence of significant effects on pain symptoms relief[28,29]. This was true particularly when mirror therapy was combined with conventional therapy[28,29].

Recent developments have led to more interactive MVF-based technologies, such as immersive virtual reality and augmented reality, to manipulate the illusory immersion, enhance the range of movement, and produce unilateral movements of the affected limb that are impossible with the use of a simple mirror[16,30–34]. In this vein, studies applying virtual technologies to produce the illusory effect of one limb movement in amputees or post-stroke showed significant pain reduction as well as motor improvement after augmented[30,35–40] or virtual[41–45] reality interventions (see Dunn et al., 2017 for a review[46]). However, it must be considered that, due to their hardly suitable equipment, virtual MVF techniques are usually applied only in research settings and are scarcely adaptable to conventional home therapy[47].

1.1.2. CORTICAL BASES AND VISUO-MOTOR THEORY OF MVF

To better understand the brain areas and mechanisms underlying the MVF illusory phenomenon, mirror-based techniques have been largely used in the research settings in neurologically healthy individuals. Functional magnetic resonance imaging (fMRI) studies comparing MVF hand movement conditions with control conditions without MVF showed significant cortical activation in the motor, premotor, supplementary motor, and occipital areas ipsilaterally to the actual moving hand and contralaterally to the mirrored image of the moving hand[48–55]. Using transcranial magnetic

stimulation (TMS), other studies found that – when coupled to the MVF procedure – unilateral motor tasks caused increased excitability of the primary motor cortex (M1) ipsilateral to the moving limb[56–60]. Similarly, EEG studies analyzed negative voltage signal deflections as a neurophysiological marker to reflect the hemispheric different activation during unilateral movements. These studies showed a low hemispheric divergence of the sensory-motor cortex (i.e., similar bi-hemispheric activity) when unilateral hand movements were perceived as bi-manual movements via MVF illusion[61–64].

Although a few studies using fMRI, TMS and EEG failed in showing a significant cortical activation related to MVF in healthy subjects[65–69], a conspicuous amount of evidence demonstrated the central role of the sensory-motor cortex[27,51,53,57,58,61,70–75]. Recent EEG and fMRI studies demonstrated the involvement of fronto-parietal (spatial attention) and centro-parietal (motor coordination) networks in the elaboration of the MVF-induced illusory perception of movements[53,59,73,76–78]. Therefore, a modern theory proposes a posterior-to-central mechanism responsible for the transformation of visual stimuli into illusory sensory-motor experience[78].

In this light, the present work takes its position within the visuo-motor transformation theoretical framework of MVF illusion and aims to provide further insights regarding the cortical spatiotemporal features involved in this deceptive phenomenon.

1.2. SENSORY-MOTOR ELECTROENCEPHALOGRAPHIC (EEG) ALPHA RHYTHM DE/SYNCHRONIZATION (ERD/ERS)

Electroencephalography (EEG) is a non-invasive technique that reads the scalp electrical activity generated by the brain structures with a high temporal resolution (milliseconds) and a relatively moderate spatial resolution (centimeters). One of the EEG's primary outcomes is the brainwaves at different frequencies (i.e., the number of times a wave repeats in one second). The typical EEG frequency rhythms and their relative frequency bands are classified as *Delta* (<4 Hz), *Theta* (4-8 Hz), *Alpha* (8-12 Hz), *Beta* (12-30 Hz), and *Gamma* (>30 Hz)[79]. This section of the introduction will describe the role of the cortical EEG alpha rhythm oscillations in response to motor and somatosensory events.

1.2.1. CENTRAL ALPHA RHYTHM

It has been known for almost a century that certain events can modulate the ongoing EEG alpha activity[80]. In a resting state condition, the ongoing EEG activity recorded from healthy adults shows prominent oscillations at the alpha frequency band (about 8-12 Hz) in the central and posterior brain regions[81,82]. Alpha oscillations are evident in the occipital areas during eyes-closed quiet wakefulness, thus reflecting an "*idling*"

state[81,83,84]. A distinct centro-parietal alpha rhythm, termed *Rolandic mu (μ) rhythm*, represents a sign of cortical inhibition of the somatomotor networks during physical and psychological relaxation and sensory deprivation[†] [82,83,85,86]. Just as opening the eyes may suppress the EEG occipital alpha rhythm, sensory-motor events may attenuate the centro-parietal alpha oscillations, generally in favour of faster EEG frequencies, such as *beta* (12-30 Hz) or *gamma* (30-40/50 Hz) waves[81–83,87–91]. These event-related changes reflect the decrease or increase of the EEG power in given frequency bands, respectively due to the *desynchronization* or *synchronization* of the populations of neurons underlying a specific cortical region. It is common to address these EEG changes in synchrony of the alpha band as alpha event-related desynchronization/synchronization (ERD/ERS)[81,90,92].

1.2.2. ALPHA ERD/ERS CALCULATION

The basic characteristic of the alpha ERD/ERS estimation is that the EEG power within the alpha frequency band is extrapolated as a percentage in relation to a reference (or baseline) period occurring a few seconds before the event of interest, in the same EEG recording[81]. A brief procedure of the alpha ERD/ERS calculation is hereby reported. After filtering the EEG data at the alpha frequency band, the following formula gives the final percentage output:

$$ERD/ERS\% = \frac{E - R}{R} * 100$$

Where the ***E*** is defined as the "*event*" period, whereas the ***R*** is defined as the "*rest*" or "*baseline*" period. The resulting negative percentage values represent a decrease in the alpha waves' synchrony (i.e., event-related desynchronization or ERD) and it is acknowledged as an index of cortical activity, while positive percentage values represent an increase in the alpha synchrony (i.e., event-related synchronization or ERS), representing cortical inhibition[81]. See **Figure 1** for a graphical example of how the baseline and the events period were calculated in this project relative to the experimental paradigms proposed in the current PhD project.

1.2.3. EEG ALPHA ERD/ERS DURING SENSORY-MOTOR EVENTS

Previous evidence established that an active interaction between the thalamic nuclei and the cortical circuits is the basis of the cortical alpha oscillatory mechanism[93–96]. In particular, the alpha oscillations in the centro-parietal cortex are thought to represent thalamo-cortical and cortico-cortical sensory-motor feedback loops characteristic of self-initiated movements or somatic and tactile

[†] Since in this work several regions of interest of the brain were considered other than the sensory-motor area, for uniformity purposes only the nomenclature "alpha rhythm" will be used throughout the dissertation.

sensations[81,86,87,91,97,98]. The next section will describe the different patterns of the EEG alpha ERD/ERS related to the anticipation/execution of motor events and the expectancy/experience of somatosensory events.

Motor Events

Extensive research has shown that active self-paced movements of one limb are characterized by an anticipatory desynchronization (ERD) of the dominant alpha rhythm in the sensory-motor cortex contralateral to the movement or stimulation, starting between 1 and 2 seconds before the event[81,85,86,89,99–103]. Furthermore, the "pre-movement" phase has been also related to the synchronization (ERS) of the alpha rhythm ipsilateral to the moving limb, supposedly as a strategy to avoid involuntary automatic specular movements of both limbs[89,104,105]. This anticipatory alpha ERD/ERS pattern reflects preparatory mechanisms underpinning voluntary movements planning mental process[81,86,91,102,106] and is, in fact, absent during passive movements[83,107–110], probably due to a lack of attention toward the sensory-motor processes that are necessary for the control and regulation of active voluntary movements[111]. Conversely, the literature regarding the alpha ERD/ERS patterns during the execution of the movement becomes less consistent. With reference to the moving limb, the majority of the studies observed a contralateral sensory-motor alpha ERD and ipsilateral sensory-motor alpha ERS in response to active movements[81,85,102,107,109,112–115]. However, a bi-hemispheric central alpha ERD has been observed in a few studies investigating the EEG oscillatory patterns during unilateral hand movements[73,81]. Further investigations proposed that only the high-alpha band ERD (about 10-12 Hz) begins as contralateral to the moving limb before the movement and becomes bilateral during the movement execution[83,107]. Finally, the literature recognizes a *high beta* band rebound (beta ERS, about 17-30 Hz) occurring after self-paced voluntary movements in the contralateral cortex as a consequence of movement offset (with a latency of about 1500 ms after the movement onset)[74,83,116–120].

Somatosensory Events

A similar EEG alpha ERD/ERS pattern in the sensory-motor cortex has been observed during the expectancy and the experience of painful or non-painful tactile stimuli. fMRI evidence showed as the anticipation and perception of tactile stimuli evoked similar responses in the primary somatosensory cortex contralateral to the stimulus[121] and that this anticipatory activity may occur in the somatotopic region corresponding to the body area where the subject is expecting the stimulus[122]. Using EEG, other studies demonstrated as the anticipatory suppression of the high-frequency alpha band (10-12 Hz) over the primary sensory-motor cortex contralateral to the stimulation was higher in amplitude when anticipating painful rather than non-painful stimuli[115,123–125]. Interestingly, in those studies, decreased anticipatory alpha ERD (less cortical activity) was linearly correlated to a lower individual evaluation of the perceived pain

intensity[115,123,126]. However, it has to be noted that another study with a different expectancy paradigm did not confirm that correlation[102]. Consistently, non-painful thermal (heat and cold) stimulations on the forearm produced an alpha suppression (alpha ERD) in the sensorimotor cortex contralaterally to the stimulated arm approximately 1 second after the temperature peak of the heat/cold stimulation and this suppression was also correlated with lower perceived stimulus intensity and shorter latency[127,128]. A recent review on pain-related brain rhythms, indicated as phasic (shorter) and tonic (longer) pain stimuli suppress the alpha rhythm in the sensory-motor and occipital cortical areas between 300 and 1000 milliseconds after the stimulus delivering[129]. However, the alpha ERD related to tonic pain (it can last several minutes) has to be considered less pain-specific, as several mental processes represent confounder factors in the alpha waves suppression[129]. Furthermore, similar to motor execution, after the initial alpha suppression in response to painful stimuli perception, alpha and beta band rebound have been observed in magnetoencephalography (MEG) studies over the contralateral sensory-motor centro-parietal areas approx. 800ms after the electrical non-painful[130] and painful[117,131] stimuli, whereas other MEG and EEG studies observed a beta band rebound 1500 ms after electrical painful stimuli[132,133].

1.3. SENSORY-MOTOR GATING EFFECT

Pain is a complex multidimensional phenomenon controlled by a large variety of central and peripheral nervous system functions, such as attentional, cognitive, somatic, and motor components[134–136]. To better understand the afferent perceptive mechanisms, experimental pain has been often induced in the research context through experimental protocols in healthy individuals[137,138]. It is acknowledged that motor behaviors may attenuate the brain cortical responses to painful stimuli as a strategy for pain relief[89,102,139–141]. One of these strategies is represented by an intrinsic interaction mechanism of the brain's sensory-motor system known as the cortical *gating* effect[89,142].

The current theory recognizes two types of sensory-motor gating effects during voluntary movements. In the first one, the interaction between the afferent painful signals and afferent information from the muscles is thought to occur at the peripheral level. This mechanism is known as *centripetal* gating[140,143–146]. Conversely, in *centrifugal* gating, the interaction occurs at the cortical or subcortical level between the somatosensory painful signals and the efferent signals induced by the motor commands[139,143–147]. In the present PhD project, the EEG cortical activity will be related to the experience (motor execution and pain perception) and the anticipation (motor preparation and pain expectancy) of sensory-motor events during MVF illusion. Consequently, only centrifugal gating effects will be considered hereinafter.

1.3.1. NEUROPHYSIOLOGICAL INVESTIGATIONS OF CORTICAL GATING EFFECT

In paragraph 1.2.3, it has been described how sensory-motor events produce a suppression of the central alpha oscillations before and after sensory-motor events. A series of studies investigated the cortical sensory-motor gating through the analysis of the EEG central alpha ERD in response to motor preparation and execution and painful or non-painful tactile stimuli expectancy and experience (for a review, see Babiloni et al., 2014[142]). In the mentioned studies, somatosensory stimuli (laser or electrical) were delivered on the left hand, thus followed by imperative motor tasks of the same or opposite hand. Results demonstrated a reduced anticipatory alpha ERD in the primary sensory-motor cortex contralateral to the stimulated/moving hand when somatosensory painful stimuli and motor actions involved the same hand, as compared to control conditions where the interaction involved opposite hands[102,148]. Anticipatory central sensory-motor cortical responses were diminished (lower alpha ERD) also by the effect of distraction during cognitive tasks, with a consequent decrease in the subjective pain sensation[144,148–151]. Furthermore, when involving the same hand, sensorimotor processes preceding painful somatosensory stimuli were related to a lower perception of the pain intensity as well as to a delayed and less accurate performance of the motor task, as an indication of reciprocal interference between the motor and somatosensory cortices[89]. Overall, the discoveries regarding the interaction between somatosensory and motor events occurring either on the same hand or opposite hands have been interpreted as reflecting a functional facilitatory or inhibitory mechanism of the nociceptive and motor systems within the thalamo-cortical and cortico-cortical loops, as indicated by the modulation of the EEG alpha rhythm oscillations[81,88,142]. Keeping in mind the cortical gating model will facilitate the comprehension of the research questions proposed in the present work.

1.4. AIM OF THE PHD PROJECT

In this chapter, we learned that MVF is a therapeutic tool meant for treating patients with chronic pain and motor impairment by restoring the sensory-motor loops via movement illusion. Several studies probed this cortical reorganization and the sensory-motor interaction by detecting the EEG alpha rhythm oscillations as an index of cortical activation/inhibition (alpha ERD/ERS). Given these premises, the objective of the present PhD work was to investigate the spatial distribution and temporal evolution of the EEG alpha oscillations in response to sensory-motor tasks during MVF illusion. The specific research questions are listed in the following section.

1.4.1. RESEARCH QUESTIONS

In the light of the above-described notions, this project addressed the following questions:

- Do the anticipation and experience of MVF-induced illusory movements produce cortical activity in the sensory-motor area ipsilaterally to the actual moving side and contralaterally to the mirrored side, as reflected by EEG alpha ERD/ERS on the scalp?

- Are the cortical sources of the alpha ERD/ERS related to MVF illusion localized in widespread cortical areas, as indicated by the voxel-based analysis with high-density EEG?

- Is the MVF-induced illusion of finger movements strong enough to interfere with afferent sensory inputs from the same finger, as resulting from the mitigation of the sensory-motor EEG alpha ERD?

Three studies were designed and conducted to address these questions, resulting in 2 peer-reviewed studies and 1 submitted study:

- ***Study 1***[152]: Rizzo, M., Petrini, L., Del Percio, C., Lopez, S., Arendt-Nielsen, L., & Babiloni, C. (2022). Mirror visual feedback during unilateral finger movements is related to the desynchronization of cortical electroencephalographic somatomotor alpha rhythms. *Psychophysiology*.

- ***Study 2***: Rizzo, M., Del Percio, C., Petrini, L., Lopez, S., Arendt-Nielsen, L., & Babiloni, C. Cortical sources of electroencephalographic alpha rhythms related to the anticipation and experience of mirror visual feedback-induced illusion of finger movements. *Psychophysiology*, Under review.

- ***Study 3***: Rizzo, M., Petrini, L., Del Percio, C., Lopez, S., Arendt-Nielsen, L., & Babiloni, C. Neurophysiological correlates of sensory-motor interaction during Mirror Visual Feedback: Analysis of the electroencephalographic alpha rhythms. *NeuroImage*, In preparation.

In the coming chapters of the present dissertation, the spatial and temporal dynamics of the cortical alpha ERD/ERS during MVF movement illusion will be outlined and discussed. This will lead to analyzing how the MVF illusion might be utilized to interfere with somatosensory stimuli at the cortical level. Furthermore, a

neurophysiological model underpinning the MVF illusion, and based on the EEG alpha oscillations as a reflection of the thalamo-cortical and cortico-cortical sensory-motor loops, will be proposed. Finally, a discussion of how these findings may have an impact in the clinical context will conclude the work.

1.4.2. METHODOLOGICAL CONSIDERATIONS

To better understand the MVF paradigm and the sensory-motor interaction model designed for the three studies considered in the current PhD project, an overview of the main method will be reported in this section.

In all the studies, subjects were asked to perform auditory-triggered movements of the right index finger. In the experimental condition (MVF), the mirror was oriented to induce the illusion of simultaneous left index finger movements (reflecting side on the right). The image of the left arm and hand corresponded to the position of the actual left arm and hand behind the mirror. In the control conditions, subjects were asked to perform the same movement or bilateral movement without the MVF illusion. The hypothesis was that unilateral movements in the MVF condition could activate the primary sensory-motor cortex (alpha ERD) contralateral to the real movement (**Figure 2**, blue area) as well as the primary sensory-motor cortex contralateral to the MVF illusory movements (**Figure 2**, green area).

In the third study, the conditions remained unchanged, but electrical stimulations were delivered in the left index finger after 100 ms from the auditory cue. The idea was to experimentally produce cortical sensory-motor interaction in the right hemisphere between real electrical stimuli (**Figure 2**, red area) and MVF-induced illusory movements (**Figure 2**, green area).

A fixed interstimulus interval of 10 s was set between each trial for two main reasons. Firstly, 10 s is a sufficient period to reset the synchronization of the alpha rhythm oscillations[102,153]. Secondly, the paradigm aimed to create a sort of predictability of the upcoming auditory trigger cue to elicit a clear anticipatory cortical response. However, subjects were not informed about the fixed interval to avoid confounding effects of variable mental strategies during the expectation period (e.g., counting).

In all the analyses, the alpha ERD/ERS was calculated following the procedure described in paragraph 1.2.2. Specifically, the 0 (zero) time was represented by the auditory cue triggering the movements. The rest period was defined as the period from 5000 ms to 4000 ms before the cue; the anticipatory period was defined as the period of 1000 ms before the cue; finally, the execution period was defined as the period between 250 ms and 1250 ms after the cue. Figure 1 shows the time windows considered for the ERD/ERS calculation and the related left-movement onset, as recorded by electromyography (EMG).

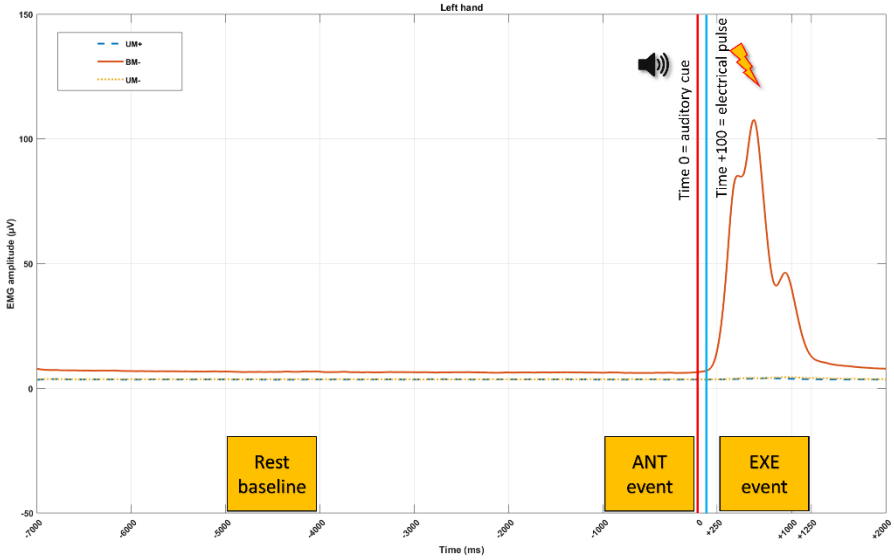

***Figure 1**. The image shows the "Rest" and anticipation and execution "Event" periods considered for the alpha event-related de/synchronization (ERD/ERS) calculation in relation to the electromyographic activity recorded from the left hand. The Y-axis shows the EMG power (microvolt), whereas the X-axis shows the time in milliseconds (ms). In all the experiments, the alpha ERD/ERS is calculated in relation to the time 0 (zero), represented by the auditory cue triggering the movement (red line). In the third study, electrical stimuli (blue line) were delivered on the left hand 100 ms after the auditory cue.*

1.4.3. GRAPHICAL SUMMARY

For the readers' convenience, a graphical summary is represented in **Figure 2** and will show the alleged cortical mechanism underlying the MVF-induced movement illusion as conceived for Studies I and II, followed by the paradigm designed to produce the interaction mechanism between the illusory movements and actual somatosensory stimuli for Study III.

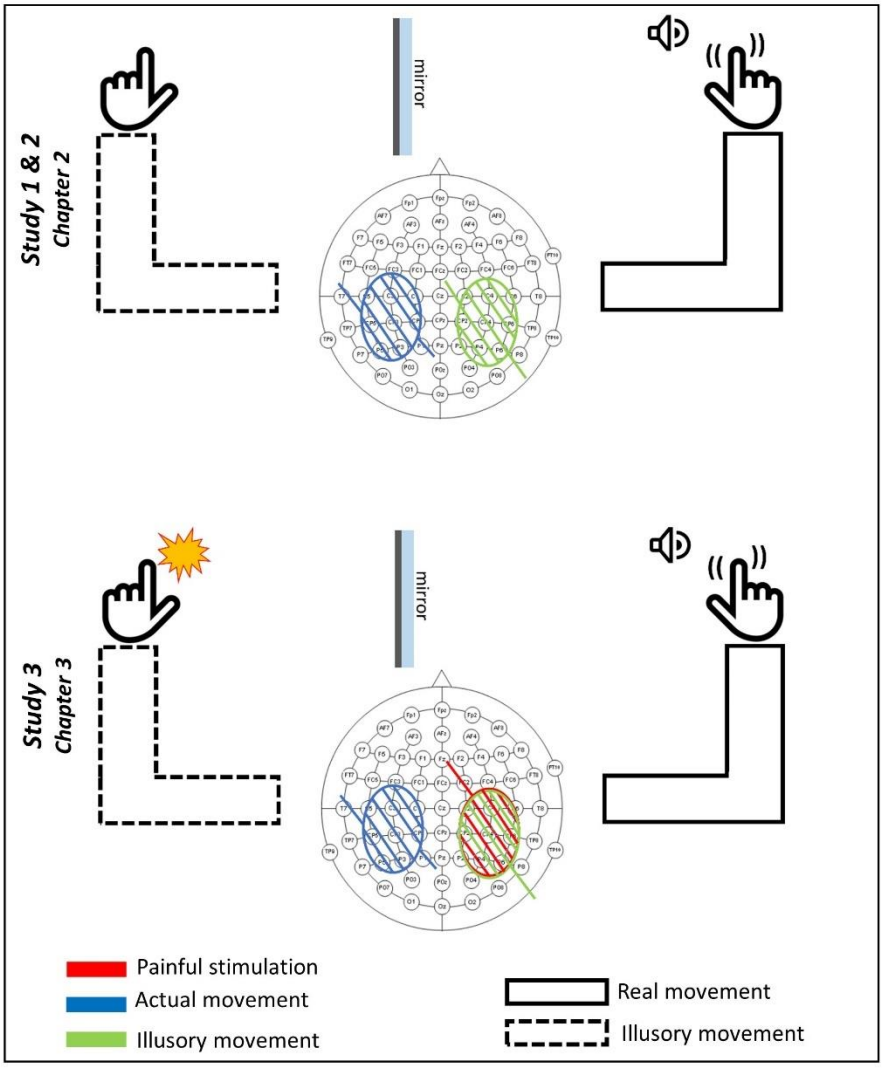

Figure 2. *The figure shows the schematic design of the Mirror Visual Feedback (MVF) models that are of interest to the project. The top figure represents the MVF-induced illusory movements conceived for Study I and II. The image reflected in the mirror of the actual right finger movements (blue lines) induces the illusion of the simultaneous left-finger moving (green lines). The cortical activity due to illusory movements is supposed to occur ipsilaterally to the actual movement and contralaterally to the mirrored image (i.e., in the right hemisphere). The bottom figure represents the sensory-motor interaction model designed for Study III. The cortical interaction occurs in the right hemisphere contralateral to the actual painful stimuli (red lines) and illusory movements in the right hemisphere (green lines). The colored areas cover the EEG electrodes underlying the sensory-motor cortex.*

CHAPTER 2. NEURAL ELECTROPHYSIOLOGICAL CORRELATES OF MVF-INDUCED MOVEMENT ILLUSION

In the previous chapter, it was outlined that the anticipation and the experience of sensory-motor events cause a modulation of the EEG alpha oscillations, as a reflection of cortical activity. Study I and II of the current project tested the hypothesis that such a neurophysiological mechanism may be involved in the perception of MVF-induced illusory movements. The relative findings will be addressed in the following chapter. In particular, the first two sections will review the current literature about the MVF illusion, with a special focus on the temporal and spatial characteristics in relation to the results obtained in Study I and II. Finally, a potential neurophysiological model based on the oscillatory EEG alpha rhythm underlying the MVF illusion will be proposed in section 2.3. This will include the preparatory and executory processes of illusory movements as well as the related neural correlates.

2.1. TEMPORAL FEATURES: ANTICIPATION AND EXECUTION OF MVF ILLUSION

Due to their high temporal resolution, electrophysiological investigations (i.e., EEG or MEG) are an ideal tool to draw the time-course of the cortical reactions to motor processes and MVF-induced illusory movements. Essential hints about real and illusory movements' temporal characteristics are derived from studies that analyzed the lateralized readiness potentials (LRPs), an electrophysiological correlate of premotor activation occurring in the M1 contralaterally to the moving limb even in absence of actual muscle contraction[154–156]. Two studies with healthy subjects used cue-triggered unilateral finger movements with and without MVF illusion to investigate the related LRPs[63,64]. Results showed LRPs with lower amplitude (i.e., balanced hemispherical activity) in the MVF condition as compared to the control condition with no illusion. Interestingly, the average latency of the LRPs was 128 ms from the cue for the control condition and 193 ms from the cue for the MVF condition, namely, before the motor response onset. This delay can be attributed to premotor processes that are responsible for inhibiting involuntary movements of the immobile hand behind the mirror[104,105]. Notably, an exceeded excitation was found at the electrode sites contralateral to the reflected hand (and ipsilateral to the real movement) as compared to that at the electrode sites contralateral to the actual moving hand[63,64].

Using a similar paradigm in healthy individuals, Debnath & Franz found that the LRPs commenced approx. 200 ms before the EMG onset in both the conditions with and without mirror illusion[157]. In addition, the maximal statistically significant difference in the hemispheric asymmetry occurred within the first 100 ms from the EMG onset, showing a clear bilateral cortical activation during unilateral movement under the MVF condition[157]. Despite the use of a different measure of cortical activation (alpha ERD), the results from Study I[152] and II demonstrated sensory-motor anticipatory activity contralateral to the mirrored hand as compared to the condition without MVF. Namely, MVF induces sensory-motor cortical excitation even in absence of overt motor response (see Figure 2 in Study I[152]). Furthermore, results from Study I and II found that the sensory-motor alpha ERD was always stronger at the central electrode sites contralateral to the real movement as compared to the alpha ERD contralateral to the MVF, in accordance with the study from Debnath & Franz[157]. Nonetheless, the opposite trend was observed when considering the frontal electrodes: the activity induced by the reflected movement (right frontal area) is stronger than the activity induced by the moving hand (left frontal area), although not at a statistically significant level (see Table 1 in Study I). This result may be explained by cognitive and attentional processes occurring selectively during the contralateral elaboration of the MVF illusory movement perception[158,159]. Additionally, results from Study I and II observed a significant alpha ERS (cortical inhibition) in the sensory-motor cortex contralaterally to the immobile hand in the anticipatory phase of the unilateral movement control condition without the mirror (**Figure 3**, or see Fig. 2, Study I; Fig. 3, Study II), as shown by numerous previous neurophysiological studies on voluntary movements[81,85,102,107,109,112–115].

Cortical EEG oscillations provided relevant information on the temporal features and functional properties of the MVF-induced illusory effect. In a well-designed paradigm, Ding and colleagues[160] asked healthy volunteers to perform voluntary cue-triggered movements of one hand under MVF illusion and tap a pedal with the foot (same side of the actual moving hand) as soon as the MVF procedure generated the *sensation of the embodiment* of the mirrored hand (i.e., *the feeling that the hand belonged to their body*[161]). The average response time (pedal press) was 4.4 s after the beginning of the task, as reflected also by a bilateral central EEG alpha ERD (C3 and C4 electrodes). Interestingly, when vibrotactile stimulation was introduced to the muscle tendon of the moving hand to strengthen the proprioceptive feedback, the average response time was reduced to 3.6 s, followed by an earlier bilateral central alpha ERD. An EEG study by Lee and colleagues[72] applied virtual reality to produce a delayed (2 s) MVF condition, in comparison to a real-time MVF and no-MVF. A bilateral alpha ERD in response to unilateral MVF movements started 0,5 s before the movement onset and lasted up to 1,5 s after that onset. The same temporal evolution has been demonstrated for the EEG central beta suppression[162]. These outcomes coincide with the temporal dynamics observed in Study I, describing an anticipatory suppression of the central alpha oscillation starting 1 s before the auditory cue triggering the movement up to more than 1 s after that cue. The short difference in the

anticipatory phase might be explained by the nature of the task: in contrast to triggered movements, self-paced movements do not set the brain in an expectancy state, excluding higher-order preparatory motor processes[163,164]. Finally, findings from Lee's study showed a second alpha ERD peak corresponding to the 2 s delay in the MVF-delayed condition[72]. This striking result not only demonstrates that the EEG alpha ERD can detect the instantaneous MVF-related cortical changes but might also explain how the superimposition of the visual system (in this case, the MVF delayed illusion) may play a greater role than the visuo-motor matching mechanism in the MVF-illusory perception.

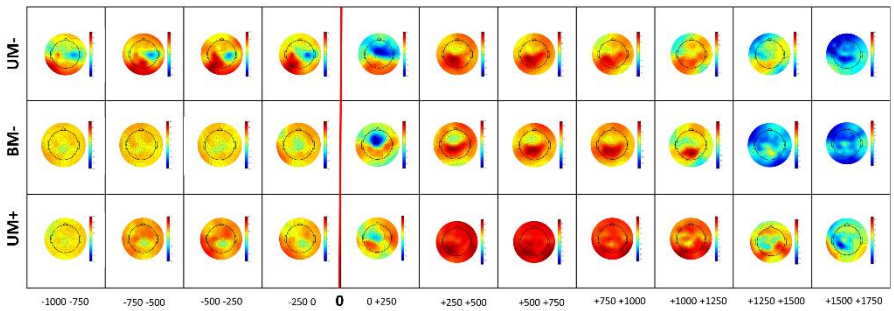

Figure 3 *– Across subjects mean of the alpha event-related de/synchronization (ERD/ERS) distribution over the scalp from Study I. The image shows the 2D maps for the three conditions: Unilateral noMVF (UM-), Bilateral noMVF (BM-), and Unilateral MVF (UM+). The 0 (zero) represents the auditory cue triggering the movement (red line). The maps (250 ms time windows) start from 1000 ms before the 0 (anticipatory phase) and end at 1750 ms after the 0. The execution phase considers the interval between +250 and +1250 after the cue. The color legends indicate the maximal percent values of ERD (dark red) and ERS (dark blue).*

2.2. CORTICAL CORRELATES OF MVF ILLUSORY MOVEMENTS

The illusory perception of MVF movements has been often attributed to increased activity of the neural substrate underlying the primary motor and somatosensory cortices. These cortical areas – along with associative areas such as the premotor cortex (PMC) and supplementary motor area (SMA) – are responsible for motor planning, control, and execution (M1, PMC, and SMA) as well as for perception and processing of external sensory information (S1). Reviewing neuroimaging and neurostimulation studies, this section offers an overview of the brain structures involved in the MVF illusion.

Transcranial magnetic stimulation (TMS), transcranial direct current stimulation, and continuous theta burst stimulation are brain stimulation techniques commonly used to test the M1 excitability in neurologically healthy individuals. Evidence agrees in

showing enhanced M1 excitability ipsilaterally to the moving hand when MVF provided the illusion of the opposite (reflected) moving hand[57,58,60,66,75,165]. In addition, the bi-hemispheric M1 excitability was similar when comparing unilateral hand tasks with MVF to bimanual movements (without MVF)[58,66]. This phenomenon was evident also in Study I[152], where the *Unilateral+MVF* and *Bilateral* conditions were linked to a bi-hemispheric central alpha ERD, significantly different from the alpha ERD caused by the *Unilateral* condition without MVF. Remarkably, these observations led the M1 to be the target area for neurorehabilitative brain stimulation in post-stroke patients with motor disorders. Indeed, clinical trials showed facilitated corticospinal excitability with a consequent significant improvement in motor recovery when combining MVF training with TMS[59,166] or tDCS[167] over the M1, as compared to brain stimulation alone[168].

Due to its high spatial resolution (one millimeter), fMRI technique provided fine spatial details of the MVF-induced illusion and extended the focus of the investigation also to other brain areas. Several fMRI observations indicated a clear activity in the anterior intraparietal sulcus[52] (hand movement control), in the M1[25,51] and PMC[51] ipsilateral to the moving hand and contralateral to the reflected hand when comparing hand motor tasks performed with and without MVF. This is in line with the aforementioned brain stimulation studies. However, a wider cortical substrate responsible for the integration of visual, motor, sensory, and proprioceptor information and the MVF illusion perception has been suggested[169]. This assumption is supported by evidence demonstrating that MVF illusion was linked also to the activation of (i) occipital cortex, which elaborates visual information[52–54], (ii) posterior parietal cortical areas that control visuo-motor transformation[25,53,170,171], and (iii) frontal and temporal cortical areas that play a key role in the attentional processes toward the mirror illusion [48,54].

As mentioned above, EEG can be used to map the scalp distribution of the alpha and beta band oscillations in response to sensory-motor events. In this context, the majority of the EEG studies observed a clear activity in the sensory-motor area ipsilateral to the moving limb and contralateral to the mirror illusion[72,74,160] or reduced asymmetry in the hemispheric activation at the central electrode sites (C3 or C4)[62–64,157,162]. In a comprehensive study, Al-Wasity and colleagues investigated the functional cortical domains related to the comparison of bimanual or unimanual+MVF tasks[74]. Results showed that the two conditions share the same sensory-motor and visuo-motor functional domains, whereas cortical regions linked to motor planning (PMC) and awareness of action (SMA) were activated exclusively during the MVF procedure. However, the absence of a unilateral movement condition without the mirror may represent a limit in that investigation.

Study I[152] was designed to test the hypothesis that the MVF illusion of bilateral finger movements (during actual unilateral finger movements) was related to bilateral sensory-motor as well as frontal (attentional) and posterior (visual) EEG alpha ERD.

As a methodological step forward, a 64-channel montage was deemed suitable for a larger 2D topographical mapping of the scalp alpha ERD, in contrast to the above-mentioned EEG studies. As compared to the condition without MVF, the MVF condition showed a stronger alpha ERD (cortical activity) in the centro-parietal cortex contralateral to the hand reflected in the mirror (i.e., C4, CP4, and P4 electrodes) during the preparatory phase of the movement. The results also demonstrated a widespread alpha ERD in the frontal, centro-frontal (see Study I: Fig. 2 and 3) and occipital regions (see Study I[152]: Supporting Information) in the MVF condition as compared to the control conditions during movement execution. In Study II, the cortical sources of the alpha ERD were estimated using the eLORETA freeware (see Method section in Study II for further details) to investigate the brain cortical structures (3D mapping) involved during the MVF-induced illusion maintaining high temporal resolution which allowed the analysis of the anticipation and execution stages of the movement (**Figure 4**). In the anticipation phase, voxel-by-voxel comparisons between the MVF and noMVF conditions showed a significantly stronger alpha ERD in the sensory-motor, lateral premotor, polar prefrontal, and posterior parietal areas contralateral to the hand reflected in the mirror (Study II: Fig. 4, Table 1). The main differences during the execution phase of the movement were delimited within the sensory-motor, lateral premotor, and posterior parietal cortical areas (Study II: Fig. 5, Table 2).

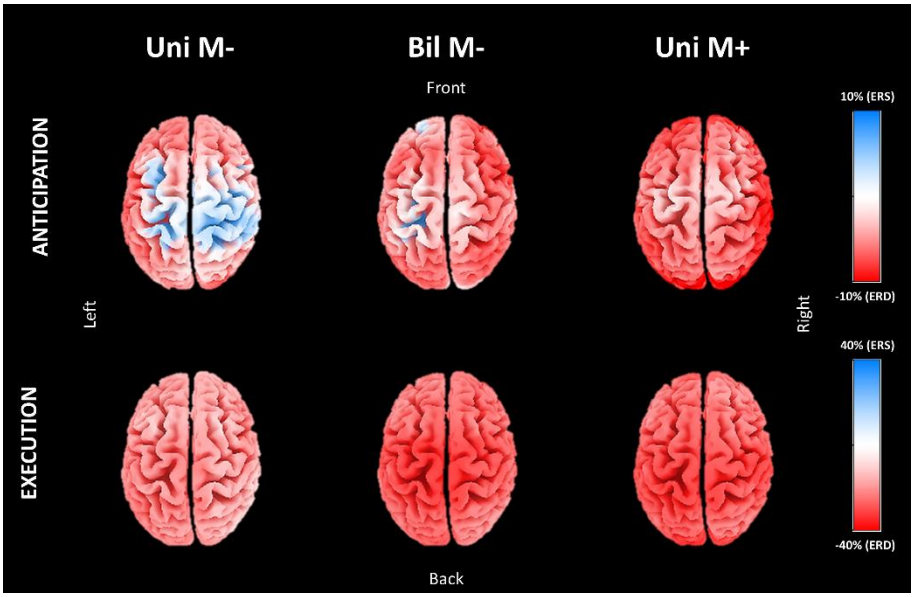

Figure 4 *– Grand average of the cortical sources of the alpha ERD/ERS values as estimated by eLORETA. The image shows the 3D maps (top view) for the three conditions Unilateral noMVF (Uni M-), Bilateral noMVF (Bil M-), and Unilateral MVF (Uni M+). The anticipation (top line) and execution (bottom line) phases of the event are represented. The color legends indicate the maximal percent values of ERD (dark red) and ERS (dark blue).*

2.3. NEUROPHYSIOLOGICAL OSCILLATORY MECHANISM UNDERPINNING THE MVF-INDUCED ILLUSORY MOVEMENTS

The results found in Study I and II are in line with previous literature showing as the activation in the primary and associative sensory-motor cortical areas is associated with the MVF illusory experience. As a novelty, findings from Study I and II connected the EEG alpha oscillatory mechanism to the cortical areas activated during MVF-induced movement illusion. Grounded on the existing theoretical framework, the spatiotemporal information observed in Study I and II will be accounted for to propose a neurophysiological model at the basis of the MVF illusion.

2.3.1. ANTICIPATION AND EXECUTION PHASES OF THE MVF ILLUSION

As compared to unilateral right finger movements alone, the MVF condition during the anticipation of the event (i.e., 1000 ms before the auditory cue triggering the right finger movement) showed a clear alpha ERD distributed in the polar prefrontal (BAs 10-11), lateral premotor (BA 6), inferior posterior parietal (BA 40), and primary sensory-motor (BAs 1-2-3, and 4) cortical areas in the hemisphere ipsilateral to the moving hand and contralateral to the image of the opposite hand reflected in the mirror (see Study I and II). Keeping the same comparison, during the movement execution (i.e., from 250 ms to 1250 ms after the auditory cue triggering the right finger movement) the alpha ERD was delimited in the lateral premotor, primary sensory-motor, and inferior posterior parietal cortical areas in the hemisphere contralateral to the image of the moving hand in the mirror. The temporal evolution and the spatial distribution of the alpha ERD in response to MVF finger movement led to the formulation of the following neurophysiological model underpinning the MVF illusion.

The anticipatory activation of the polar prefrontal cortex might represent a "switch-on" mechanism of the attentional mental processes that facilitate the elaboration of the upcoming auditory trigger cue, the finger movement, and the observation of the same movement in the mirror. The prefrontal activation might also facilitate the illusory sensation by anticipating the activation of the neural moving-body representations distributed in the lateral premotor and primary somatomotor cortical areas contralateral to the mirrored movement[118,172–174]. Moreover, the prefrontal activation may also trigger the anticipatory activity of the inferior posterior parietal cortex that may concur to the pre-excitation of the mentioned neural body representations by its neural network underpinning the visuo-somatomotor transformations to be induced by the upcoming observation of the MVF[16,78,175–177]. The anticipatory activity of the posterior parietal cortex (PPC) may be also associated with multisensory integration of proprioceptive and visuo-motor information occurring during the MVF condition. This speculation relies on evidence demonstrating functional reciprocal connections between the PPC and premotor and

primary sensory-motor areas[16,53,67,78,178]. Finally, the anticipatory alpha ERD observed in the primary sensory-motor, premotor, and posterior parietal areas may be explained by the mitigation of interhemispheric inhibition (IHI), a mechanism occurring during unilateral movements[179,180]. In this process, the activation of the moving body representations localized in the M1, S1 and PPC contralateral to the moving limb does transcallosally inhibit the homologous representations of the passive hemisphere[181–184]. In Study I and II, this cortical inhibition is represented by the alpha ERS (see paragraph 2.12.1) contralaterally to the immobile hand in the condition without MVF (see Fig. 2, Study I and Fig. 3 Study II). That inhibition might be mitigated by the excitatory effects exerted by the anticipatory activity impinging in the M1, S1 and PCC contralateral to the mirrored hand.

During the execution phase of the movement, the activation of the dorsal-ventral cortical network including the PPC, lateral PMC, and sensory-motor cortical areas may play a key role in the experience of the MVF illusion. Specifically, the image of the finger moving in the mirror activates the occipital (visual representation) areas, the posterior parietal (visuospatial, motor, and somatosensory representation) associative area, the lateral premotor (visuomotor and motor representation), and the primary sensory-motor (motor and somatosensory representation) areas in the hemisphere contralateral to the MVF illusory finger movement. In this framework, the MVF illusion may be related to the neural representations of the spatial co-localization of the perceived finger movement in the mirror and its immobile finger behind the mirror. Again, these assumptions are in line with evidence that demonstrated the primary role of the functional connections between the PPC and the sensory-motor cortex in the multisensory integration of visuomotor integration[16,53,67,78,178]. Mitigation of the IHI may occur also in this case in the primary sensory-motor, premotor and posterior parietal areas[179,180]. In this phase, the visual information of the mirrored finger movement would reduce the transcallosal inhibitory effects of the active hemisphere towards the homologous finger representation in the passive hemisphere[179,180], making possible the MVF illusory experience.

2.3.2. FROM THE ALPHA ERD/ERS TO THE NEUROPHYSIOLOGICAL MODEL OF THE MVF ILLUSION

From the previous chapter we learned that the sensory-motor EEG alpha rhythms (8-12 Hz) result from synchronized oscillatory signals conveyed within a cortical pyramidal, basal ganglia, and thalamic neurons loop[81,84,97,185,186] and characterize an *idling* state of the sensory-motor areas[81,97,185,187]. Furthermore, it is acknowledged that EEG alpha rhythms reduce in amplitude during the anticipation and the experience of sensory-motor events[81,86,89,102]. In light of the temporal evolution and spatial distribution of the alpha ERD observed in Study I and II of this project and described above, the following assumptions can be posited. Firstly, real movements and MVF-induced illusory movements share the same neurophysiological oscillatory

mechanism, activating the primary and associative sensory-motor cortical areas. Secondly, that neurophysiological mechanism serves additionally the visuomotor transformation processes occurring during MVF-induced illusion of finger movement, as observed by the modulation of the EEG alpha oscillations in the frontal and posterior cortical areas. Thirdly, the anticipation and the experience of the MVF illusion would interrupt (ERD) the inhibitory alpha frequency synchronization in the hemisphere contralateral to the mirrored finger[81,89,188], inducing the conscious and vivid MVF illusory experience.

CHAPTER 3. INVESTIGATING THE NEURAL CORRELATES OF MVF THROUGH SENSORY-MOTOR INTERACTION

In the previous chapter, the spatial and temporal features of MVF-induced illusory movements have been discussed concerning the findings observed in Study I and II of the present project. As stated in the Introduction (paragraph 1.4), Study III aimed to investigate the experience of electrical stimuli perception and the interaction with MVF-induced illusory movements. In the following paragraphs, research on sensory-motor interaction and MVF will be reviewed and discussed in relation to the findings observed in Study III. Successively, a model of the presumed analgesic mechanisms enacted with or without MVF will be proposed. Finally, the findings will be framed in the context of the attentional triple network and its role in nociceptive processes.

3.1. CORTICAL INVESTIGATION OF MVF IN PATIENTS WITH CHRONIC PAIN

It is well known that lesions occurring in the central and peripheral nervous systems and the resulting functional impairment can lead to maladaptive neuroplasticity[37,189–191]. MVF-based techniques are thought to reverse the maladaptive cortical neuroplasticity, induce motor recovery, and improve symptoms in patients with motor functional deficits (e.g., hemiparesis following a stroke) or chronic pain conditions (e.g., PLP following amputations, CRPS, fibromyalgia)[16,22,78,192,193]. Despite its potential for cortical reorganization, MVF techniques have been poorly applied in the research context in relation to experimentally-induced sensory-motor interaction in healthy individuals. Moreover, when MVF was applied in the clinical context, the majority of the studies focused on the motor recovery trajectory or pain relief outcomes rather than the brain neural correlates. However, some clinical studies on stroke patients and amputees indicated the primary sensory-motor cortex (S1-M1) as the main area influenced by MVF-induced neuroplasticity. In two fMRI[194] and EEG[195] studies, chronic stroke patients were assigned to either MVF (experimental) or noMVF (control) groups and underwent conventional motor therapy. Four weeks after the beginning of the intervention, cortical recordings were collected to probe differences in cortical activation in response to motor tasks performed with the affected hand. As compared to the control groups, the experimental groups (undergoing MVF training) showed a significant increase in cortical activity in the

M1, PMC, and SMA as well as stronger EEG alpha rhythm suppression (as a marker of motor recovery) contralateral to the affected limb[194]. In addition, the MVF group obtained higher scores in the functional Fugl-Meyer Assessment[194] and manual function test[195]. Similarly, Foell and colleagues analyzed the fMRI outcomes before and after an MVF training program (4 weeks) in patients with PLP following unilateral arm amputation[196]. The significant reduction of the PLP symptoms was accompanied by a restricted activation of the primary somatosensory and inferior parietal cortical areas. The Authors attributed this cortical narrowed activity to a reversal of the dysfunctional cortical reorganization following the amputation[196]. However, recent research challenged the primary role of the sensory-motor cortex in the neuroplastic processes induced by the MVF. Neuroimaging studies, using fMRI[197,198] and near-infrared spectrometry[199], observed that a reduction of PLP symptoms was associated with prefrontal cortical activity in patients with lower limb amputation[198], whereas the balanced activation of the precunei may (i) discriminate between MVF therapy responders and non-responders, and (ii) play a role in the motor cortex stimulation and reorganization through the connections between the precuneus and SMA[199]. Furthermore, the findings from Saleh and colleagues suggested that MVF triggers the activity of a frontoparietal action observation network that, in turn, modulates the activity of the M1[197].

Studying the MVF effects on sensory-motor interaction by applying experimental pain may be misleading. The electrical phasic stimulations used in Study III do not properly resemble the chronic pain symptoms associated with PLP nor simulate the motor impairment observed in patients with hemiparesis. However, a number of connections between the results of Study III and the aforementioned studies on patients can be made. Although the scalp distribution of the alpha ERD observed in Study III does not allow to make clear inferences on the cortical responses to painful or non-painful electrical stimuli during the MVF illusion, the cortical source analysis showed the role of the precuneus and parietal posterior cortical areas for the internal representation of observed movements (such as MVF illusory movements) and lower nociceptive individual perception. Moreover, the results from Study III are in line with those from Saleh and colleagues[197], indicating the involvement of a wide fronto-parietal visuomotor integrative network as responsible for the modulation of motor commands and inhibition of painful stimuli.

The nociceptive processes, as modulated by sensory-motor interaction tasks with and without MVF, will be treated in detail in the next paragraphs and will conclude this chapter.

3.2. ATTENTIONAL FACTORS INVOLVED IN PAIN MODULATION

In the course of this dissertation, we learned that pain is defined as a sensory unpleasant experience and can be shaped by psychological, cognitive, attentional, and affective factors[134,135,200,201]. Additionally, previous evidence showed as sensory-motor interaction occurring in the same limb can reduce the painful experience through the cortical gating effect[89,102,142]. In Study III, that sensory-motor interaction was obtained by combining MVF-induced illusory movements of the left index finger and electrical stimuli applied to the true left index finger. As nociception processes present substantial inter- and intra-individual variability[202], stimuli at individually fixed amperage produced fluctuations in the subjective perception of the stimulation intensity. The investigation of those fluctuations suggests that the analgesic effects during MVF may be served by a different neurophysiological mechanism as compared to the gating effect mentioned in the Introduction. Specifically, internally and externally oriented attention may play a key role in the nociception processes.

3.2.1. PREFRONTAL INHIBITORY MECHANISMS

Results from Study III indicated as reduced painful sensations are characterized by a clear activity in the dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), anterior cingulate cortex (ACC), and inferior parietal lobule (IPL). These areas have been subsumed under a dorsal attentional network (IPL and IFG)[203,204] and a top-down sensory-motor inhibitory circuit (DLPFC and ACC)[204–206]. In particular, the IFG plays a central role in maintaining sustained attention during task execution (e.g., finger movements in Study III) and in modulating appropriate motor actions in response to external sensory stimuli[207–211]. In this scenario, the anticipatory activation observed in the prefrontal and sensory-motor cortical areas during the control condition in Study III (see Table 1) might be a sign of prefrontal-induced movement planning and stimulus expectancy enacted to prepare adaptive brain responses to the electrical noxious stimuli. These adaptive responses are represented by the subsequent combined activation of the DLPFC and ACC (contralateral to the electrically stimulated hand), which have been proven to play an important role in pain suppression[204,206,212–214] via the inhibition of brain structures centrally involved in nociception processes such as the amygdala, insula, thalamus, and hippocampus[206,215–218]. In an fMRI study, Brascher and colleagues allowed the participants to manipulate the intensity of phasic pain (control condition), in contrast with an uncontrollable pain experimental condition[219]. Results demonstrated that the DLPFC suppressed the insula and thalamus in the control condition, whereas this inhibitory effect did not occur in the uncontrollable condition[219]. A suggestive comparison can be made between the results observed by Brascher and colleagues and the results observed in Study III. Since the subjects were not informed about the fixed interstimulus interval (10 s), their prediction of the upcoming auditory-electrical stimulus is to be considered nearly aleatory. As a consequence, if the prediction of the upcoming stimulus was wrong (i.e., unexpected stimulus), the DLPFC did not promptly induce the inhibitory

signals toward the nociceptive system's structures (i.e., subjects perceived pain). On the contrary, a correct prediction of the upcoming stimulus permitted the proper action of the inhibitory signals from the DLPFC, IFG, and ACC, resulting in a reduced subjective experience of the electrical stimulation.

3.2.2. CORTICAL MIDLINE STRUCTURES INVOLVED DURING MVF

The literature on human nociception processes indicated the involvement of several brain structures in the conscious elaboration of different pain-related domains. Specifically, the medial prefrontal cortex as well as anterior and posterior cingulate (PCC and ACC) cortices have been associated with the elaboration of the affective component of pain[220,221]. Furthermore, the activity of a posterior subnetwork of the brain responds to the cognitive and affective processes of nociception, such as self-awareness and expectation of pain[222]. This subnetwork is represented by widespread cortical connections among the IPL, PCC, and precuneus[222]. Finally, the unpleasant sensation induced by painful stimuli ("suffering") is related to the activation of cortical midline structures (CMS)[223,224]. The CMS can be defined as a compound of brain regions considered as a single anatomical and functional domain related to the sense-of-self and sensory-perceptual processing[223–225]. In particular, the posterior part of the CMS (i.e., posterior cingulate cortex and precuneus) is strongly engaged in the representation of the self as well as the evaluation of self-relevant sensations[226,227], whereas the ventral part (medial frontal gyrus and ACC) responds to interoceptive signals, such as painful stimuli[224].

During the MVF task in Study III, the subjects may "fall" into a self-oriented attentional state to interiorize the image of the illusory hand reflected in the mirror. Notably, the senses of ownership and agency related to this internal attentional state are induced by the activation of the ACC and IPL[224,225,228]. Moreover, given its dense connections with the structures of the limbic system (e.g., amygdala, insula, thalamus), the CMS might play a key role also in the interiorization of the nociceptive afferents signals[224] coming from the stimulated hand. Therefore, the analgesic mechanism (i.e., reduction in the subjectively perceived intensity of the electrical stimulation) observed during the MVF condition in Study III might be represented by the inhibition of the cortical midline limbic regions.

3.2.3. ROLE OF ATTENTIONAL TRIPLE NETWORK IN PAIN MODULATION

The externally- and internally-oriented attentional mechanisms and cortical areas described in the previous paragraphs belong to functionally connected circuits of the brain. These circuits encompass (i) a frontoparietal executive control network (ECN), that includes the DLPFC and PPC and is responsible for goal-oriented tasks execution and mental representation of the "outer world" [229,230]; (ii) a self-representational

default mode network (DMN), including the PCC, the medial prefrontal cortex, and the angular gyrus, normally active when the attention is self-oriented ("inner world")[231,232]; (iii) a salience network (SN), including the dorsal ACC and the anterior insula, thought to act as a switch between the ECN (correlated activity) and DMN (anticorrelated activity)[229,233]. The triple network model proposes that, when engaged by external relevant stimuli, such as painful stimuli, the SN reduces the activity and connectivity within the structures of the DMN to facilitate the activity and connectivity amongst the structures of the ECN[233].

The triple network functioning can be linked with the findings observed in Study III. In the condition without the MVF illusion (traditional cortical sensory-motor gating effect), the attention is directed to external goal-oriented tasks, namely the movement of the fingers interacting with the electrical stimuli. The externally-directed attention involved the activation of the prefrontal and parietal cortical areas, engaged to suppress the afferent nociceptive information[234,235]. In contrast, the interiorization of the illusory hand occurring during the MVF condition required self-oriented attention, thus facilitating the internal conscious representation of the afferent sensory stimuli as elaborated in the PCC, angular gyrus, and medial prefrontal cortex (the core structures of the DMN)[231,232,236]. As a result, the inhibition of these cortical areas caused a decrease in the individual perceived intensity of the electrical stimuli, and it may reflect an attenuated sense-of-self and reduced interoception. The findings from Study III are in line with previous studies showing enhanced DMN activity in response to painful[237] rather than non-painful stimulations[238] as well as the role of the ECN structures in pain suppression[204,213].

As with Study I and II, the sensory-motor interaction between electrical stimuli and MVF-induced illusory movements investigated in Study III was related to the underlying neurophysiological oscillatory mechanism at the alpha frequency (alpha ERD/ERS), an EEG rhythm acknowledged for its role in motor and sensory-nociceptive processes[89,120,123] as well as for its functional meaning within the core structures of the triple network (ECN, DMN, and SN)[239–241]. In Study III, the alpha ERD in the frontoparietal cortical areas reflects the activation of the executive efferent motor outputs enacted to interfere with the concomitant afferent sensory inputs. Contrariwise, the MVF condition is reflected by strong activity (alpha ERD) within the cortical midline structures of the DMN, reflecting self-representational thinking as well as the processing of the affective component of pain. The analgesic effects observed in the MVF condition may be related to increased alpha band oscillations in the CMS[135,148].

CHAPTER 4. LIMITATIONS

The experimental paradigms behind the present work are not free from methodological limitations. Past evidence showed that the topography and functional meaning of the alpha oscillations are different for the low alpha band (about 8-10 Hz) and high alpha band (about 10-12 Hz)[82,83,101]. The low alpha band is more distributed in the parietal areas and reflects unspecific alertness and response to relevant warning stimuli, whereas the high alpha band is prominent in the frontoparietal regions and decreases during task-specific sensory processing[88,115]. The studies proposed in this dissertation failed in finding differences in the cortical distribution and functionality between the alpha sub-bands and only the total alpha band has been reported in the analysis.

In Study III, the cortical midline structures and the triple attentional network have been associated with the affective and sensory components of nociception. However, a few issues must be considered. Firstly, although the CMS present dense connections with the limbic system (amygdala, thalamus, hippocampus, etc.), inferences about the involvement of those structures remain hypothetical, due to the intrinsic low spatial resolution of the EEG techniques. Secondly, effective measures of functional connectivity (e.g., dynamic causal modelling or Granger causality) are required for a proper comprehension of the attentional networks and their role in sensory-motor interaction. Thirdly, distinct measures of the affective (emotional) and sensory (discriminative) components of pain could have been ideal to correlate the alpha oscillations in the CMS and triple network with these two aspects of nociception.

Another element of caution is attributable to the phasic electrical stimulations applied in Study III, which do not accurately reflect the various symptoms of the chronic pain conditions that the MVF-based therapies were proposed to treat. The reason was to avoid many mental processes occurring during the experience of prolonged pain models that can affect the alpha oscillations. However, experimental prolonged tonic pain might represent a better model to investigate the MVF effects on pain and its development into persistent states.

Finally, the sample size was not calculated before the recruitment phase. This issue must be considered particularly in Study III, where a few participants did not clearly show the expected fluctuations in the perceived intensity of the electrical stimuli. Therefore, the three groups presented different sample sizes, allowing the only use of a mixed model statistical design.

CHAPTER 5. CONCLUSIONS

The present PhD project investigated the oscillatory patterns of the EEG alpha rhythm (ERD/ERS) recorded from healthy individuals in relation to the MVF illusory technique. Results from Study I demonstrated that unilateral movements performed during MVF illusion are related to bilateral cortical activation in the frontal and centroparietal sensory-motor areas, as reflected by a clear scalp alpha ERD in those brain regions. The cortical source analysis of the alpha ERD disclosed the key role of associative prefrontal, premotor, and posterior parietal cortical areas (contralateral to the illusory movement) in the transformation of visual information into somatomotor information. In Study III, the MVF illusion was used to induce cortical interference with afferent painful and non-painful sensory electrical stimuli. Such an interaction resulted in reduced activity (less alpha ERD) in the midline cortical areas of the pain neural matrix in the stimuli perceived as non-painful.

The 64-channel EEG system allowed a precise definition of the temporal evolution of the movement preparation and execution and stimulus expectancy and experience as well as the cortical correlates with a moderately high spatial resolution. The dynamic changes of the alpha ERD have been associated with the neurophysiological oscillatory mechanism underlying the MVF illusion and its interaction with sensory stimuli. In this regard, MVF-induced illusory movements and actual movements seem to share the same sensory-motor neurophysiological mechanism. Moreover, MVF illusion might affect nociception processes by reducing the activation in the cortical midline limbic regions. Further investigations on the MVF mechanism and its effects on nociception processes might be essential to developing cost-effective rehabilitative tool.

5.1. CLINICAL IMPLICATIONS

MVF-based therapies are nowadays a solid rehabilitative instrument for patients with diverse chronic pain conditions (e.g., PLP, CRPS, post-stroke hemiparesis or stiffness of one limb). Neurophysiological evidence indicated as these patients show a reduced alpha suppression during motor planning and execution[242] as well as lower interhemispheric neural communication[180]. The visuomotor transformation processes induced by the MVF illusion may facilitate the cortical reorganization of the sensory-motor cortex in the ipsilesional hemisphere[243]. Similarly, the fronto-parietal MVF-induced activity can be correlated to improvements in the patients' functions in the motor, sensory, and attentional domains[19]. Taken together, the findings observed in the present work not only lend support to these models but help also to understand the underlying thalamo-cortical mechanisms based on the EEG alpha oscillations. In this regard, motor re-learning positively correlated with the brain's ability to suppress the

alpha rhythm[244–246] and with augmented transcallosal communication[179,180]. Therefore, the clinical assessment of the alpha ERD – as an index of restored motor information processing – may represent a neural biomarker for the constant cost-effective monitoring of the patient's motor recovery trajectory. Other than MVF illusion, alpha ERD has been also associated with other mental strategies for motor simulation, such as action observation and motor imagery[46,247–249]. In this context, the detection of the alpha ERD is largely used for the control of prosthesis or mechanical devices by brain-computer interface[250] and for promoting motor rehabilitation[251,252] for those patients with unilateral limb dysfunctions.

5.2. FUTURE PERSPECTIVES

The precise mechanism underlying the MVF illusion and – particularly – its effect on pain perception remains to be elucidated. Future research may focus on functional connectivity analysis to shed light on the role of the attentional triple network. Moreover, multimodal EEG-fMRI investigations could be performed to further investigate the connectivity between cortical and subcortical (e.g., amygdala, thalamus, hippocampus) structures of the limbic system and their alterations in the activity during MVF-illusory movements and painful stimulation.

Extensive research is also needed to assess the modulatory effects of MVF illusion during prolonged pain models. Since neuroplasticity has been shown to occur even in the adult brain, motor training coupled with MVF illusion may be applied to evaluate the long-term brain changes, in both patients and healthy individuals. Furthermore, these long-term responses might be investigated during exposure to prolonged experimental pain. Finally, the importance of the congruent visuomotor correspondence in the MVF-related sensory-motor interaction could be evaluated by manipulating the subjects' viewpoint or arm position.

LITERATURE LIST

1. Gori S, Molteni M, Facoetti A. Visual Illusion: An Interesting Tool to Investigate Developmental Dyslexia and Autism Spectrum Disorder. *Front Hum Neurosci*. 2016;10(175):1-19. doi:10.3389/fnhum.2016.00175

2. Ramachandran VS, Rodgers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. *Proc R Soc B Biol Sci*. 1996;263(1369):377-386. doi:10.1098/rspb.1996.0058

3. Flor H, Elbert T, Knetch S, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature*. 1995;375:482-484. doi:10.1038/375482a0

4. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. *Neurology*. 2003;61(12):1707-1715. doi:10.1212/01.WNL.0000098939.02752.8E

5. Jutzeler C, Curt A, Kramer J. Relationship between chronic pain and brain reorganization after deafferentation: A systematic review of functional MRI findings. *Neuroimage Clin*. 2015;9:599-606. doi:10.1016/j.nicl.2015.09.018

6. Halicka M, Vittersø A, Proulx M, Bultitude J. Neuropsychological Changes in Complex Regional Pain Syndrome (CRPS). *Behav Neurol*. 2020;2020(4561831):1-30. doi:10.1155/2020/4561831

7. Gofiţă CE, Mușetescu AE, Ciurea PL, et al. Posttraumatic Complex Regional Pain Syndrome and Related Comorbidities. *Curr Heal Sci J*. 2019;45(3):321-328. doi:10.12865/CHSJ.45.03.12

8. Pfannmoller J, Strauss S, Langner I, Usichenko T, Lotze M. Investigations on maladaptive plasticity in the sensorimotor cortex of unilateral upper limb CRPS I patients. *Restor Neurol Neurosci*. 2019;37:143-153. doi:10.3233/RNN-180886

9. Verfaille C, Filbrich L, Rossetti Y, et al. Visuomotor impairments in complex regional pain syndrome during pointing tasks. *Pain*. 2021;162(3):811-822. doi:10.1097/j.pain.0000000000002068

10. Zangrandi A, Allen Demers F, Schneider C. Complex Regional Pain Syndrome. A Comprehensive Review on Neuroplastic Changes Supporting the Use of Non-invasive Neurostimulation in Clinical Settings. *Front Pain Res*. 2021;2(September):1-15. doi:10.3389/fpain.2021.732343

11. Finnmann Munk AS, Petersen KK, Bødtker S, et al. Long-Term biopsychosocial issues and health-related quality of life in young adolescents and adults treated for childhood Complex Regional Pain Syndrome, type 1. *Scand J Pain*. 2022;22(3):473-482. doi:10.1515/sjpain-2021-0217

12. Borich MR, Wolf SL, Tan AQ, Palmer JA. Targeted neuromodulation of abnormal interhemispheric connectivity to promote neural plasticity and recovery of arm function after stroke: A randomized crossover clinical trial study protocol. *Neural Plast*. 2018;2018:1-8. doi:10.1155/2018/9875326

13. Taub E, Crago JE, Uswatte G. Constraint-induced movement therapy: A new approach to treatment in physical rehabilitation. *Rehabil Psychol*. 1998;43(2):152-170. doi:10.1037/0090-5550.43.2.152

14. Mechsner F, Kerzel D, Knoblich G, Prinz W. Perceptual basis of bimanual coordination : Abstract : Nature. *Nature*. 2001;414(6859):69-73. doi:10.1038/35102060

15. Ramachandran V, Hirstein W. The perception of phantom limbs. *Brain*. 1998;121:1603-1630. doi:10.1093/brain/121.9.1603

16. Lamont K, Chin M, Kogan M. Mirror box therapy seeing is believing. *Explor J Sci Heal*. 2011;7(6):369-372. doi:10.1016/j.explore.2011.08.002

17. Egsgaard LL, Petrini L, Christoffersen G, Arendt-Nielsen L. Cortical responses to the mirror box illusion: A high-resolution EEG study. *Exp Brain Res*. 2011;215(3-4):345-357. doi:10.1007/s00221-011-2902-x

18. Samuelkamaleshkumar S, Reethajanetsureka S, Pauljebaraj P, Benshamir B, Padankatti SM, David JA. Mirror therapy enhances motor performance in the paretic upper limb after stroke: A pilot randomized controlled trial. *Arch Phys Med Rehabil*. 2014;95(11):2000-2005. doi:10.1016/j.apmr.2014.06.020

19. Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: A randomized controlled trial. *Neurorehabil Neural Repair*. 2009;23(3):209-217. doi:10.1177/1545968308324786

20. Cacchio A, De Blasis E, De Blasis V, Santilli V, Spacca G. Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. *Neurorehabil Neural Repair*. 2009;23(8):792-799. doi:10.1177/1545968309335977

21. Karmakar A, Lieberman I. Mirror box therapy for complex regional pain

syndrome. *Anesthesia*. 2006;61:412-413. doi:https://doi.org/10.1111/j.1365-2044.2006.04605.x

22. Ramachandran VS. Plasticity and functional recovery in neurology. *Clin Med J R Coll Physicians London*. 2005;5(4):368-373. doi:10.7861/clinmedicine.5-4-368

23. Ramachandran V, Rogers-Ramachandran D. Mirror feedback assisted recovery from hemiparesis following stroke. In Reply to Morkisch et al.: How to perform mirror therapy after stroke? Evidence from a meta-analysis. *Restor Neurol Neurosci*. 2019;37:437-443. doi:10.3233/RNN-190971

24. Zhang J, Fong K. Enhancing mirror visual feedback with intermittent theta burst stimulation in healthy adults. *Restor Neurol Neurosci*. 2019;37:483-495. doi:10.3233/RNN-190927

25. Rjosk V, Kaminski E, Hoff M, et al. Mirror visual feedback-induced performance improvement and the influence of hand dominance. *Front Hum Neurosci*. 2016;9(JAN2016). doi:10.3389/fnhum.2015.00702

26. Fong KNK, Ting KH, Zhang JJQ, Yau CSF, Li LSW. Event-Related Desynchronization During Mirror Visual Feedback: A Comparison of Older Adults and People After Stroke. *Front Hum Neurosci*. 2021;15(May):1-10. doi:10.3389/fnhum.2021.629592

27. Inagaki Y, Seki K, Makino H, Matsuo Y, Miyamoto T, Ikoma K. Exploring hemodynamic responses using mirror visual feedback with electromyogram-triggered stimulation and functional near-infrared spectroscopy. *Front Hum Neurosci*. 2019;13(February):1-8. doi:10.3389/fnhum.2019.00060

28. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Cochrane Database of Systematic Reviews Mirror therapy for improving motor function after stroke (Review). *Cochrane Database Syst Rev*. 2012;(3):1-12. doi:10.1002/14651858.CD008449.pub2.www.cochranelibrary.com

29. Thieme H, Morkisch N, Mehrholz J, et al. Mirror therapy for improving motor function after stroke Review). *Cochrane Database Syst Rev*. 2018;2018(7):1-154. doi:10.1002/14651858.CD008449.pub3

30. Murray CD, Patchick E, Pettifer S, et al. Investigating the efficacy of a virtual mirror box in treating phantom limb pain in a sample of chronic sufferers. *Int J Disabil Hum Dev*. 2006;5(3):227-234. doi:10.1515/IJDHD.2006.5.3.227

31. Ortiz-Catalan M, Sander N, Kristoffersen MB, Håkansson B, Brånemark R.

Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: A case study of a chronic PLP patient. *Front Neurosci*. 2014;8(8 FEB):1-7. doi:10.3389/fnins.2014.00024

32. Rey B, Oliver A, Monzo J, Riquelme I. Development and Testing of a Portable Virtual eality-Based Mirror Visual Feedback System with Behavioral Measures Monitoring. *Int J Environ Res Public Health*. 2022;19(4):1-20. doi:10.3390/ijerph19042276

33. Trojan J, Diers M, Fuchs X, et al. An augmented reality home-training system based on the mirror training and imagery approach. *Behav Res*. 2014;46:634-640. doi:https://doi.org/10.3758/s13428-013-0412-4

34. Won AS, Barreau AC, Gaertner M, et al. Assessing the feasibility of an open-source virtual reality mirror visual feedback module for complex regional pain syndrome: Pilot usability study. *J Med Internet Res*. 2021;23(5):1-8. doi:10.2196/16536

35. Thøgersen M, Andoh J, Milde C, Graven-Nielsen T, Flor H, Petrini L. Individualized Augmented Reality Training Reduces Phantom Pain and Cortical Reorganization in Amputees: A Proof of Concept Study. *J Pain*. 2020;21(11-12):1257-1269. doi:10.1016/j.jpain.2020.06.002

36. Mercier C, Sirigu A. Training with virtual visual feedback to alleviate phantom limb pain. *Neurorehabil Neural Repair*. 2009;23(6):587-594. doi:10.1177/1545968308328717

37. Ortiz-Catalan M, Guðmundsdóttir RA, Kristoffersen MB, et al. Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain. *Lancet*. 2016;388(10062):2885-2894. doi:10.1016/S0140-6736(16)31598-7

38. Murray C. *Amputation, Prosthesis Use, and Phantom Limb Pain. An Interdisciplinary Perspective*.; 2010. doi:10.1007/978-0-387-87462-3

39. Mouraux D, Brassinne E, Sobczak S, et al. 3D augmented reality mirror visual feedback therapy applied to the treatment of persistent, unilateral upper extremity neuropathic pain: a preliminary study. *J Man Manip Ther*. 2017;25(3):137-143. doi:10.1080/10669817.2016.1176726

40. Penelle B, Mouraux D, Brassinne E, Tuna T, Nonclercq A, Warzée N. 3D augmented reality applied to the treatment of neuropathic pain. In: *Virtual*

Reality & Associated Technologies Laval 2012 ICDVRAT. ; 2012:10-12. doi:http://hdl.handle.net/2013/ULB-DIPOT:oai:dipot.ulb.ac.be:2013/126850

41. Bhasin A, Padma Srivastava M V., Kumaran SS, Bhatia R, Mohanty S. Neural interface of mirror therapy in chronic stroke patients: A functional magnetic resonance imaging study. *Neurol India*. 2012;60(6):570-576. doi:10.4103/0028-3886.105188

42. You S, Jang S, Kim Y, et al. Virtual Reality-Induced Cortical Reorganization and Associated Locomotor Recovery in Chronic Stroke. *Stroke*. 2005;36(6):1166-1171. doi:10.1161/01.STR.0000162715.43417.91. Epub 2005 May 12.

43. Osumi M, Ichinose A, Sumitani M, et al. Restoring movement representation and alleviating phantom limb pain through short-term neurorehabilitation with a virtual reality system. *Eur J Pain (United Kingdom)*. 2017;21(1):140-147. doi:10.1002/ejp.910

44. Perry B, Mercier C, Pettifer S, Cole J, Tsao J. Virtual reality therapies for phantom limb pain. *Eur J Pain (United Kingdom)*. 2014;18(7):897-899. doi:10.1002/ejp.559.

45. Perry B, Armiger R, Wolde M, et al. Clinical Trial of the Virtual Integration Environment to Treat Phantom Limb Pain With Upper Extremity Amputation. *Front Neurol*. 2018;9:770-779. doi:10.3389/fneur.2018.00770

46. Dunn J, Yeo E, Moghaddampour P, Chau B, Humbert S. Virtual and augmented reality in the treatment of phantom limb pain: A literature review. *NeuroRehabilitation*. 2017;40(4):595-601. doi:10.3233/NRE-171447

47. Sato K, Fukumori S, Muyake K, Obata D, Gofuku A, Morita K. *A Novel Application of Virtual Reality for Pain Control: Virtual Reality-Mirror Visual Feedback Therapy*.; 2012. doi:http://dx.doi.org/10.5772/51139

48. Wang J, Fritzsch C, Bernarding J, et al. A comparison of neural mechanisms in mirror therapy and movement observation therapy. *J Rehabil Med*. 2013;45(4):410-413. doi:10.2340/16501977-1127

49. Wang J, Fritzsch C, Bernarding J, et al. Cerebral activation evoked by the mirror illusion of the hand in stroke patients compared to normal subjects. *NeuroRehabilitation*. 2013;33(4):593-603. doi:10.3233/NRE-130999

50. Milde C, Rance M, Kirsch P, et al. Do mirror glasses have the same effect on brain activity as a mirror box? Evidence from a functional magnetic resonance

imaging study with healthy subjects. *PLoS One*. 2015;10(5):1-15. doi:10.1371/journal.pone.0127694

51. Hamzei F, Läppchen CH, Glauche V, Mader I, Rijntjes M, Weiller C. Functional plasticity induced by mirror training: The mirror as the element connecting both hands to one hemisphere. *Neurorehabil Neural Repair*. 2012;26(5):484-496. doi:10.1177/1545968311427917

52. Numata K, Murayama T, Takasugi J, Monma M, Oga M. Mirror observation of finger action enhances activity in anterior intraparietal sulcus: A functional magnetic resonance imaging study. *J Japanese Phys Ther Assoc*. 2013;16(1):1-6. doi:10.1298/jjpta.Vol16_001

53. Matthys K, Smits M, Van der Geest JN, et al. Mirror-Induced Visual Illusion of Hand Movements: A Functional Magnetic Resonance Imaging Study. *Arch Phys Med Rehabil*. 2009;90(4):675-681. doi:10.1016/j.apmr.2008.09.571

54. Dohle C, Kleiser R, Seitz RJ, Freund HJ. Body Scheme Gates Visual Processing. *J Neurophysiol*. 2004;91(5):2376-2379. doi:10.1152/jn.00929.2003

55. Diers M, Kamping S, Kirsch P, et al. Illusion-related brain activations: A new virtual reality mirror box system for use during functional magnetic resonance imaging. *Brain Res*. 2015:1-10. doi:10.1016/j.brainres.2014.11.001

56. Aziz-Zadeh L, Maeda F, Zaidel E, Mazziotta J, Iacoboni M. Lateralization in motor facilitation during action observation: A TMS study. *Exp Brain Res*. 2002;144(1):127-131. doi:10.1007/s00221-002-1037-5

57. Fukumura K, Sugawara K, Tanabe S, Ushiba J, Tomita Y. Influence of mirror therapy on human motor cortex. *Int J Neurosci*. 2007;117(7):1039-1048. doi:10.1080/00207450600936841

58. Garry MI, Loftus A, Summers JJ. Mirror, mirror on the wall: Viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability. *Exp Brain Res*. 2005;163(1):118-122. doi:10.1007/s00221-005-2226-9

59. Kang YJ, Park HK, Kim HJ, et al. Upper extremity rehabilitation of stroke: Facilitation of corticospinal excitability using virtual mirror paradigm. *J Neuroeng Rehabil*. 2012;9(1):1. doi:10.1186/1743-0003-9-71

60. Carson RG, Ruddy KL. Vision modulates corticospinal suppression in a functionally specific manner during movement of the opposite limb. *J Neurosci*. 2012;32(2):646-652. doi:10.1523/JNEUROSCI.4435-11.2012

61. Debnath R, Franz EA. Perception of hand movement by mirror reflection evokes brain activation in the motor cortex contralateral to a non-moving hand. *Cortex*. 2016;81:118-125. doi:10.1016/j.cortex.2016.04.015

62. Touzalin-Chretien P, Ehrler S, Dufour A. Behavioral and electrophysiological evidence of motor cortex activation related to an amputated limb: A multisensorial approach. *J Cogn Neurosci*. 2009;21(11):2207-2216. doi:10.1162/jocn.2009.21218

63. Touzalin-Chretien P, Dufour A. Motor cortex activation induced by a mirror: Evidence from lateralized readiness potentials. *J Neurophysiol*. 2008;100(1):19-23. doi:10.1152/jn.90260.2008

64. Touzalin-Chretien P, Ehrler S, Dufour A. Dominance of vision over proprioception on motor programming: Evidence from ERP. *Cereb Cortex*. 2010;20(8):2007-2016. doi:10.1093/cercor/bhp271

65. Fritzsch C, Wang J, Dos Santos LF, Mauritz KH, Brunetti M, Dohle C. Different effects of the mirror illusion on motor and somatosensory processing. *Restor Neurol Neurosci*. 2014;32(2):269-280. doi:10.3233/RNN-130343

66. Funase K, Tabira T, Higashi T, Liang N, Kasai T. Increased corticospinal excitability during direct observation of self-movement and indirect observation with a mirror box. *Neurosci Lett*. 2007;419(2):108-112. doi:10.1016/j.neulet.2007.04.025

67. Mehnert J, Brunetti M, Steinbrink J, Niedeggen M, Dohle C. Effect of a mirror-like illusion on activation in the precuneus assessed with functional near-infrared spectroscopy. *J Biomed Opt*. 2013;18(6):066001. doi:10.1117/1.jbo.18.6.066001

68. Hadoush H, Mano H, Sunagawa T, Nakanishi K, Ochi M. Optimization of mirror therapy to excite ipsilateral primary motor cortex. *NeuroRehabilitation*. 2013;32(3):617-624. doi:10.3233/NRE-130884

69. Praamstra P, Torney L, Rawle CJ, Chris Miall R. Misconceptions about mirror-induced motor cortex activation. *Cereb Cortex*. 2011;21(8):1935-1940. doi:10.1093/cercor/bhq270

70. Lin SH, Cheng CH, Wu CY, Liu CT, Chen CL, Hsieh YW. Mirror visual feedback induces M1 excitability by disengaging functional connections of perceptuo-motor-attentional processes during asynchronous bimanual movement: A magnetoencephalographic study. *Brain Sci*. 2021;11(8).

doi:10.3390/BRAINSCI11081092

71. Qiu Y, Zheng Y, Liu Y, et al. Synergistic Immediate Cortical Activation on Mirror Visual Feedback Combined With a Soft Robotic Bilateral Hand Rehabilitation System: A Functional Near Infrared Spectroscopy Study. *Front Neurosci*. 2022;16(February):1-10. doi:10.3389/fnins.2022.807045

72. Lee HM, Li PC, Fan SC. Delayed mirror visual feedback presented using a novel mirror therapy system enhances cortical activation in healthy adults. *J Neuroeng Rehabil*. 2015;12(1):1-11. doi:10.1186/s12984-015-0053-1

73. Bartur G, Pratt H, Dickstein R, Frenkel-Toledo S, Geva A, Soroker N. Electrophysiological manifestations of mirror visual feedback during manual movement. *Brain Res*. 2015;1606:113-124. doi:10.1016/j.brainres.2015.02.029

74. Al-Wasity SMH, Pollick F, Sosnowska A, Vuckovic A. Cortical functional domains show distinctive oscillatory dynamic in bimanual and mirror visual feedback tasks. *Front Comput Neurosci*. 2019;13(May). doi:10.3389/fncom.2019.00030

75. Nojima I, Mima T, Koganemaru S, Thabit MN, Fukuyama H, Kawamata T. Human motor plasticity induced by mirror visual feedback. *J Neurosci*. 2012;32(4):1293-1300. doi:10.1523/JNEUROSCI.5364-11.2012

76. Wasaka T, Kakigi R. Conflict caused by visual feedback modulates activation in somatosensory areas during movement execution. *Neuroimage*. 2012;59:1501-1507. doi:10.1186/1471-2202-13-138

77. Dohle C, Stephan KM, Valvoda JT, et al. Representation of virtual arm movements in precuneus. *Exp Brain Res*. 2011;208(4):543-555. doi:10.1007/s00221-010-2503-0

78. Arya KN. Underlying neural mechanisms of mirror therapy: Implications for motor rehabilitation in stroke. *Neurol India*. 2016;64(1):38-44. doi:10.4103/0028-3886.173622

79. Kropotov J. Quantitative EEG, Event-Related Potentials and Neurotherapy. In: Inc E, ed. ; 2009:29-58.

80. Berger H. *Über Das Elektrenkephalogramm Des Menschen - Dritte Mitteilung*. Vol 94.; 1931. doi:10.1007/BF01835097

81. Pfurtscheller G, Lopes Da Silva F. Event-related EEG/MEG synchronization

and desynchronization: Basic principles. *Clin Neurophysiol*. 1999;110(11):1842-1857. doi:10.1016/S1388-2457(99)00141-8

82. Babiloni C, Barry RJ, Başar E, et al. International Federation of Clinical Neurophysiology (IFCN) – EEG research workgroup: Recommendations on frequency and topographic analysis of resting state EEG rhythms. Part 1: Applications in clinical research studies. *Clin Neurophysiol*. 2020;131(1):285-307. doi:10.1016/j.clinph.2019.06.234

83. Ramos-Murguialday A, Birbaumer N. Brain oscillatory signatures of motor tasks. *J Neurophysiol*. 2015;113(10):3663-3682. doi:10.1152/jn.00467.2013

84. Lopes da Silva F. EEG and MEG: Relevance to neuroscience. *Neuron*. 2013;80(5):1112-1128. doi:10.1016/j.neuron.2013.10.017

85. Pfurtscheller G, Neuper C. Chapter 28 Future prospects of ERD/ERS in the context of brain-computer interface (BCI) developments. *Prog Brain Res*. 2006;159:433-437. doi:10.1016/S0079-6123(06)59028-4

86. Pfurtscheller G, Neuper C. Event-related synchronization of mu rhythm in the EEG over the cortical hand area in man. *Neurosci Lett*. 1994;174(1):93-96. doi:10.1016/0304-3940(94)90127-9

87. Brunia CHM. Neural aspects of anticipatory behavior. *Acta Psychol (Amst)*. 1999;101(2-3):213-242. doi:10.1016/s0001-6918(99)00006-2

88. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a rKlimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Research Reviews, 29(2-3), 169–195. doi:10.1016/S016. *Brain Res Rev*. 1999;29(2-3):169-195. doi:10.1016/S0165-0173(98)00056-3

89. Babiloni C, Capotosto P, Del Percio C, et al. Sensorimotor interaction between somatosensory painful stimuli and motor sequences affects both anticipatory alpha rhythms and behavior as a function of the event side. *Brain Res Bull*. 2010;81(4-5):398-405. doi:10.1016/j.brainresbull.2009.11.009

90. Pfurtscheller G, Aranibar A. Evaluation of event-related desynchronization (ERD) preceding and following voluntary self-paced movement. *Electroencephalogr Clin Neurophysiol*. 1979;46(2):138-146. doi:10.1016/0013-4694(79)90063-4

91. Neuper C, Wörtz M, Pfurtscheller G. Chapter 14 ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Prog Brain Res*. 2006;159:211-222.

doi:10.1016/S0079-6123(06)59014-4

92. Babiloni C, Carducci F, Cincotti F, et al. Human movement-related potentials vs desynchronization of EEG alpha rhythm: A high-resolution EEG study. *Neuroimage*. 1999;10(6):658-665. doi:10.1006/nimg.1999.0504

93. Isaichev SA, Derevyankin VT, Koptelov YM, Sokolov EN. Rhythmic alpha-activity generators in the human EEG. *Neurosci Behav Physiol*. 2001;31(1):49-53. doi:10.1023/A:1026622229972

94. Basar E, Schurmann M, Basar-Eroglu C, Karakas S. Alpha oscillations in brain functioning: an integrative theory. *Int J Psychophysiol*. 1997;26(1-3):5-29. doi:10.1016/s0167-8760(97)00753-8

95. Schürmann M, Demiralp T, Başar E, Başar Eroglu C. Electroencephalogram alpha (8-15 Hz) responses to visual stimuli in cat cortex, thalamus, and hippocampus: A distributed alpha network? *Neurosci Lett*. 2000;292(3):175-178. doi:10.1016/S0304-3940(00)01456-7

96. Hughes SW, Crunelli V. Thalamic mechanisms of EEG alpha rhythms and their pathological implications. *Neuroscientist*. 2005;11(4):357-372. doi:10.1177/1073858405277450

97. Lörincz ML, Crunelli V, Hughes SW. Cellular dynamics of cholinergically induced α (8 -13 Hz) rhythms in sensory thalamic nuclei in vitro. *J Neurosci*. 2008;28(3):660-671. doi:10.1523/JNEUROSCI.4468-07.2008

98. Steriade M, Llinás R. The Functional States of the Thalamus and the Associated Neuronal Interplay. *Psychol Rev*. 1988;68(3):649-742. doi:https://doi.org/10.1152/physrev.1988.68.3.649

99. Pfurtscheller G, Klimesch W. Functional Topography During a Visuoverbal Judgment Task Studied with Event-Related Desynchronization Mapping. *J Clin Neurophysiol*. 1992;9(1):120-131. doi:10.1097/00004691-199201000-00013

100. Filipović SR, Jahanshahi M, Rothwell JC. Uncoupling of contingent negative variation and alpha band event-related desynchronization in a go/no-go task. *Clin Neurophysiol*. 2001;112(7):1307-1315. doi:10.1016/S1388-2457(01)00558-2

101. Pfurtscheller G, Berghold A. Patterns of cortical activation during planning of voluntary movement. *Electroencephalogr Clin Neurophysiol*. 1989;72(3):250-258. doi:10.1016/0013-4694(89)90250-2

102. Babiloni C, Capotosto P, Brancucci A, et al. Cortical Alpha Rhythms Are Related to the Anticipation of Sensorimotor Interaction Between Painful Stimuli and Movements: A High-Resolution EEG Study. *J Pain*. 2008;9(10):902-911. doi:10.1016/j.jpain.2008.05.007

103. Urbano A, Babiloni C, Onorati P, et al. Responses of human primary sensorimotor and supplementary motor areas to internally triggered unilateral and simultaneous bilateral one-digit movements. A high-resolution EEG study. *Eur J Neurosci*. 1998;10(2):765-770. doi:10.1046/j.1460-9568.1998.00072.x

104. Mordkoff JT, Gianaros PJ. Detecting the onset of the lateralized readiness potential: A comparison of available methods and procedures. *Psychophysiology*. 2000;37(3):347-360. doi:10.1017/S0048577200982039

105. Pinet S, Hamamé CM, Longcamp M, Vidal F, Alario FX. Response planning in word typing: Evidence for inhibition. *Psychophysiology*. 2015;52(4):524-531. doi:10.1111/psyp.12373

106. Brunia CHM, Haagh SAVM, Scheirs JGM. Waiting to Respond: Electrophysiological Measurements in Man During Preparation for a Voluntary Movement. *Mot Behav*. 1985:35-78. doi:10.1007/978-3-642-69749-4_2

107. Alegre M, De Gurtubay IG, Labarga A, Iriarte J, Malanda A, Artieda J. Alpha and beta oscillatory activity during a sequence of two movements. *Clin Neurophysiol*. 2004;115(1):124-130. doi:10.1016/S1388-2457(03)00311-0

108. Keinrath C, Wriessnegger S, Müller-Putz GR, Pfurtscheller G. Post-movement beta synchronization after kinesthetic illusion, active and passive movements. *Int J Psychophysiol*. 2006;62(2):321-327. doi:10.1016/j.ijpsycho.2006.06.001

109. Müller-Putz GR, Zimmermann D, Graimann B, Nestinger K, Korisek G, Pfurtscheller G. Event-related beta EEG-changes during passive and attempted foot movements in paraplegic patients. *Brain Res*. 2007;1137(1):84-91. doi:10.1016/j.brainres.2006.12.052

110. Cho W, Vidaurre C, Hoffmann U, Birbaumer N, Ramos-Murguialday A. Afferent and efferent activity control in the design of brain computer interfaces for motor rehabilitation. *Proc Annu Int Conf IEEE Eng Med Biol Soc EMBS*. 2011:7310-7315. doi:10.1109/IEMBS.2011.6091705

111. Mima T, Sadato N, Yazawa S, et al. Brain structures related to active and

passive finger movements in man. *Brain*. 1999;122(10):1989-1997. doi:10.1093/brain/122.10.1989

112. Pfurtscheller G, Berghold A. Patterns of cortical activation during planning of voluntary movement. *Electroencephalogr Clin Neurophysiol*. 1989;72(3):250-258. doi:10.1016/0013-4694(89)90250-2

113. Cassim F, Monaca C, Szurhaj W, et al. Does post-movement beta synchronization reflect an idling motor cortex? *Neuroreport*. 2001;12(17):3859-3863. doi:10.1097/00001756-200112040-00051

114. Hummel F, Andres F, Altenmüller E, Dichgans J, Gerloff C. Inhibitory control of acquired motor programmes in the human brain. *Brain*. 2002;125(2):404-420. doi:10.1093/brain/awf030

115. Babiloni C, Arendt-Nielsen L, Chen ACN, et al. Alpha event-related desynchronization preceding a Go/No-Go task: A high-resolution EEG study. *Neuropsychology*. 2004;18(4):719-728. doi:10.1037/0894-4105.18.4.719

116. Jurkiewicz MT, Gaetz WC, Bostan AC, Cheyne D. Post-movement beta rebound is generated in motor cortex: Evidence from neuromagnetic recordings. *Neuroimage*. 2006;32(3):1281-1289. doi:10.1016/j.neuroimage.2006.06.005

117. Raij TT, Forss N, Stancák A, Hari R. Modulation of motor-cortex oscillatory activity by painful Aδ- and C-fiber stimuli. *Neuroimage*. 2004;23(2):569-573. doi:10.1016/j.neuroimage.2004.06.036

118. Babiloni C, Babiloni F, Carducci F, et al. Human Cortical Electroencephalography (EEG) Rhythms during the Observation of Simple Aimless Movements: A High-Resolution EEG Study. *Neuroimage*. 2002;17(2):559-572. doi:10.1006/nimg.2002.1192

119. Lin SH, Cheng CH, Wu CY, Liu CT, Chen CL, Hsieh YW. Mirror visual feedback induces M1 excitability by disengaging functional connections of perceptuo-motor-attentional processes during asynchronous bimanual movement: A magnetoencephalographic study. *Brain Sci*. 2021;11(8). doi:10.3390/brainsci11081092

120. Neuper C, Scherer R, Wriessnegger S, Pfurtscheller G. Motor imagery and action observation: Modulation of sensorimotor brain rhythms during mental control of a brain-computer interface. *Clin Neurophysiol*. 2009;120(2):239-247. doi:10.1016/j.clinph.2008.11.015

121. Carlsson K, Ingvar M, Petersson KM, Petrovic P, Skare S. Tickling Expectations: Neural Processing in Anticipation of a Sensory Stimulus. *J Cogn Neurosci*. 2000;12(4):691-703. doi:10.1162/089892900562318

122. Porro CA, Baraldi P, Pagnoni G, et al. Does anticipation of pain affect cortical nociceptive systems? *J Neurosci*. 2002;22(8):3206-3214. doi:10.1523/jneurosci.22-08-03206.2002

123. Babiloni C, Brancucci A, Babiloni F, et al. Anticipatory cortical responses during the expectancy of a predictable painful stimulation. A high-resolution electroencephalography study. *Eur J Neurosci*. 2003;18(6):1692-1700. doi:10.1046/j.1460-9568.2003.02851.x

124. Hu L, Peng W, Valentini E, Zhang Z, Hu Y. Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations. *J Pain*. 2013;14(1):89-99. doi:10.1016/j.jpain.2012.10.008

125. Ohara S, Crone NE, Weiss N, Lenz FA. Attention to a painful cutaneous laser stimulus modulates electrocorticographic event-related desynchronization in humans. *Clin Neurophysiol*. 2004;115(7):1641-1652. doi:10.1016/j.clinph.2004.02.023

126. Babiloni C, Brancucci A, Percio C Del, et al. Anticipatory Electroencephalography Alpha Rhythm Predicts Subjective Perception of Pain Intensity. *J Pain*. 2006;7(10):709-717. doi:10.1016/j.jpain.2006.03.005

127. Mulders D, De Bodt C, Lejeune N, et al. Dynamics of the perception and EEG signals triggered by tonic warm and cool stimulation. *PLoS One*. 2020:1-25. doi:https://doi.org/10.1371/journal.pone.0231698

128. Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A. Pain suppresses spontaneous brain rhythms. *Cereb Cortex*. 2006;16(4):537-540. doi:10.1093/cercor/bhj001

129. Ploner M, Sorg C, Gross J. Brain Rhythms of Pain. *Trends Cogn Sci*. 2017;21(2):100-110. doi:10.1016/j.tics.2016.12.001

130. Bauer M, Oostenveld R, Peeters M, Fries P. Tactile Spatial Attention Enhances Gamma-Band Activity in Somatosensory Cortex and Reduces Low-Frequency Activity in Parieto-Occipital Areas. *J Neurosci*. 2006;26(2):490-501. doi:DOI: https://doi.org/10.1523/JNEUROSCI.5228-04.2006

131. Hauck M, Lorenz J, Engel AK. Attention to painful stimulation enhances γ-

band activity and synchronization in human sensorimotor cortex. *J Neurosci*. 2007;27(35):9270-9277. doi:10.1523/JNEUROSCI.2283-07.2007

132. Della Penna S, Torquati K, Pizzella V, et al. Temporal dynamics of alpha and beta rhythms in human SI and SII after galvanic median nerve stimulation. A MEG study. *Neuroimage*. 2004;22(4):1438-1446. doi:10.1016/j.neuroimage.2004.03.045

133. Chien J, Liu C, Kim J, Markman T, Lenz F. Painful cutaneous laser stimuli induce event-related oscillatory EEG activities that are different from those induced by nonpainful electrical stimuli. *J Neurophysiol*. 2014;112:824-833. doi:doi: 10.1152/jn.00209.2014. Epub 2014 May 21.

134. Arendt-Nielsen L, Yarnitsky D. Experimental and Clinical Applications of Quantitative Sensory Testing Applied to Skin, Muscles and Viscera. *J Pain*. 2009;10(6):556-572. doi:10.1016/j.jpain.2009.02.002

135. Babiloni C, Arendt-Nielsen L, Chen ACN, Brancucci A, Capotosto P, Rossini PM. Expectancy of pain is influenced by motor preparation: A high-resolution EEG study of cortical alpha rhythms. *Behav Neurosci*. 2005;119(2):503-511. doi:10.1037/0735-7044.119.2.503

136. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: A salience detection system for the body. *Prog Neurobiol*. 2011;93(1):111-124. doi:10.1016/j.pneurobio.2010.10.005

137. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain (United Kingdom)*. 2015;19(6):805-806. doi:10.1002/ejp.605

138. Hoegh M, Petersen KK, Graven-Nielsen T. Effects of repeated conditioning pain modulation in healthy volunteers. *Eur J Pain (United Kingdom)*. 2018;22(10):1833-1843. doi:10.1002/ejp.1279

139. Kida T, Nishihira Y, Wasaka T, Sakajiri Y, Tazoe T. Differential modulation of the short- and long-latency somatosensory evoked potentials in a forewarned reaction time task. *Clin Neurophysiol*. 2004;115(10):2223-2230. doi:10.1016/j.clinph.2004.04.017

140. Nakata H, Inui K, Wasaka T, Nishihira Y, Kakigi R. Mechanisms of differences in gating effects on short- and long-latency somatosensory evoked potentials relating to movement. *Brain Topogr*. 2003;15(4):211-222. doi:10.1023/A:1023908707851

141. Shimazu H, Kaji R, Murase N, et al. Pre-movement gating of short-latency somatosensory evoked potentials. *Neuroreport*. 1999;10(12):2457-2460. doi:10.1097/00001756-199908200-00004

142. Babiloni C, Del Percio C, Arendt-Nielsen L, et al. Cortical EEG alpha rhythms reflect task-specific somatosensory and motor interactions in humans. *Clin Neurophysiol*. 2014;125(10):1936-1945. doi:10.1016/j.clinph.2014.04.021

143. Jones SJ, Halonen JP, Shawkat F. Centrifugal and centripetal mechanisms involved in the "gating" of cortical SEPs during movement. *Electroencephalogr Clin Neurophysiol Evoked Potentials*. 1989;74(1):36-45. doi:10.1016/0168-5597(89)90049-X

144. Wasaka T, Nakata H, Kida T, Kakigi R. Changes in the centrifugal gating effect on somatosensory evoked potentials depending on the level of contractile force. *Exp Brain Res*. 2005;166:118-125. doi:10.1007/s00221-005-2333-7

145. Wasaka T, Kida T, Kakigi R. Facilitation of indormation processing in the primary somatosensory area in the ball rotation task. *Sci Rep*. 2017;7(15507):1-10. doi:10.1038/s41598-017-15775-x

146. Cohen LG, Starr A. Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. *Brain*. 1987;110(2):451-467. doi:10.1093/brain/110.2.451

147. Murase N, Kaji R, Shimazu H, et al. Abnormal premovement gating of somatosensory input in writer's cramp. *Brain*. 2000;123(9):1813-1829. doi:10.1093/brain/123.9.1813

148. Del Percio C, Le Pera D, Arendt-Nielsen L, et al. Distraction affects frontal alpha rhythms related to expectancy of pain: An EEG study. *Neuroimage*. 2006;31(3):1268-1277. doi:10.1016/j.neuroimage.2006.01.013

149. May ES, Butz M, Kahlbrock N, Hoogenboom N, Brenner M, Schnitzler A. Pre- and post-stimulus alpha activity shows differential modulation with spatial attention during the processing of pain. *Neuroimage*. 2012;62(3):1965-1974. doi:10.1016/j.neuroimage.2012.05.071

150. Peng W, Hu L, Zhang Z, Hu Y. Changes of spontaneous oscillatory activity to tonic heat pain. *PLoS One*. 2014;9(3):1-11. doi:10.1371/journal.pone.0091052

151. Foxe JJ, Snyder AC. The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Front Psychol*. 2011;2(JUL):1-13. doi:10.3389/fpsyg.2011.00154

152. Rizzo M, Petrini L, Del Percio C, Lopez S, Arendt-Nielsen L, Babiloni C. Mirror visual feedback during unilateral finger movements is related to the desynchronization of cortical electroencephalographic somatomotor alpha rhythms. *Psychophysiology*. 2022;(April):1-13. doi:10.1111/psyp.14116

153. Bromm B, Lorenz J. Neurophysiological evaluation of pain. *Electroencephalogr Clin Neurophysiol*. 1998;107(4):227-253. doi:10.1016/S0013-4694(98)00075-3

154. Galdo-Álvarez S, Carrillo-De-La-Peña MT. ERP evidence of MI activation without motor response execution. *Neuroreport*. 2004;15(13):2067-2070. doi:10.1097/00001756-200409150-00014

155. Minelli A, Marzi CA, Girelli M. Lateralized readiness potential elicited by undetected visual stimuli. *Exp Brain Res*. 2007;179(4):683-690. doi:10.1007/s00221-006-0825-8

156. Mittelstadt V, Mackenzie I, Leuthold H, Miller J. Electrophysiological evidence against parallel motor processing during multitasking. *Psychophysiology*. 2022;59(1):1-18. doi:10.1111/psyp.13951

157. Debnath R, Franz EA. Perception of hand movement by mirror reflection evokes brain activation in the motor cortex contralateral to a non-moving hand. *Cortex*. 2016;81:118-125. doi:10.1016/j.cortex.2016.04.015

158. Szczepanski SM, Konen CS, Kastner S. Mechanisms of Spatial Attention Control in Frontal and Parietal Cortex. 2010;30(1):148-160. doi:10.1523/JNEUROSCI.3862-09.2010

159. Misselhorn J, Friese U, Engel AK. Frontal and parietal alpha oscillations reflect attentional modulation of cross-modal matching. *Sci Rep*. 2019;(March):1-11. doi:10.1038/s41598-019-41636-w

160. Ding L, He J, Yao L, et al. Mirror Visual Feedback Combining Vibrotactile Stimulation Promotes Embodiment Perception: An Electroencephalogram (EEG) Pilot Study. *Front Bioeng Biotechnol*. 2020;8(October):1-12. doi:10.3389/fbioe.2020.553270

161. Longo MR, Schüür F, Kammers MP, Tsakiris M, Haggard P. What is embodiment? A psychometric approach. *Cognition*. 2008;107(3):978-998.

doi:10.1016/j.cognition.2007.12.004

162. Rohafza M, Saleh S, Adamovich S. EEG Based Analysis of Cortical Activity during Mirror Visual Feedback Target-Directed Movement. *Conf Proc . Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf*. 2019;2019:5156-5159. doi:10.1109/EMBC.2019.8857945

163. Ball T, Schreiber A, Feige B, Wagner M, Lücking CH, Kristeva-Feige R. The role of higher-order motor areas in voluntary movement as revealed by high-resolution EEG and fMRI. *Neuroimage*. 1999;10(6):682-694. doi:10.1006/nimg.1999.0507

164. Nambu I, Hagura N, Hirose S, Wada Y, Kawato M, Naito E. Decoding sequential finger movements from preparatory activity in higher-order motor regions: A functional magnetic resonance imaging multi-voxel pattern analysis. *Eur J Neurosci*. 2015;42(10):2851-2859. doi:10.1111/ejn.13063

165. Kang YJ, Ku J, Kim HJ, Park HK. Facilitation of Corticospinal Excitability According to Motor Imagery and Mirror Therapy in Healthy Subjects and Stroke Patients. *Ann Rehabil Med*. 2011;35(6):747. doi:10.5535/arm.2011.35.6.747

166. Libera DD, Regazzi S, Fasoletti C, Ruggieri DD, Rossi P. Beneficial effect of transcranic magnetic stimulation combined with mirror therapy in stroke patients: a pilot study in neurorehabilitative setting. *Brain Stimul*. 2015;8(2):377. doi:10.1016/j.brs.2015.01.206

167. Cho HS, Cha HG. Effect of mirror therapy with tDCS on functional recovery of the upper extremity of stroke patients. *J Phys Ther Sci*. 2015;27(4):1045-1047. doi:10.1589/jpts.27.1045

168. Xiaolin Zhao, Mengxue Lan, Huixiang Li JY. Frequency-dependent modulation of neural oscillations across the gait cycle. *Hum Brain Mapp*. 2022;43:3404-3415. doi:10.1002/hbm.25856

169. Chen Y, Wang P, Bai Y, Wang Y. Effects of mirror training on motor performance in healthy individuals: A systematic review and meta-analysis. *BMJ Open Sport Exerc Med*. 2019;5(1). doi:10.1136/bmjsem-2019-000590

170. Bai Z, Fong KNK, Zhang J, Hu Z. Cortical mapping of mirror visual feedback training for unilateral upper extremity: A functional near-infrared spectroscopy study. *Brain Behav*. 2020;10(1):1-13. doi:10.1002/brb3.1489

171. Ramachandran V, Altschuler E. The visual feedback , in particualr mirror

visual feedback, in restoring brain function. *Brain*. 2009;132:1693-1710. doi:10.1093/brain/awp135

172. Balconi M, Crivelli D, Bove M. 'Eppur si move': The Association Between Electrophysiological and Psychophysical Signatures of Perceived Movement Illusions. *J Mot Behav*. 2018;50(1):37-50. doi:10.1080/00222895.2016.1271305

173. Torta DM, Cauda F. Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. *Neuroimage*. 2011;56(4):2157-2172. doi:10.1016/j.neuroimage.2011.03.066

174. Raichle ME, Snyder AZ. A default mode of brain function: A brief history of an evolving idea. *Neuroimage*. 2007;37(4):1083-1090. doi:10.1016/j.neuroimage.2007.02.041

175. Lega C, Pirruccio M, Bicego M, Parmigiani L, Chelazzi L, Cattaneo L. The Topography of Visually Guided Grasping in the Premotor Cortex: A Dense-Transcranial Magnetic Stimulation (TMS) Mapping Study. *J Neurosci*. 2020;40(35):6790-6800. doi:https://doi.org/10.1523/JNEUROSCI.0560-20.2020

176. Wager TD, Jonides J, Reading S. Neuroimaging studies of shifting attention: A meta-analysis. *Neuroimage*. 2004;22(4):1679-1693. doi:10.1016/j.neuroimage.2004.03.052

177. Witt S, Stevens M. FMRI task parameters influence hemodynamic activity in regions implicated in mental set switching. *Neuroimage*. 2013;65:139-151. doi:10.1016/j.neuroimage.2012.09.072.FMRI

178. Medina J, Khurana P, Branch Coslett H. The Influence of Embodiment on Multisensory Integration using the Mirror Boc Illusion. *Conscious Cogn*. 2015;37:71-82. doi:10.1016/j.concog.2015.08.011.The

179. Yavuzer G, Selles R, Sezer N, et al. Mirror Therapy Improves Hand Function in Subacute Stroke: A Randomized Controlled Trial. *Arch Phys Med Rehabil*. 2008;89(3):393-398. doi:10.1016/j.apmr.2007.08.162

180. Carson RG. Neural pathways mediating bilateral interactions between the upper limbs. *Brain Res Rev*. 2005;49(3):641-662. doi:10.1016/j.brainresrev.2005.03.005

181. Avanzino L, Raffo A, Pelosin E, et al. Training based on mirror visual feedback influences transcallosal communication. *Eur J Neurosci*.

2014;40:2581-2588. doi:10.1111/ejn.12615

182. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R. The mechanisms of interhemispheric inhibition in the human motor cortex. *J Physiol*. 2002;543(1):317-326. doi:10.1113/jphysiol.2002.017673

183. Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. *J Physiol*. 1992;453(1):525-546. doi:10.1113/jphysiol.1992.sp019243

184. Hanajima R, Ugawa Y, Machii K, et al. Interhemispheric facilitation of the hand motor area in humans. *J Physiol*. 2001;531(3):849-859. doi:10.1111/j.1469-7793.2001.0849h.x

185. Klimesch W. Alpha-band oscillations, attention, and controlled access to stored information. *Trends Cogn Sci*. 2012;16(12):606-617. doi:https://doi.org/10.1016/j.tics.2012.10.007

186. Lopes da Silva F. Neural mechanisms underlying brain waves: from neural membranes to networks. *Electroencephalogr Clin Neurophysiol*. 1991;79(2):81-93. doi:10.1016/0013-4694(91)90044-5

187. Babiloni C, del Percio C, Triggiani AI, et al. Frontal-parietal responses to "oddball" stimuli depicting "fattened" faces are increased in successful dieters: An electroencephalographic study. *Int J Psychophysiol*. 2011;82(2):153-166. doi:10.1016/j.ijpsycho.2011.08.001

188. Ribary U, Doesburg SM, Ward LM. Unified principles of thalamo-cortical processing: the neural switch. *Biomed Eng Lett*. 2017;7(3):229-235. doi:10.1007/s13534-017-0033-4

189. Li X, Hu L. The role of stress regulation on neural plasticity in pain chronification. *Neural Plast*. 2016;2016. doi:10.1155/2016/6402942

190. Pascual-Leone A, Amedi A, Fregni F, Merabet L. The Plastic Human Brain Cortex. *Annu Rev Neurosci*. 2005;28:377-401. doi:10.1146/annurev.neuro.27.070203.144216

191. Makin TR, Flor H. Brain (re)organisation following amputation: Implications for phantom limb pain. *Neuroimage*. 2020;218(September 2019):116943. doi:10.1016/j.neuroimage.2020.116943

192. Deconinck FJA, Smorenburg ARP, Benham A, Ledebt A, Feltham MG, Savelsbergh GJP. Reflections on mirror therapy: A systematic review of the

effect of mirror visual feedback on the brain. *Neurorehabil Neural Repair*. 2015;29(4):349-361. doi:10.1177/1545968314546134

193. Thieme H, Morkisch N, Mehrholz J, et al. Mirror Therapy for Improving Motor Function After Stroke (Review). *Stroke*. 2019;50(2):1-155. doi:10.1161/STROKEAHA.118.023092

194. Michielsen ME, Selles RW, Van Der Geest JN, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: A phase II randomized controlled trial. *Neurorehabil Neural Repair*. 2011;25(3):223-233. doi:10.1177/1545968310385127

195. Bae SH, Jeong WS, Kim KY. Effects of mirror therapy on subacute stroke patients' brain waves and upper extremity functions. *J Phys Ther Sci*. 2012;24(11):1119-1122. doi:10.1589/jpts.24.1119

196. Foell J, Bekrater-Bodmann R, Diers M, Flor H. Mirror therapy for phantom limb pain: Brain changes and the role of body representation. *Eur J Pain (United Kingdom)*. 2014;18(5):729-739. doi:10.1002/j.1532-2149.2013.00433.x

197. Saleh S, Yarossi M, Manuweera T, Adamovich S, Tunik E. Network interactions underlying mirror feedback in stroke: A dynamic casual modeling study. *Neuroimage Clin*. 2017;13:46-54. doi:10.1016/j.nicl.2016.11.012

198. Seidel S, Kasprian G, Furtner J, et al. Mirror therapy in lower limb amputees - Alookbeyondprimary motor cortex reorganization. *RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgeb Verfahren*. 2011;183(11):1051-1057. doi:10.1055/s-0031-1281768

199. Brunetti M, Morkisch N, Fritzsch C, et al. Potential determinants of efficacy of mirror therapy in stroke patients - A pilot study. *Restor Neurol Neurosci*. 2015;33(4):421-434. doi:10.3233/RNN-140421

200. Khera T, Rangasamy V. Cognition and Pain: A Review. *Front Psychol*. 2021;12(May):1-11. doi:10.3389/fpsyg.2021.673962

201. International Association for the Study of Pain. Terminology | International Association for the Study of Pain. International Association for the Study of Pain (IASP). https://www.iasp-pain.org/resources/terminology/#Pain. Published 2021.

202. Mun CJ, Suk HW, Davis MC, et al. Investigating intraindividual pain variability: Methods, applications, issues, and directions. *Pain*.

2019;160(11):2415-2429. doi:10.1097/j.pain.0000000000001626

203. Jimenez AM, Lee J, Wynn JK, et al. Abnormal ventral and dorsal attention network activity during single and dual target detection in schizophrenia. *Front Psychol*. 2016;7(MAR):1-11. doi:10.3389/fpsyg.2016.00323

204. Seminowicz DA, Moayedi M. The Dorsolateral Prefrontal Cortex in Acute and Chronic Pain. *J Pain*. 2017;18(9):1027-1035. doi:10.1016/j.jpain.2017.03.008

205. Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. *J Neuroimmune Pharmacol*. 2013;8(3):518-534. doi:10.1007/s11481-012-9386-8

206. Wilcox C, Mayer A, Teshiba T, et al. The Subjective Experience of Pain: An FMRI Study of Percept-Related Models and Functional Connectivity. *Pain Med*. 2015;16:2121-2133. doi:DOI: 10.1111/pme.12785

207. Chikazoe J, Jimura K, Hirose S, Yamashita KI, Miyashita Y, Konishi S. Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. *J Neurosci*. 2009;29(50):15870-15877. doi:10.1523/JNEUROSCI.3645-09.2009

208. Suda A, Osada T, Ogawa A, et al. Functional organization for response inhibition in the right inferior frontal cortex of individual human brains. *Cereb Cortex*. 2020;30(12):6325-6335. doi:10.1093/cercor/bhaa188

209. Verbruggen F, Aron AR, Stevens MA, Chambers CD. Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. *Proc Natl Acad Sci U S A*. 2010;107(31):13966-13971. doi:10.1073/pnas.1001957107

210. Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage*. 2010;50(3):1313-1319. doi:10.1016/j.neuroimage.2009.12.109

211. Hartwigsen G, Neef NE, Camilleri JA, Margulies DS, Eickhoff SB. Functional Segregation of the Right Inferior Frontal Gyrus: Evidence from Coactivation-Based Parcellation. *Cereb Cortex*. 2019;29(4):1532-1546. doi:10.1093/cercor/bhy049

212. Brighina F, De Tommaso M, Giglia F, et al. Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex. *J Headache Pain*. 2011;12(2):185-191. doi:10.1007/s10194-011-0322-8

213. Lorenz J, Minoshima S, Casey K. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain*. 2003;126:1079-1091. doi:DOI: 10.1093/brain/awg102

214. Lorenz J, Cross D, Minoshima S, Morrow T, Paulson P, Casey K. A Unique Representation of Heat Allodynia in the Human Brain. *Neuron*. 2002;35:383-393. doi:DOI: 10.1016/s0896-6273(02)00767-5

215. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: One decade on. *Trends Cogn Sci*. 2014;18(4):177-185. doi:10.1016/j.tics.2013.12.003

216. Neugebauer V. Amygdala pain mechanisms. *Handb Exp Pharmacol*. 2015;227:261-284. doi:doi: 10.1007/978-3-662-46450-2_13

217. Schaum M, Pinzuti E, Sebastian A, et al. Right inferior frontal gyrus implements motor inhibitory control via beta-band oscillations in humans. *Elife*. 2021;10:1-26. doi:10.7554/eLife.61679

218. Tops M, Boksem MAS, Luu P, Tucker DM. Brain substrates of behavioral programs associated with self-regulation. *Front Psychol*. 2011;2(AUG):1-14. doi:10.3389/fpsyg.2010.00152

219. Brascher A, Becker S, Hoeppli M, Schweinhardt P. Different Brain Circuitries Mediating Controllable and Uncontrollable Pain. *J Neurosci*. 2016;36(18):5013-5025. doi:DOI: 10.1523/JNEUROSCI.1954-15.2016

220. Peng K, Steele SC, Becerra L, Borsook D. Brodmann area 10: Collating, integrating and high level processing of nociception and pain. *Prog Neurobiol*. 2018;161:1-22. doi:10.1016/j.pneurobio.2017.11.004

221. Tolomeo S, Christmas D, Jentzsch I, et al. A causal role for the anterior mid-cingulate cortex in negative affect and cognitive control. *Brain*. 2016;139(6):1844-1854. doi:10.1093/brain/aww069

222. Fauchon C, Faillenot I, Quesada C, et al. Brain activity sustaining the modulation of pain by empathetic comments. *Sci Rep*. 2019;9(1):1-10. doi:10.1038/s41598-019-44879-9

223. Araujo HF, Kaplan J, Damasio A. Cortical midline structures and autobiographical-self processes: An activation-likelihood estimation meta-analysis. *Front Hum Neurosci*. 2013;7(SEP):1-10. doi:10.3389/fnhum.2013.00548

224. Northoff G, Bermpohl F. Cortical midline structures and the self. *Trends Cogn Sci*. 2004;8(3):102-107. doi:10.1016/j.tics.2004.01.004

225. Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain-A meta-analysis of imaging studies on the self. *Neuroimage*. 2006;31(1):440-457. doi:10.1016/j.neuroimage.2005.12.002

226. Cavanna AE, Trimble MR. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*. 2006;129(3):564-583. doi:10.1093/brain/awl004

227. Goffaux P, Girard-Tremblay L, Marchand S, Daigle K, Whittingstall K. Individual Differences in Pain Sensitivity Vary as a Function of Precuneus Reactivity. *Brain Topogr*. 2014;27:366-374. doi:DOI: 10.1007/s10548-013-0291-0

228. Ehrsson HH, Spence C, Passingham RE. That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science (80-)*. 2004;305(5685):875-877. doi:10.1126/science.1097011

229. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27(9):2349-2356. doi:10.1523/JNEUROSCI.5587-06.2007

230. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J Neurophysiol*. 2008;100(6):3328-3342. doi:10.1152/jn.90355.2008

231. Gusnard D, Raichle M. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci*. 2001;2(October):685-694. doi:10.1038/35094500

232. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001;98(2):676-682. doi:10.1073/pnas.98.2.676

233. De Ridder D, Vanneste S, Smith M, Adhia D. Pain and the Triple Network Model. *Front Neurol*. 2022;13(March):1-13. doi:10.3389/fneur.2022.757241

234. Rusconi E, Pinel P, Dehaene S, Kleinschmidt A. The enigma of Gerstmann's syndrome revisited: A telling tale of the vicissitudes of neuropsychology. *Brain*. 2010;133(2):320-332. doi:10.1093/brain/awp281

235. Rusconi E, Walsh V, Butterworth B. Dexterity with numbers: rTMS over left angular gyrus disrupts finger gnosis and number processing. *Neuropsychologia*. 2005;43(11):1609-1624. doi:10.1016/j.neuropsychologia.2005.01.009

236. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: A systematic review. *Neurosci Biobehav Rev*. 2009;33(3):279-296. doi:10.1016/j.neubiorev.2008.09.002

237. Ter Minassian A, Ricalens E, Humbert S, Duc F, Aubé C, Beydon L. Dissociating anticipation from perception: Acute pain activates default mode network. *Hum Brain Mapp*. 2013;34(9):2228-2243. doi:10.1002/hbm.22062

238. Kong J, Loggia ML, Zyloney C, Tu P, Laviolette P, Gollub RL. Exploring the brain in pain: activations, deactivations in their relation. *Pain*. 2011;148(2):1-22. doi:10.1016/j.pain.2009.11.008

239. Kim JA, Davis KD. Neural Oscillations: Understanding a Neural Code of Pain. *Neuroscientist*. 2021;27(5):544-570. doi:10.1177/1073858420958629

240. Sauseng P, Klimesch W, Schabus M, Doppelmayr M. Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *Int J Psychophysiol*. 2005;57(2):97-103. doi:10.1016/j.ijpsycho.2005.03.018

241. Alhajri N, Boudreau SA, Graven-Nielsen T. Angular gyrus connectivity at alpha and beta oscillations is reduced during tonic pain – Differential effect of eye state. *NeuroImage Clin*. 2022;33:102907. doi:10.1016/j.nicl.2021.102907

242. Frenkel-Toledo S, Bentin S, Perry A, Liebermann DG, Soroker N. Mirror-neuron system recruitment by action observation: Effects of focal brain damage on mu suppression. *Neuroimage*. 2014;87:127-137. doi:10.1016/j.neuroimage.2013.10.019

243. Small SL, Buccino G, Solodkin A. Brain repair after stroke - A novel neurological model. *Nat Rev Neurol*. 2013;9(12):698-707. doi:10.1038/nrneurol.2013.222

244. Carino-Escobar RI, Carrillo-Mora P, Valdés-Cristerna R, et al. Longitudinal analysis of stroke patients' brain rhythms during an intervention with a brain-computer interface. *Neural Plast*. 2019;2019. doi:10.1155/2019/7084618

245. Gandolfi M, Formaggio E, Geroin C, et al. Electroencephalographic Changes of Brain Oscillatory Activity After Upper Limb Somatic Sensation Training in a Patient With Somatosensory Deficit After Stroke. *Clin EEG Neurosci*. 2015;46(4):347-352. doi:10.1177/1550059414536895

246. Jochumsen M, Rovsing C, Rovsing H, et al. Quantification of movement-related EEG correlates associated with motor training: A study on movement-related cortical potentials and sensorimotor rhythms. *Front Hum Neurosci*. 2017;11(December):1-12. doi:10.3389/fnhum.2017.00604

247. Gonzalez-Rosa JJ, Natali F, Tettamanti A, et al. Action observation and motor imagery in performance of complex movements: Evidence from EEG and kinematics analysis. *Behav Brain Res*. 2015;281:290-300. doi:10.1016/j.bbr.2014.12.016

248. Pfurtscheller G, Brunner C, Schlögl A, Lopes da Silva FH. Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. *Neuroimage*. 2006;31(1):153-159. doi:10.1016/j.neuroimage.2005.12.003

249. Wriessnegger SC, Brunner C, Müller-Putz GR. Frequency specific cortical dynamics during motor imagery are influenced by prior physical activity. *Front Psychol*. 2018;9(OCT):1-16. doi:10.3389/fpsyg.2018.01976

250. Tang Z, Sun S, Zhang S, Chen Y, Li C, Chen S. A brain-machine interface based on ERD/ERS for an upper-limb exoskeleton control. *Sensors (Switzerland)*. 2016;16(12):1-14. doi:10.3390/s16122050

251. Daly JJ, Cheng R, Rogers J, Litinas K, Hrovat K, Dohring M. Feasibility of a new application of noninvasive brain computer interface (BCI): A case study of training for recovery of volitional motor control after stroke. *J Neurol Phys Ther*. 2009;33(4):203-211. doi:10.1097/NPT.0b013e3181c1fc0b

252. Marquez-Chin C, Marquis A, Popovic MR. EEG-Triggered Functional Electrical Stimulation Therapy for Restoring Upper Limb Function in Chronic Stroke with Severe Hemiplegia. *Case Rep Neurol Med*. 2016;2016:1-11. doi:10.1155/2016/9146213

SUMMARY

Placing a mirror adequately oriented, unilateral movements produce the illusion of the opposite limb moving synchronously. This Mirror Visual Feedback (MVF) illusion has been proposed to promote neurorehabilitation in patients with chronic pain conditions and motor deficits. However, the cortical areas and the mechanisms related to this illusory phenomenon are poorly understood. Through the analysis of the EEG alpha rhythms, the present PhD project aims to investigate the neurophysiological mechanisms underlying the MVF-induced illusion of finger movements and its effects on nociceptive processes. In the first part of the work, unilateral movements of the index finger during MVF were associated with a bi-hemispheric activity of the central sensory-motor cortical areas. Moreover, the source estimation of the EEG alpha oscillations unveiled the involvement of the premotor and posterior parietal associative cortical areas as responsible for visuomotor integration during MVF illusion. In the second part, sensory-motor interaction between MVF-induced illusory movements and electrical stimulations indicated that the inhibition of the midline limbic regions is associated with an individually lower perception of the stimulation intensity. A better understanding of these mechanisms might be relevant to developing therapies for those patients with unilateral limb impairment.

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-830-4

AALBORG UNIVERSITY PRESS