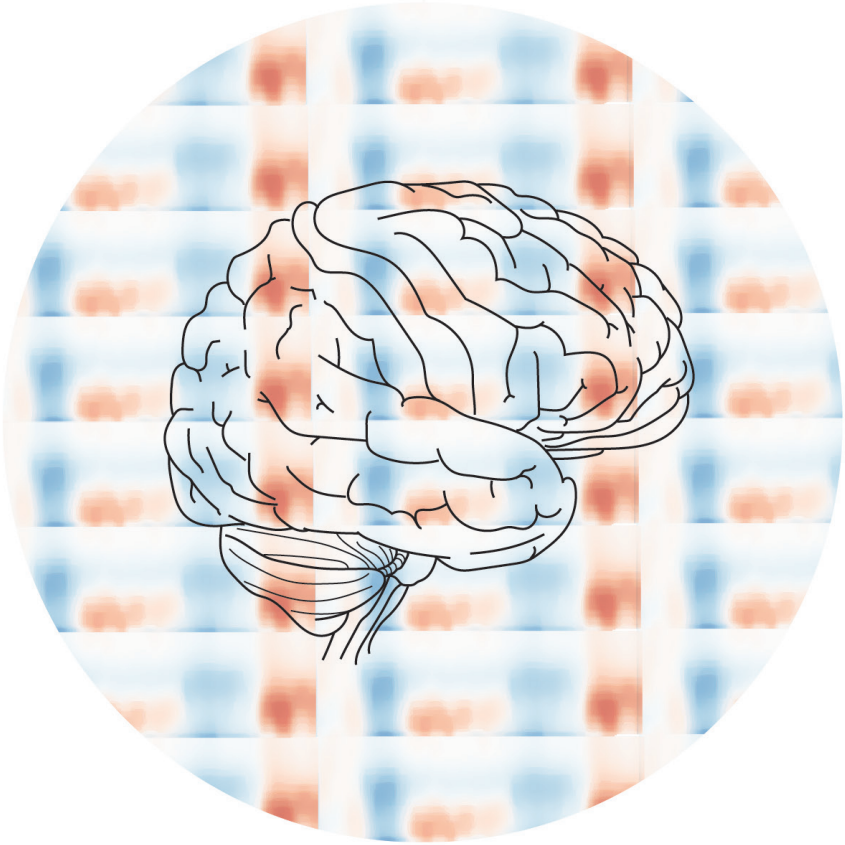
JYU DISSERTATIONS 622

Mia Illman

Beta Rhythm Modulation in the Evaluation of Cortical Sensorimotor Function



UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF SPORT AND
HEALTH SCIENCES

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Beta Rhythm Modulation in the Evaluation of Cortical Sensorimotor Function

Esitetään Jyväskylän yliopiston liikuntatieteellisen tiedekunnan suostumuksella
julkisesti tarkastettavaksi yliopiston päärakennuksen salissa C4
huhtikuun 21. päivänä 2023 kello 12.

Academic dissertation to be publicly discussed, by permission of
the Faculty of Sport and Health Sciences of the University of Jyväskylä,
in building Capitoliun, Auditorium C4, on April 21, 2023, at 12 o'clock noon.

JYVÄSKYLÄN YLIOPISTO
UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2023

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Cover picture by Mia Illman

ISBN 978-951-39-9522-5 (PDF)
URN:ISBN:978-951-39-9522-5
ISSN 2489-9003

Permanent link to the online version of this publication: http://urn.fi/URN:ISBN:978-951-39-9522-5

ABSTRACT

Illman, Mia
Beta Rhythm Modulation in the Evaluation of Cortical Sensorimotor Function
Jyväskylä: University of Jyväskylä, 2023, 78 p.
JYU Dissertations,
ISSN 2489-9003, 622
ISBN 978-951-39-9522-5

The cortical ~20-Hz beta rhythm that arises mainly from the primary sensorimotor (SM1) cortex reacts to voluntary movements or motor imagery as well as to somatosensory stimuli. The decrease in beta power shortly after somatosensory stimulus or movement is called beta suppression, and the subsequent increase in beta power is called beta rebound. Beta suppression has been proposed to reflect excitation and the rebound inhibition of the SM1 cortex. As excitatory–inhibitory regulation of the SM1 cortex is essential for brain plasticity and recovery, beta modulation may be a useful biomarker to objectively assess the effect of various interventions, such as medical therapies and rehabilitation methods, on the recovery of stroke patients. However, the reproducibility of beta modulation and how it is affected by confounding factors such as reduced alertness during MEG or EEG recordings are still poorly known, which may weaken its reliability as a biomarker, especially in clinical follow-up studies. The objective of this dissertation was to investigate these issues in healthy subjects. In addition, the beta modulation strength was compared between MEG and EEG recordings to evaluate EEG as an alternative method to MEG, since EEG would facilitate the availability of studies in clinical applications. In addition, the SM1 cortex beta modulation dynamics were explored in adolescents with hemiplegic and diplegic cerebral palsy (CP). In the series of studies, the beta rhythm was modulated with tactile and/or proprioceptive finger stimulation. The stimulus-related beta rhythm changes were analyzed using temporal spectral evolution. The results showed that both MEG and EEG successfully detected beta modulation well, although the suppression and rebound strengths were more pronounced in MEG. The long-term reproducibility of beta modulation was found to be good, and the reduced alertness did not significantly change the strength of beta modulation at the group level. In adolescents with diplegic CP, the SM1 cortex excitation and inhibition were bilaterally altered, but no similar changes were detected in hemiplegic CP. Overall, the results showed that beta modulation offers a feasible, reliable, and easy-to-implement method to detect the cortical function of the SM1, which may in the future be used as a biomarker, for example, in the evaluation of the recovery potential of patients.

Keywords: neurophysiological biomarker, cortical excitation–inhibition, sensorimotor cortex disturbance, proprioception, cutaneous tactile sense

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Illman, Mia
Beta-rytmin modulaatio tunto- ja liikeaivokuoren toiminnan arvioinnissa
Jyväskylä: Jyväskylän yliopisto, 2023, 78 s.
JYU Dissertations, ISSN2489-9003, 622
ISBN 978-951-39-9522-5

Primäärisellä tunto- ja liikeaivokuorella (SM1) syntyvän ~20 Hz taajuisen beta-rytmin voimakkuus reagoi aktiivisiin ja passiivisiin liike- ja tuntoärsykkeisiin sekä liikkeiden kuvittelemiseen. Beta-rytmi vaimenee (ns. beta-vaimeneminen) pian liikkeen tai tuntoärsykkeen jälkeen ja sitä seuraa beta-rytmin voimistuminen (ns. beta-vahvistuminen). Beta-vaimenemisen ajatellaan heijastavan SM1-aivokuoren eksitaatiota ja beta-vahvistumisen inhibitiota. Beta-rytmin moduloitumista onkin täten ehdotettu SM1-aivokuoren toiminnallista tilaa kuvaavaksi neurofysiologiseksi mittariksi. SM1-aivokuoren eksitaatio-inhibition säätely on välttämätöntä hermoston uudelleenmuovautumiskyvylle ja vaurioiden korjautumiselle, ja siten beta-rytmin modulaatio voisi toimia hyödyllisenä biomarkkerina esimerkiksi tutkittaessa uusien lääkehoitojen ja kuntoutusmenetelmien toimivuutta aivoinfarktista toipumisen yhteydessä. Beta-rytmin modulaation toistettavuus sekä sitä mahdolliset häiritsevät tekijät, kuten alentuneen vireystason vaikutus, tunnetaan kuitenkin huonosti. Tämä voi heikentää sen käytettävyyttä biomarkkerina erityisesti kliinisissä seurantatutkimuksissa. Näiden tekijöiden lisäksi väitöskirjan tavoitteena oli selvittää beta-rytmin modulaation vertailtavuus MEG- ja EEG-rekisteröintien välillä. EEG:n käyttö helpottaisi merkittävästi beta-rytmin modulaation käyttöä biomarkkerina kliinisessä ympäristössä EEG:n huomattavasti paremman saatavuuden vuoksi. Viimeisessä osatyössä tutkittiin SM1-aivokuoren eksitaatio-inhibition tasapainoa nuorilla, joilla on hemipleginen tai dipleginen CP-vamma. Kaikissa väitöskirjan tutkimuksissa beta-rytmin moduloimiseen käytettiin etusormen tunto- ja/tai liikeaistiärsykkeitä. Beta-rytmin voimakkuuden muutosten analysoinnissa käytettiin TSE-menetelmällä (engl. temporal spectral evolution). Tulokset osoittavat MEG:n ja EEG:n havaitsevan hyvin beta-rytmin modulaatiota, vaikka se näkyi voimakkaampana MEG:llä mitattuna. Pitkittäistutkimus osoitti beta-rytmin modulaation olevan hyvin toistettava vuoden aikavälillä ja lisäksi alentuneen vireystilan ei todettu vaikuttavan merkitsevästi beta-rytmin modulaation ryhmätasolla. Diplegisessä CP-vammassa SM1-aivokuoren eksitaation ja inhibition havaittiin muuttuneen molemmissa aivopuoliskoissa, mutta vastaavia muutoksia ei nähty hemiplegisessä CP-vammassa. Väitöskirjan tulokset osoittavat beta-rytmin modulaation olevan luotettava ja helposti toteutettava menetelmä SM1-aivokuoren toiminnan tutkimiseen. Menetelmää voidaan tulevaisuudessa mahdollisesti käyttää biomarkkerina esim. potilaan toipumispotentiaalin arvioinnissa.

Asiasanat: neurofysiologinen biomarkkeri, aivokuoren eksitaatio-inhibitio,
tunto- ja liikeaivokuoren häiriö, proprioseptiikka, tuntoaisti

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KIITOKSET (ACKNOWLEDGEMENT IN FINNISH)

Tämä väitöskirja tehtiin Jyväskylän yliopiston Liikuntatieteelliseen tiedekuntaan vuosina 2019–2023. Tutkimusten MEG- ja EEG-rekisteröinnit toteutettiin Aalto NeuroImaging MEG Core -aivokuvantamislaboratoriossa. Haluan kiittää HUS Neurokeskusta, Aalto-yliopistoa, Jyväskylän yliopistoa ja Suomen Akatemiaa saamastani tuesta ja tutkimusyhteistyöstä. Lisäksi haluan osoittaa kiitokseni Jyväskylän yliopiston professoreille Jari Parkkarille ja Urho Kujalalle avoimesta ja kannustavasta ilmapiiristä sekä joustavuudesta.

Suurimman kiitollisuuteni osoitan loistaville asiantunteville ohjaajilleni professori Harri Piitulaiselle, dosentti Nina Forssille ja Kristina Laaksoselle. Teistä jokainen on tuonut väitöskirjaani aivan erityisen, omanlaisen ja arvokkaan panoksen. Harria haluan kiittää erityisesti ystävällisestä ja kannustavasta ohjauksesta niin väitöskirjan osatutkimuksissa kuin väitöskirjan loppuvaiheen kiemuroissa. Välimatkasta huolimatta olet ollut aina nopeasti tavoitettavissa ja valmiina vastaamaan kysymyksiini. Ninalle suuri kiitos tukemisesta, luottamuksesta ja lämpimästä kannustuksesta läpi väitöskirjaprojektin. Ihailen suuresti sinun tehokkuuttasi tieteellisessä työssä kiireisen sairaalatyön ohella. Sinun taitosi muokata ja tiivistää tieteellistä tekstiä on aivan oma luokkaansa. Kiitos Kristina kaikesta saamastani avusta, tuesta ja ystävyydestä tämän projektin aikana. Sinun innostuksesi tutkimusta kohtaan on ollut tarttuvaa ja se on kantanut minut läpi tutkimusten haastavampienkin vaiheiden. Lopuksi vielä iso kiitos kaikille ohjaajilleni tutkimusrahoitusten hankkimisesta. Ilman teitä tätä väitöskirjaa ei olisi ollut mahdollista tehdä.

Olen kiitollinen väitöskirjani esitarkastajille dosentti Päivi Nevalaiselle ja professori Lau Andersenille huolellisesta ja tarkasta paneutumisesta väitöskirjaani. Teiltä saamani kritiikin ja rakentavien kommenttien pohjalta pystyin kehittämään, selkeyttämään ja täydentämään väitöskirjaa paremmaksi kokonaisuudeksi. Lisäksi haluan kiittää väitöskirjani seurantaryhmän jäsentä professori Hanna Renvallia kannustuksesta, ystävyydestä ja iloisista kohtaamisista vuosien varrella.

Aalto NeuroImaging -tutkimusinfrastruktuuri on tarjonnut erinomaisen tutkimusympäristön tämän väitöskirjan tekemiselle. Suuri kiitos siitä kuuluu Aalto NeuroImaging johtaja Veikko Jousmäelle. Sinun kannustava ja positiivinen suhtautumisesi väitöskirjaprojektiani kohtaan jo heti sen alkumetreillä mahdollisti suurelta osin ryhtymiseni väitöskirjatutkijaksi. Lisäksi haluan kiittää koko Aalto NeuroImagingin henkilökuntaa kaikesta saamastani tuesta, ystävyydestä ja mukavasta työilmapiiristä.

Lämmin kiitos Aalto-yliopiston Neurotieteen ja lääketieteellisen tekniikan laitoksen henkilökunnalle, jolta olen aina saanut tarvitsemani tuen. Erityisesti muiden tutkijoiden kannustus ja vertaistuki ovat olleet ensiarvoisen tärkeitä. Vilpitön kiitokseni dosentti Mia Liljeströmille ystävyydestä sekä asiantuntevasta ja kärsivällisestä opastuksesta koodaukseen ja MNE-pythonin käytön ihmeelliseen maailmaan. Erityiskiitos Julia Jaatelalle ystävyydestä, kaikesta saamastani avusta ja tuesta. Arvokkaat tieteelliset sekä arkipäiväisemmät keskustelut ovat tehneet

tutkimuksen parissa puurtamisesta niin paljon kevyempää ja mukavampaa. Kiitos Timo Nurmelle ja Jaakko Vallinojalle vertaistuesta ja antoisista keskusteluista, jotka ovat avanneet uusia näkökulmia aiheeseen. Helena Mäenpäätä haluan kiittää yhteistyöstä ja inspiroivista keskusteluista.

Haluan kiittää kaikkia MEG-/EEG-tutkimuksiin osallistuneita. Ilman teidän vapaaehtoista osallistumistanne tutkimuksiin näitä tärkeitä tutkimuksia ei olisi voitu tehdä.

Kiitos kuuluu myös kaikille läheisilleni ja ystävilleni. Olette olleet kullan arvoisia tämän projektin aikana. Teidän seurassanne olen pystynyt irrottautumaan väitöskirjakuplastani aina hetkellisesti. Haluan erityisesti kiittää Eevaa lämpimästä kannustuksesta ja tuesta, jonka sain läpi väitöskirjaprojektin. Olet ollut läheinen tukijani, mutta ennen kaikkea olet kulkenut rinnalla luotettavana hyvänä ystävänä.

Lopuksi haluan kiittää rakasta perhettäni yhdessäolosta, lämmöstä ja välittämisestä. Rakkaalle äidilleni ja edesmenneelle isälleni olen erityisen kiitollinen saamastani loputtomasta kannustuksesta ja avusta, sekä lämpimästä ja huolehtivasta kasvuympäristöstä. Kiitos veljeni Mika sekä Satu, Ida ja Antti kaikesta saamastani tuesta ja erityisesti iloisista vapaa-ajan kohtaamisista. Kiitos kummitätini Roine välittämisestä ja kiinnostuksesta tutkimustani kohtaan. Kiitos rakkaimpani Milena ja Roope myötäelämisestä, ymmärryksestä, avusta ja kannustuksesta. Te olette pitäneet minut sopivasti mukana arjen pyörteessä.

Espoo, Maaliskuu 2023
Mia Illman

ORIGINAL PUBLICATIONS AND AUTHOR CONTRIBUTION

This thesis is based on the following original publications:

I Illman, M., Laaksonen, K., Liljeström, M., Jousmäki, V., Piitulainen, H., & Forss, N. (2020). Comparing MEG and EEG in detecting the ~20-Hz rhythm modulation to tactile and proprioceptive stimulation. *NeuroImage*, 215, 116804. doi: 10.1016/j.neuroimage.2020.116804

II Illman, M., Laaksonen, K., Liljeström, M., Piitulainen, H., & Forss N (2021). The effect of alertness and attention on the modulation of the beta rhythm to tactile stimulation. *Physiological Reports*, 9(12), e14818. doi: 10.14814/phy2.14818

III Illman, M., Laaksonen, K., Jousmäki, V., Forss, N., & Piitulainen, H. (2022). Reproducibility of Rolandic beta rhythm modulation in MEG and EEG. *Journal of Neurophysiology,* 127, 559-570. doi:10.1152/jn.00267.2021

IV Illman, M., Jaatela, J., Vallinoja, J., Nurmi, T., Mäenpää, H., & Piitulainen, H. (2023). Altered excitation-inhibition balance in the primary sensorimotor cortex to proprioceptive hand stimulation in cerebral palsy. Submitted.

All four publications of this dissertation are the result of the contribution of the entire research team. The author was the principal author in the original publications listed above.

Study I, II, and III: The author participated in designing the experiments and recruiting healthy adult subjects. The author performed the MEG/EEG recordings and designed the MEG/EEG analysis pipelines together with the co-authors. The author conducted the analyses and was mainly responsible for the interpretation of the results. The author prepared the figures and the manuscripts of the publications.

Study IV: The author conducted the CP participants' MEG measurements together with the co-authors. The author was mainly responsible for the interpretation of the results. The author was responsible for performing the MEG analysis, preparing the figures, and writing the manuscript.

FIGURES

TABLES

LIST OF ABBREVIATIONS

AASM	American academy of sleep medicine manual for the scoring of sleep and associated events
CP	Cerebral palsy
EEG	Electroencephalography
ERD	Event-related desynchronization
ERS	Event-related synchronization
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GMFCS	Gross motor function classification system
MEG	Magnetoencephalography
M1	Primary motor cortex
MSR	Magnetically shielded room
PD	Parkinson's disease
PM	Premotor cortex
SM1	Primary sensorimotor cortex
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SMA	Supplementary motor area
SNR	Signal-to-noise ratio
SQUID	Superconducting quantum interference device
TMS	Transcranial magnetic stimulation
TRF	Time-frequency representation
TSE	Temporal spectral evolution

CONTENTS

1 INTRODUCTION

The cortical ~20 Hz beta rhythm that arises mainly from the primary sensorimotor (SM1) cortex is one of the earliest identified brain rhythms. However, the behavior and functional significance of this rhythm remains poorly understood. A deeper understanding of beta rhythm is necessary especially since beta rhythm modulation (i.e. amplitude fluctuations) has been suggested as a cortical biomarker for assessing the functional state of the SM1 cortex in various disorders affecting motor functions, such as stroke (Laaksonen et al., 2012), Parkinson's disease (PD) (Degardin et al., 2009), and CP (Hoffman et al., 2019).

Beta rhythm is known to be modulated by different stimuli, such as tactile and (Cheyne et al., 2003; Gaetz & Cheyne, 2006; Houdayer et al., 2006; Salmelin & Hari, 1994; Stančák et al., 2003) proprioceptive stimulation (i.e. passive movement) (Alegre et al., 2002; Cassim et al., 2001; Müller et al., 2003; Parkkonen et al., 2015), voluntary movement (Feige et al., 1996; Neuper & Pfurtscheller, 2001a; Stančák et al., 2000), or even during motor imagery (Pfurtscheller et al., 2005; Schnitzler et al., 1997). Beta rhythm typically decreases soon after stimulus or task onset, that is, the arrival of somatosensory afference to the SM1 cortex. This reduction of the beta rhythm power is referred to as beta suppression or event-related desynchronization (ERD), and it is followed by a subsequent increase of the rhythm, which is called beta rebound or event-related synchronization (ERS). Beta suppression is thought to reflect cortical activation or excitation (Neuper et al., 2006; Pfurtscheller & Lopes da Silva, 1999), while beta rebound reflects deactivation or active inhibition of the SM1 cortex (Cassim et al., 2001; Gaetz et al., 2011; Salmelin et al., 1995).

The modulation of beta rhythm is shown to be a useful tool for assessing excitability changes in the SM1 cortex, and it has also been proposed to be associated with cortical plasticity (Gaetz et al., 2010; Mary et al., 2015). Since the strength of beta modulation is suggested to reflect disturbances in the excitation-

inhibition balance of the SM1 cortex, it has been utilized to characterize alterations in the SM1 cortex in various neurological and psychiatric disorders, such as stroke (Laaksonen et al., 2012; Parkkonen et al., 2018; Tang et al., 2020), CP (Hoffman et al., 2019; Pihko et al., 2014), PD (Hall et al., 2014), epilepsy (Silen et al., 2000), and schizophrenia (Liddle et al., 2016; Uhlhaas & Singer, 2010). Above all, changes in the strength of the beta rebound have been shown to correlate with motor recovery after acute ischemic stroke (Laaksonen et al., 2012; Parkkonen et al., 2018; Tang et al., 2020).

MEG and EEG are both suitable methods for detecting the SM1 cortex beta rhythm non-invasively, yet the most pertinent and interesting results have been found primarily through MEG such as in the studies previously mentioned above. However, the use of EEG is an attractive alternative, especially for clinical trials, due to its better availability and affordability, and therefore it is important to clarify the comparability of beta modulations measured by MEG and EEG. Moreover, the reproducibility is a prerequisite and necessity for a valid biomarker, especially in longitudinal follow-up studies. If the modulation of beta rhythm is highly variable within time in healthy subjects, the usage of beta modulation as a biomarker is uncertain. Furthermore, a change in alertness during the MEG/EEG measurements may affect beta modulation strength and lead to misleading conclusions.

The aim of this dissertation was to evaluate the suitability of beta modulation as a tool for clinical studies by (1) comparing results obtained with MEG and EEG, (2) clarifying the effect of alertness on beta modulation, and (3) determining the long-term reproducibility of beta modulation. In addition, beta modulation (4) has been applied to adolescents with hemiplegic and diplegic CP, which may assist with future studies and the designing of more individualized rehabilitation. The motivator for this dissertation was to improve the validity, reliability, and interpretations of future beta modulation studies and clinical applications related to this biomarker.

2 BACKGROUND

2.1 The human sensorimotor system

The sensorimotor system consists of both somatosensory and motor systems. The somatosensory system includes somatosensory receptors in the skin, muscle spindles, joints, tendons, and connective tissues, and peripheral afferent neurons that convey somatosensory information through the thalamus located in the midbrain into the cerebral cortex (Martin & Jessell, 1991b). Somatosensory information is transmitted in addition to the somatosensory cortex to the motor cortical areas to adjust appropriate motor commands that are relayed via efferent neural connections to the muscles. Touch and proprioceptive sensation are essential for performing proper voluntary movements as well as for the stability of body posture. The primary somatosensory (S1) and motor (M1) cortices are substantially responsible for somatosensory and motor functions, while the secondary somatosensory and motor areas complement and are more responsible for maintaining complex movements, such as combining environmental information or object identification (e.g. distance, shape, size, and material) for proper movement planning. Maintaining voluntary movements requires continuous processing of the received somatosensory information and intra- and interhemispheric integration between the primary and secondary somatosensory and motor cortices, ensuring that movements are well-balanced, fine-tuned, and functional entities. Cerebellum and basal ganglia have an important role in motor control, especially in targeting and fine-tuning movements. In addition, information from the visual, auditory, and vestibular systems is combined with information from the sensorimotor cortices. (Ghez, 1991; Martin & Jessell, 1991a)

2.1.1 Anatomy of the sensorimotor cortices

2.1.1.1 Primary somatosensory and motor cortices

The sensorimotor cortex consists of primary somatosensory and motor areas, which are located on both sides of the central sulcus (FIGURE 1A). The **primary somatosensory cortex** (**S1**) is located at the bottom and in the posterior bank of the central sulcus reaching to the postcentral gyrus in the parietal lobe, and it consists of four distinct Brodmann areas: 3a, 3b, 1, and 2 (Kelly & Dodd, 1991). The **primary motor cortex** *(***M1***)* is located adjacent to the S1, in the anterior wall of the central sulcus in the frontal lobe (Brodmann area 4; FIGURE 1B). Different body parts are represented in somatotopic order in both the S1 and M1 cortices (FIGURE 1C), with the M1 including one complete somatotopic map of the body and the S1 cortex one in each of areas 3a, 3b, 1, and 2. The representation areas of the feet are located the most medial and the head in the lateral part of the S1 and M1 cortices. The size of a body part in the somatosensory representation areas is in relation to the tactile sensitivity of a body part and in the M1 to the density of motor efference to that part of the body (e.g. digits, hands, and lips have larger representation areas than feet in the S1 and M1 cortices), indicating better tactile sensitivity and more precise fine control of movements in these body parts (Hsiao, 2008). Moreover, the somatotopic organization exists throughout the sensorimotor system from the dorsal column of the spinal cord to the associative areas of the brain. (Martin & Jessell, 1991a)

The S1 receives sensory information from the contralateral half of the body through afferent input via the thalamus and conveys sensations, such as touch, temperature, and pain. Cutaneous information arrives primarily in Brodmann areas 3b and 1, while proprioceptive information is directed mainly to area 3a, and both are combined in area 2. Receptive fields are larger in areas 1 and 2 than in 3b and the stimuli-eliciting activation in these more posterior areas are more complex than in 3b. Cortical information from S1 is transferred to secondary somatosensory brain areas, as well as to the M1. The M1 is mainly responsible for initiating and controlling individual movements through motor commands, which are relayed through efferent nerve fibres via the corticospinal tract to a proper set of lower alpha motor neurons. (Martin & Jessell, 1991a).

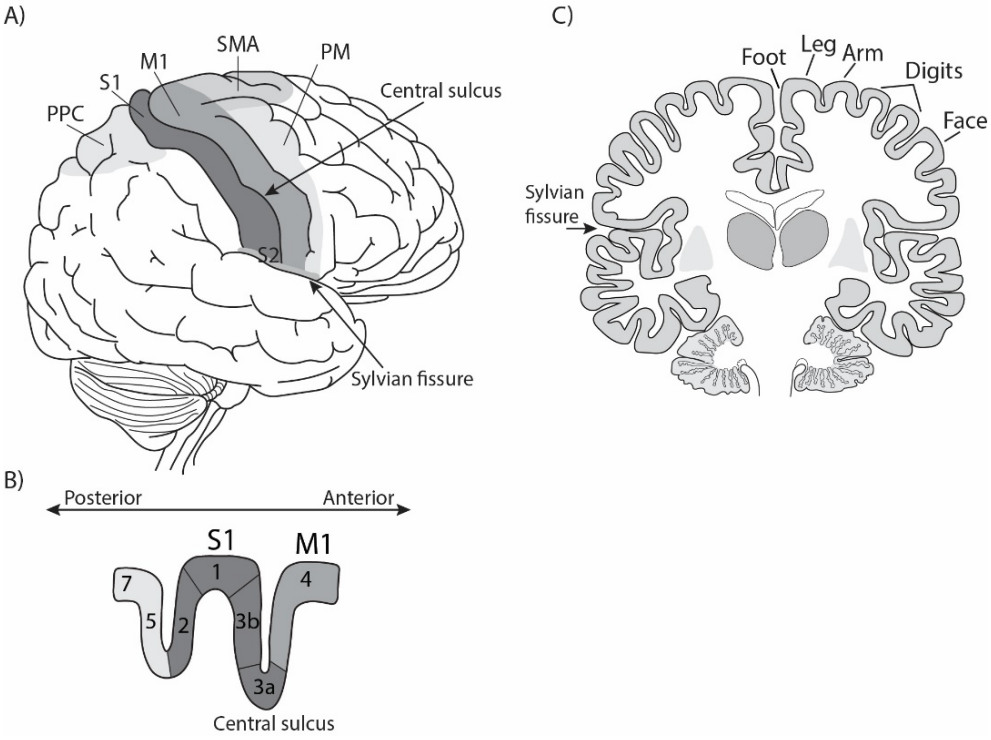

FIGURE 1 Anatomy of the sensorimotor cortex. A) Lateral view of the sensorimotor areas of the right hemisphere. B) The cross section of the sensorimotor regions shows the distinct cytoarchitectural Brodmann areas. C) Coronal section of the brain describes the somatotopic organization of different body parts in the S1 and M1 cortices.

2.1.1.2 Non-primary somatosensory cortices

The cortical somatosensory system also includes secondary brain areas, which are responsible for higher-order functions, such as integration of movement and sensory information, awareness of the environment, and motor learning (Martin & Jessell, 1991a). The most well-known of these areas is the secondary somatosensory cortex (S2), which locates in the superior bank of the Sylvian fissure (FIGURE 1A). The S2 is known to be roughly somatotopically organized; the representation area of the face is located close to the lateral sulcus, while the foot area is deeper in the Sylvian fissure (Disbrow et al., 2000). The S2 is responsible for the integration of sensorimotor information, for example in the detection of the three-dimensional size and shape of an object (Forss & Jousmäki, 1998; Hinkley et al., 2007; Hsiao, 2008; Simões & Hari, 1999). The posterior parietal cortex (PPC) is a substantial somatosensory association area located posterior to the S1

cortex, mainly in Brodmann areas 5 and 7 (FIGURE 1). The PPC integrates information from different sensory modalities (e.g. somatosensory-, motor-, visual- and auditory areas), and thus it perceives information from different body parts in extra personal space and guides movement related to higher-level cognitive functions (Andersen & Buneo, 2002; Sack, 2009).

2.1.1.3 Non-primary motor cortices

The supplementary motor area (SMA) and premotor cortex (PM) form the secondary motor cortex. They are located in the frontal lobe anterior of the M1 cortex (Brodmann area 6), with the SMA located more medially and the PM laterally (FIGURE 1A). Both SMA and PM are roughly somatotopically organized, with the face in the anterior and the legs in the posterior part (Mitz & Wise, 1987). The SMA has a clear role in executing and controlling movements, especially in coordinating complex, bimanual, and visually controlled movements, and maintaining body posture. Patterns of previously learned movement sequences are mostly maintained in the SMA (Gerloff, 1997; Halsband et al., 1993; Picard, 2003; Serrien et al., 2002). The PM receives information from the thalamus, cerebellum, and basal ganglia, and it focuses mostly on planning movements (Ghez, 1991).

2.1.2 Connections within the sensorimotor cortex

The cortical sensorimotor system is densely connected. The neural networks of a healthy brain are constantly reorganized based on their use and needs. For example, learning new skills leads to the strengthening of related neural connections, while less used connections are reduced. This ability of the nervous system to adapt to new situations is called brain reorganization or neural plasticity, which is an outcome of complex structural and functional modifications (Carcea & Froemke, 2013; Vogels et al., 2011). Brain plasticity is also essential for recovery from brain damage caused by, for example stroke, enabling the relocation of the functions of the damaged brain areas to the healthy areas and the formation of novel connections bypassing the damaged areas (Sanes & Donoghue, 2000).

2.1.2.1 Somatosensory and motor pathways

Voluntary movements require complex interactions between somatosensory and motor cortices to integrate sensory inputs into motor strategies. Sensory information from cutaneous mechanoreceptors and mechanical displacements of joints and muscles conveys via afferent nerves through the dorsal column-medial lemniscal pathway of the spinal cord to the thalamus and thereon to the target area of the contralateral S1 cortex (FIGURE 2). The first-order afferent neuron in the somatosensory system is called the dorsal ganglion cell. Its distal branch

forms the sensory receptor and the central branch the primary afferent nerve fiber. The cell bodies are accumulated in the dorsal root ganglions close to the dorsal root of the spine, where it passes through the dorsal column of the spinal cord, and further along the ipsilateral dorsal column to the gracile and cuneate nuclei of the medulla. After synapsing in the medulla, the afferent nerve fibre crosses over to the contralateral side and thereafter continues via the medial lemniscal pathway to the ventral posterior lateral (VPL) nucleus of the thalamus. From the thalamus, the axons spread to the target area of the S1 cortex and, to a lesser extent, directly to the S2 and the posterior parietal (PPC) cortices. (Martin & Jessell, 1991a)

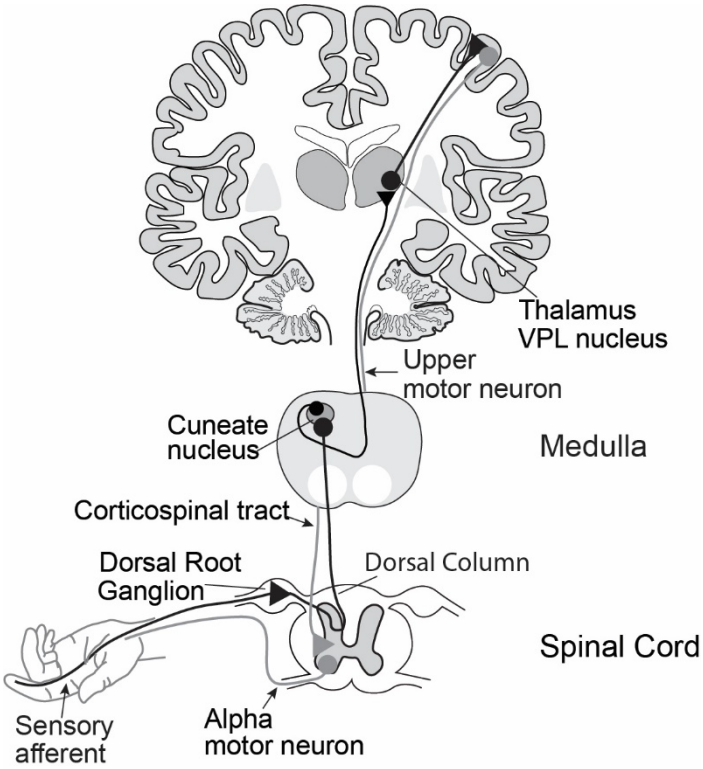

FIGURE 2 Organization of the somatosensory dorsal column medial lemniscal pathway (shown in black) and the motor lateral corticospinal track (shown in gray).

The M1 cortex receives direct input from the premotor areas, S1 and S2 cortices and thalamus, and indirectly from the cerebellum and basal ganglia through the ventral lateral (VL) nucleus of the thalamus (Ghez, 1991). The connectivity of the M1 cortices has been shown to be asymmetric, as well as more extensive in the dominant hemisphere, reflecting the importance of the dominant hemisphere in movement regulation (Guye et al., 2003). From the M1 cortex, efferent neurons transfer information about the desired movement to the pyramidal tract system (via the corticospinal or corticobulbar tracts) to initiate a voluntary movement.

2.1.2.2 Inter- and intra-hemispheric connections of the SM1 cortex

The corpus callosum is a large bundle of myelinated nerve fibres that connect the cortical areas of the two hemispheres allowing the transfer of brain signals. The callosal fibers of the somatosensory areas pass through the more posterior part of the corpus callosum than the motor fibers, with the SMA fibers being the most anterior (Aboitiz, 1992; Wahl et al., 2007). The somatosensory information from the S1 cortex transfers via reciprocal callosal connections to the contralateral S2 and PPC areas. The S2 cortices are strongly interconnected via the corpus callosum, reflecting their important function in combining somatosensory information from both body halves. The PPC cortices are also interconnected via the corpus callosum. Corticocortical connections between the M1 cortices are thought to be important for relaying inhibitory signals that play an important role in the modulation and optimization of movements, especially for hand movement (Carson, 2005).

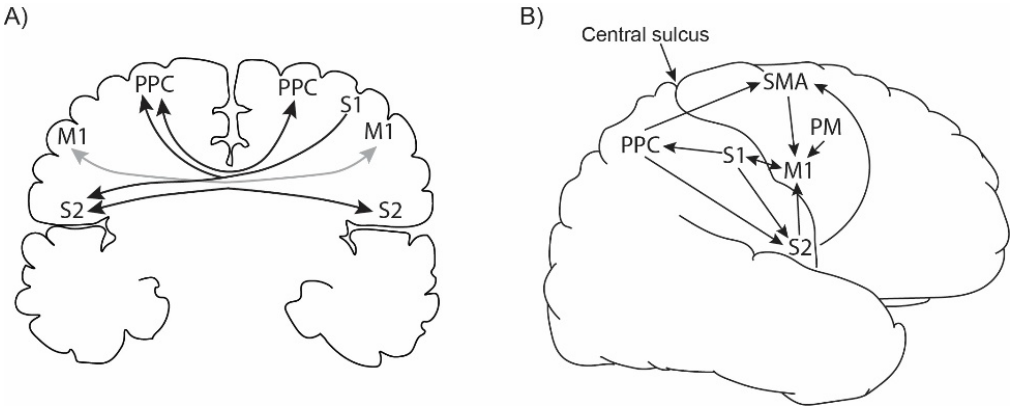

FIGURE 3 Cortical connection of the sensorimotor areas. A) Interhemispheric connections of the somatosensory and motor areas. B) Intra-hemispheric connections between the somatosensory and motor areas.

Intra-hemispheric neural pathways between various somatosensory and motor areas as well as indirect corticothalamic pathways are essential for the proper function of the sensorimotor system. Many of these intra-hemispheric connections are bidirectional (FIGURE 3B), conveying tactile, proprioceptive, and movement information. There are strong connections from the S1 especially to the S2, but also to the PPC and the M1. M1 receives also input from the S2, which is considerably stronger than input from the S1. In addition, the M1 receives connections from the SMA and PM cortices (Hinkley et al., 2007). The S2 has an essential role in sensorimotor integration, thus it connects directly both to the M1

and SMA regions. The PPC is known to combine information from different sensory modalities, and it projects to the S2 and SMA cortices. (Ghez, 1991; Kandel & Jessell, 1991)

2.2 Cortical rhythms

2.2.1 Overview

Spontaneous brain oscillations at various frequencies can be detected in a multitude of brain areas. In general, rhythmical cortical oscillations are most visible at rest and are thus considered to reflect a resting or idling state of a certain brain area, whereas activation dampens rhythmical activity (Engel & Fries, 2010). Brain oscillations have been suggested to contribute to binding information between different brain areas and to participate in higher cognitive processes (Florin & Baillet, 2015; Fries, 2005; Hari & Salmelin, 1997; Jensen et al., 2007; Palva & Palva, 2007). The thalamus has an essential role in driving cortical rhythmic activity (Steriade et al., 1990), and lesions in the thalamus have been shown to reduce cortical rhythmic activity (Mäkelä et al., 1998). Cortical brain rhythms and changes in oscillatory activity in relation to external stimuli can be quantified with MEG and EEG.

The longest-known spontaneous brain rhythm in humans is the alpha rhythm at around 10 Hz frequency, originally found by Hans Berger in 1929. The alpha rhythm arises from the posterior and occipital parts of the cerebral cortex, and it is tightly related to the function of the visual cortex. The alpha rhythm responds to the opening and closing of the eyes, being more pronounced when a person has eyes closed or is tired or bored. Thus, the alpha rhythm is thought to reflect the resting-state of cortical processing in the absence of sensory input. Another well-known brain rhythm is the SM1 cortex mu rhythm at 10 to 30 Hz frequency (discussed in more detail in Section 2.2.2.). In addition, the auditory cortex produces a rhythm of about 10 Hz called tau rhythm, which is attenuated by sounds, but it does not react to visual stimuli like the alpha rhythm (Tiihonen et al., 1991). Lower frequency rhythms, such as theta (4–8 Hz) and delta (<3.5 Hz) rhythms, are also seen over different brain areas. These lower frequencies are mainly seen during drowsiness and sleep or in connection with brain pathology. The higher gamma rhythm includes a wide range of frequencies over 30 Hz. These rhythms are thought to be associated with both inhibitory and facilitatory activity of perception and cognition. (Hari & Puce, 2017)

2.2.2 Mu rhythm

The mu rhythm mainly originates in the primary SM1 area. It consists of at least two separate frequency components: one at around 10 Hz (**mu alpha**) and the other at around 20 Hz (**mu beta**) (Hari, 2006). In this dissertation, the mu beta is called beta rhythm, and it is the focus point of the studies. The sources of these two frequency components of mu rhythm are slightly separated, with the 10 Hz component arising predominantly in the S1 cortex, while the 20 Hz component has been located mainly in the M1 cortex (Hari & Salmelin, 1997). The 20 Hz mu beta has been shown to be somatotopically organized for the stimulation of different body parts, whereas no clear somatotopy has been observed for the 10 Hz mu alpha (Salmelin et al., 1995). Moreover, the mu alpha and beta rhythms have functional differences. Both rhythms are suppressed shortly after sensory stimulation or movement, but the mu beta suppression begins earlier and is more spatially focused than the mu alpha suppression. The rebound that occurs soon after the suppression, is typically quicker and more marked for the mu beta than it is for the mu alpha rhythm (Salenius et al., 1997; Salmelin & Hari, 1994; Wijk et al., 2012). The mu alpha is thought to reflect mainly the S1 cortex function, whereas the mu beta is more connected to motor cortex functions and top-down inhibitory processes (Cheyne, 2013; Kilavik et al., 2013; Klimesch et al., 2007).

According to current understanding, the dynamics of sensorimotor beta oscillations occurs in brief bursts of transient amplitude change rather than being sustained over time (Feingold et al., 2015; Jones, 2016; Sherman et al., 2016). These oscillations have been detected mainly from the sensorimotor cortex areas, the thalamus, and the structures of the basal ganglia, such as the striatum (Baker, 2007; Holgado et al., 2010). The functional role of the beta bursts has been considered to be involved in both somatosensory processing and motor control, and they are proposed to shape human corticospinal excitability, especially in cortico-subcortical networks (Diesburg et al., 2021; Hussain et al., 2019). A shorter duration and lower frequency of the beta burst associated with the beginning of movement has been proposed to correspond with better known beta suppression, while post-movement beta rebound corresponds to a higher frequency and longer duration of the burst (Seedat et al., 2020).

2.2.2.1 Modulation of the cortical sensorimotor beta rhythm

The intensity of the SM1 cortex mu beta rhythm (also called Rolandic beta rhythm) changes in relation to somatosensory stimuli or movement. The beta rhythm decreases temporarily soon after a stimulus or movement, and it is followed by a subsequent increase of the rhythm until it slowly returns to the baseline level (FIGURE 4A). Beta rhythm typically decreases around 200 to 350 ms after

stimulus onset, and it is referred to as beta suppression (or ERD; or movement-related beta desynchronization, MRBD). It is noteworthy that beta suppression can occur well before the onset of voluntary movement (even 2 s before). This is thought to be related to the preparation and planning of movement. The increase in beta rhythm, in turn, is called beta rebound (or event-related synchronization, ERS; or post-movement beta rebound, PMBR). The peak time and duration of the rebound vary according to the stimulus. (Hari, 1997; Pfurtscheller & Lopes da Silva, 1999)

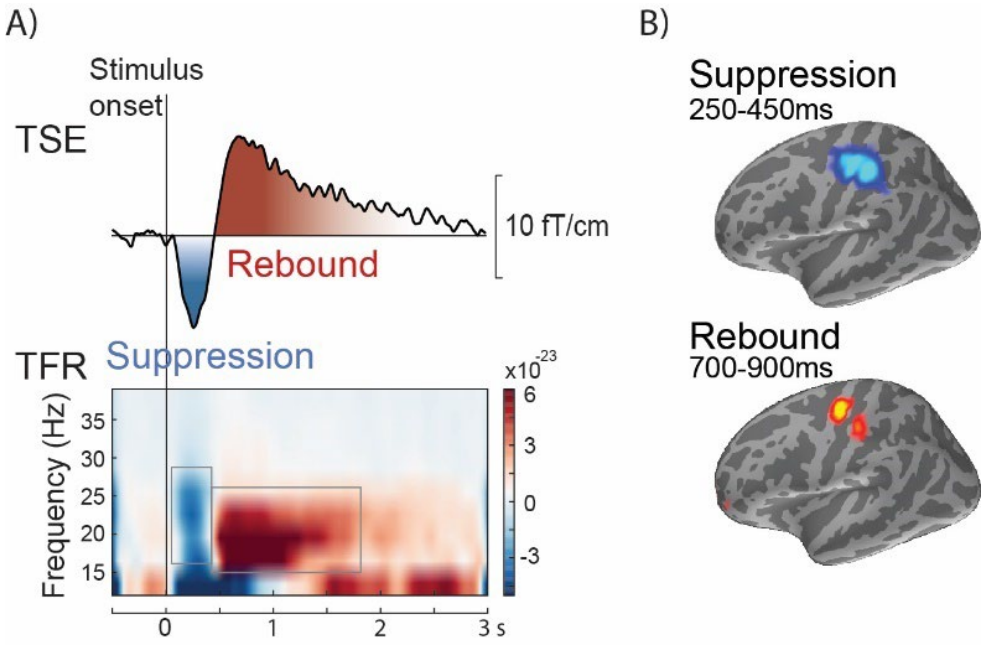

FIGURE 4 Beta rhythm modulation to somatosensory stimulation. A) Both grand averaged (n = 21) temporal spectral evolution (TSE) and time–frequency representation (TFR) show a decrease in the beta rhythm (suppression, visible in blue) soon after stimulus onset and a subsequent increase (rebound, visible in red) immediately after the suppression. B) The rebound locates more anteriorly mostly in the M1 cortex than the suppression, which locates predominantly in the S1 cortex. Localization of the suppression and rebound have been calculated with dynamic imaging of coherent sources (DICS) (n = 9) in MEG.

The beta suppression and rebound are detected bilaterally over the SM1 cortices for unilateral stimulation. However, the rebound is typically stronger in the contralateral hemisphere with respect to the stimulus, whereas there is little difference between the ipsilateral and contralateral hemispheres in the suppression strengths (Fry et al., 2016; Salenius et al., 1997; Salmelin & Hari, 1994). The suppression and rebound are generated in slightly different locations in the SM1 cortex, with the rebound located more anteriorly (mostly in the M1 cortex in the precentral gyrus), whereas the suppression occurs mainly post-centrally in the S1 cortex. However, the cortical generator areas of beta suppression and rebound

are thought to overlap, forming a unified functional entity (Bardouille & Bailey, 2019; Fry et al., 2016; Jurkiewicz et al., 2006; Salmelin et al., 1995; Sochůrková et al., 2006) (FIGURE 4B). In addition, movement-induced beta modulation has also been observed in the SMA (Ohara, 2000; Szurhaj et al., 2003).

Beta rhythm can be modulated by various somatosensory stimuli, such as tactile (Cheyne et al., 2003; Gaetz & Cheyne, 2006; Salmelin & Hari, 1994), electrical (Houdayer et al., 2006), and proprioceptive stimulation (i.e., passive movement) (Alegre et al., 2002; Cassim et al., 2001; Parkkonen et al., 2015; Toledo et al., 2016). Initially, the modulation of the beta rhythm was mainly studied for voluntary movements of different limbs (Feige et al., 1996; Pfurtscheller et al., 1999; Salmelin et al., 1995). Beta rhythm is also modulated when observing another person's movement (Hari et al., 1998) or imagining motor actions; (Neuper et al., 2009; Pfurtscheller et al., 2005; Schnitzler et al., 1997), however, the modulation is weaker than for an actual movement. The strength of beta modulation depends on the quality of stimulus, such as electrical median nerve stimulation vs. tactile stimulation (Houdayer et al., 2006). Voluntary thumb movement has also been shown to generate stronger beta modulation than the electrical median nerve stimulus-triggered thumb movement (Salmelin & Hari, 1994). In addition, the quantity of the stimulus affects the strength of the beta rebound, that is, the larger number of active muscles the stronger the beta rebound (Pfurtscheller et al., 1998). Also, auditory and visual stimuli can affect the beta rhythm (Kilavik et al., 2013; Piitulainen et al., 2015b).

Beta rhythm power and its modulation is very individual in both intensity and frequency components (Feige et al., 1996). Beta power consists of at least two different frequency bands, a lower beta band at ~15 Hz and a higher beta band at ~20 Hz. Beta rhythm suppression and rebound have also been shown to be modulated in slightly different frequency bands, with the lower frequency band corresponding more to the beta rebound and the higher frequency band the beta suppression (Pfurtscheller et al., 1997; Pihko et al., 2014). Beta rebound has also been found to occur in several narrower frequency bands with different reactivity features (Szurhaj et al., 2003). The frequency band of beta rebound has been shown to be different for upper and lower extremity stimulation, being at a lower frequency for the hand than for foot movement (Neuper & Pfurtscheller, 2001a).

2.2.2.2 Stability of the beta rhythm and its modulation

The strength of the beta rhythm power varies between individuals, which may lower the comparison of results between different studies. Some factors can affect the baseline beta power, and thus also affect the absolute and relative strengths of beta rhythm modulation (Muthukumaraswamy et al., 2013; Walker et al., 2020). The level of beta power has been shown to change according to the circadian

rhythm, being lower in the morning and increasing towards the evening (Toth et al., 2007; Wilson et al., 2014). In addition, enhanced vigilance and active attention increases beta power and enhances the beta rebound (Bardouille et al., 2010; Dockstader et al., 2010). However, there is no information about the influence of reduced alertness on the strength of beta modulation. Drugs, such as barbiturates, benzodiazepines, and tricyclic antidepressants, are also known to increase beta activity (Marcuse et al., 2016). In addition, beta power and its modulation decrease in diseases such as Alzheimer's disease and complex pain syndrome (Kirveskari et al., 2010; Koelewijn et al., 2017). The intensity of the beta power changes with age, and it is typically slightly weaker for children than for adults (Gaetz et al., 2010; Rossiter et al., 2014; Xifra-Porxas et al., 2019). The amplitude of beta suppression has been shown to increase, whereas the rebound in contrast decreases or remains unchanged with aging (Bardouille & Bailey, 2019; Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014; Walker et al., 2020; Xifra-Porxas et al., 2019). However, the beta modulation has been shown to be well reproducible in measurements of healthy adults performed within a few weeks (Espenhahn et al., 2017; Mujunen et al., 2022).

Active or passive movement has been shown to produce a stronger beta rebound than cutaneous stimulation, while the effect on the beta suppression was not consistent (Houdayer et al., 2006; Parkkonen et al., 2015). Changes in movement features, such as speed, range, or amount of used muscles, affect the beta modulation: a faster movement, a wider movement range or a larger group of active muscles used in voluntary movement has mainly been shown to produce a stronger rebound, indicating that especially the beta rebound is sensitive to changes in stimulus modality and movement kinematics (Cassim et al., 2000; Fry et al., 2016; Parkes et al., 2006; Pfurtscheller et al., 1998; Stančák et al., 1997). However, opposite results have also been obtained (Tatti et al., 2019). In addition, long-term motor practising and motor learning have been shown to increase beta power levels (Moisello et al., 2015; Nelson et al., 2017; Tatti et al., 2020), which may also increase the amplitude of beta modulation.

2.2.3 Cortical rhythms during drowsiness and sleep

The rhythmic cortical activity of a healthy brain changes remarkably at the transition from wakefulness to drowsiness and further to deeper sleep stages. EEG registrations are typically used to study and score different sleep stages, thus various methods and criteria have been developed for EEG to determine the quantity and quality of different stages of sleep. The AASM manual (American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events)

for sleep state scoring contains instructions for assessing different stages of sleep (Berry et al., 2012).

In the new classification, sleep is divided into NREM (nonrapid-eye-movement) stages N1 to N3, and REM (rapid-eye-movement) sleep (Danker-Hopfe et al., 2009). All these sleep stages are gone through several times during a night sleep, with one sleep cycle lasting approximately 90 to 100 minutes in adults. In early drowsiness N1, the rhythmic eyes-closed alpha frequency of the parieto-occipital region first attenuates, and later vertex waves (positive polarity spikes followed by a more prominent negative wave) begin to appear. In the transition from drowsiness to light sleep N2, sleep spindles and K-complexes also emerge. Sleep spindles are bursts of neuronal oscillatory activity with a duration of around 0.5 to 1.5 seconds in adults. K-complexes are waveforms consisting of three high-voltage components (a brief negative peak followed by a slower positive and negative peak complex) with a total duration of about 0.5 seconds. Deeper sleep N3 and REM are more rarely seen in clinical EEG due to the short recording time. (Niedermeyer & Lopes da Silva, 1998)

2.3 Beta rhythm modulation as a biomarker of sensorimotor cortical function

Biomarkers are biological indicators that can be used to measure molecular or cellular processes that may be otherwise difficult to measure directly from humans (Aronson & Ferner, 2017). The general objective of biomarkers is to help understand normal biological occurrences and related disorders, as well as predict recovery, develop treatments and therapeutic interventions for various disease.

2.3.1 The functional significance of beta modulation for the SM1 cortical function

Beta rhythm suppression and rebound are considered to reflect separate cortical functions (Engel & Fries, 2010; Pfurtscheller & Lopes da Silva, 1999). The suppression has been suggested to reflect excitation or an active state of the SM1 cortex, whereas the rebound is thought to reflect the deactivation or inhibition of the motor cortex (Cassim et al., 2001; Cheyne, 2013; Neuper et al., 2006). Beta oscillations have been associated with the function of inhibitory GABAergic interneurons (Yamawaki et al., 2008). The resting state beta rhythm has been demonstrated to increase by administration of the non-selective neurotransmitter $GABA_A$ (gamma-aminobutyric acid) agonist diazepam (Hall et al., 2010; Jensen

et al., 2005). In addition, a magnetic resonance spectroscopy (MRS) study showed a positive correlation between the GABA concentration and the power of beta rebound measured by MEG in relation to finger movement. This indicates a strong connection between the beta rebound and GABAergic regulation (Gaetz et al., 2011). Beta suppression and rebound are thought to be controlled by distinct GABAergic subunits, with the suppression being mainly a $GABA_A$ and the rebound $GABA_B$ receptor-mediated process (Muthukumaraswamy et al., 2013). In a transcranial magnetic stimulation (TMS) study, magnetic stimulation combined with a somatosensory stimulus showed a decrease in beta rhythm within the time window of the beta rebound, confirming that the beta rebound reflects motor cortex inhibition (Chen et al., 1999). GABA-mediated inhibitory regulation is considered necessary for the plastic reorganization of the motor cortex. Since several studies support the view that excitation and inhibition of the SM1 cortex can be determined by measuring the beta power modulation, it provides an interesting tool for quantify alterations of the excitatory–inhibitory balance of the SM1 cortex in different patient groups, such as disorders affecting motor functions.

2.3.2 Beta rhythm modulation in motor learning

The human motor system embraces an excellent capacity to reorganize itself and thus adapt to new motor requirements, which also forms the basis of recovery from brain damage. The ability to learn new motor skills is individual and is mainly based on previously learned skills (Horton et al., 2017). Motor learning requires information from different senses and combining them via extensive neural networks. Several cortical sensorimotor areas are shown to be active when just imagining movement (Hétu et al., 2013). Furthermore, imitating motor actions has been proposed to improve the performance and timing of the movements, thus it may have significant implications for educational activities, sports training, and neurorehabilitation (Vogt & Thomaschke, 2007).

Practicing motor skills increases the SM1 cortex beta rhythm power and the strength of beta modulation in the short term (Moisello et al., 2015; Nelson et al., 2017; Tatti et al., 2020). Learning a complex bimanual motor task has been shown to increase the contralateral M1 cortex beta rebound, which is also highly correlated with motor performance (Boonstra et al., 2007; Houweling et al., 2010). However, this practice-related increase in beta rebound has not been seen in PD patients, which may reflect an impaired motor cortex plasticity in PD (Ghilardi et al., 2021; Moisello et al., 2015; Nelson et al., 2017). The ability to learn new motor skills has also been associated with the motor cortex inhibitory GABA concentrations, with high GABA levels correlating with poorer motor learning

(Kolasinski et al., 2019). GABAergic inhibition is proposed to have a crucial role in motor cortex plasticity, and it has been shown to correlate especially with the strength of beta rebound (Gaetz et al., 2011; Hall et al., 2010, 2011; Yamawaki et al., 2008).

2.4 Cerebral palsy (CP) and alteration of the SM1 cortex function

CP is a chronic non-progressive neuromotor disorder that affects a person's ability to move and maintain body posture. The most common motor symptoms are spasticity with exaggerated reflexes of the limbs and trunk, unsteady gait, and lack of balance and muscle coordination (Piitulainen et al., 2021). Different types of CP can be classified according to motor symptoms and their severity, for example into spastic diplegic and hemiplegic CP (Krigger, 2006). The Gross Motor Function Classification System (GMFCS) scale is commonly used to describe the severity of motor functions, suiting both clinical practice and research. In GMFCS, the ability of motor disability (e.g. sitting, walking, and need for assistive devices, as well as environmental and personal factors on mobility) can be categorized into a five-level scale, 1 corresponding with mild symptoms and 5 with the most severe (Palisano et al., 1997, 2008). Another classification system for CP is the Manual Ability Classification System (MACS), which describes the smoothness of using both hands in daily activities on a scale of 1 to 5 (Eliasson et al., 2006). In addition to variable motor symptoms, individuals with CP have often other neurological problems such as epilepsy, autism, and mental retardment, as well as disturbances in somatosensory perception (Krigger, 2006; Wingert et al., 2008). CP occurs because of brain injury to the immature developing brain during either the prenatal, perinatal, or postnatal period for a variety of reasons. The most common causes of CP are infarction, haemorrhage or malformation of the brain, infection during pregnancy, asphyxiation during birth, and meningitis (Oskoui et al., 2013; Rosenbaum et al., 2007). Thus, the location and extent of the brain lesion also vary greatly between individuals with CP.

Although medical care has improved, the incidence of CP has remained almost the same in the past decades. This is mainly due to the increase in survival of at-risk preterm infants (Oskoui et al., 2013). Motor and somatosensory difficulties in CP complicate everyday life, and thus may also lead to substantial economic losses (Tonmukayakul et al., 2018). Hence, more research is needed to develop effective therapy and rehabilitation methods. Several brain imaging studies have observed abnormal somatosensory cortex function as well as changes in the somatotopic organization in CP (Brun et al., 2021; Kurz et al., 2015; Kurz &

Wilson, 2011; Nevalainen et al., 2012; Trevarrow et al., 2021). In addition, the oscillatory activity of the SM1 cortex has been shown to be altered, for example, the amplitude of alpha, beta, and gamma frequencies have been reported to decrease and be delayed (Hoffman et al., 2019). MEG studies have shown that particularly beta rebound is reduced to the hand stimulation or movement in CP (Hoffman et al., 2019; Pihko et al., 2014). TMS studies have demonstrated deficits in intracortical and interhemispheric inhibitory mechanisms both in hemiplegic and diplegic CP, with more pronounced alteration correlating with an impaired upper extremity function (Mackey et al., 2014; Vry et al., 2008). In addition, the fMRI study has shown stronger contralateral activation to proprioceptive stimulus in CP compared to healthy controls (Nurmi et al., 2021).

In hemiplegic CP, cortico-spinal motor projections have been demonstrated to have abnormal reorganization, such as varying degrees of compensatory ipsilateral and enhanced bilateral projections. These modifications have been shown to corelate with the timing of brain injury and the severity of motor impairments (Eyre, 2007; Staudt, 2002, 2010). Thalamo-cortical somatosensory projections, in turn, can develop quite normally despite early on-set of brain injury. However, if the somatosensory cortex itself is affected, no signs of reorganization have been shown (Staudt, 2010). These findings indicate both structural and functional alteration in the sensorimotor system in CP. However, due to the variety of CPs and the different research arrangements in these studies, there are still many open questions about the deficits of the sensorimotor system in CP. Therefore, more studies are needed to further elucidate the neurophysiological mechanisms behind this heterogeneous group.

2.5 Magneto- and electroencephalography

Magnetoencephalography (MEG) and electroencephalography (EEG) are complementary methods that measure electrical signals elicited by brain activity. They detect brain signals non-invasively outside the head and provide accurate time information in a millisecond time scale. EEG detects directly potential differences caused by neuronal currents, while MEG measures the magnetic fields generated by these electrical currents. Both methods provide means to safe and easy studies of human subjects (Hari & Puce, 2017).

2.5.1 Neural origin of MEG/EEG signal

Both MEG and EEG detect brain signals of tens of thousands of simultaneously activated cortical pyramidal cells located perpendicular to the cortical surface.

The human cerebral cortex consists of six layers, but the structure of the layers varies slightly between different brain regions for example, the granulated layer IV is missing in the M1. The most superficial layers contain mainly dendrites of the cells in the deeper layer, such as apical dendrites of the pyramidal cells, but also axons of more distant non-pyramidal cells. The cell bodies of pyramidal cells are located in the deeper layers, mainly layer V (FIGURE 5). From there, the electrical signals are conveyed through the axons of the pyramidal cells to the target areas. (Hari & Puce, 2017)

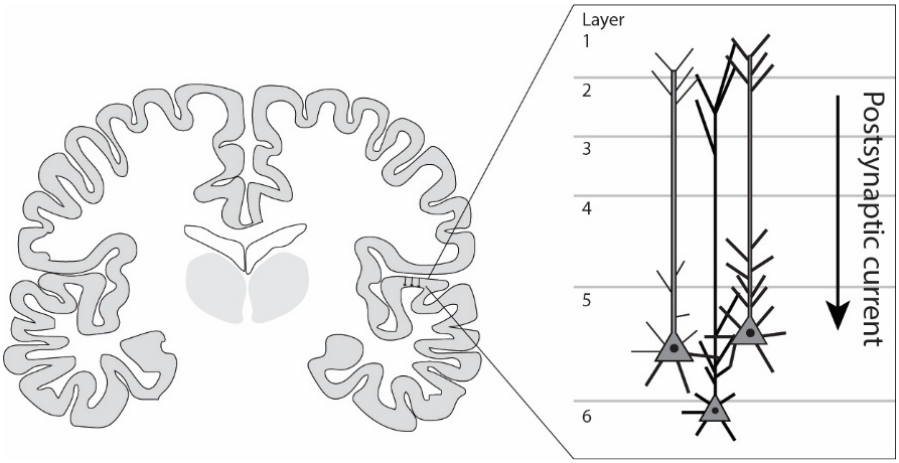

FIGURE 5 Origin of the postsynaptic currents in the cortex. Cortical intracellular postsynaptic currents are generated in pyramidal cells located perpendicular to the surface of the cortex. The arrows indicate the direction of cortical postsynaptic currents.

The signals detected with MEG and EEG are generated by intracellular postsynaptic currents of the pyramidal cells, which are formed as a summation of incoming excitatory and inhibitory synaptic currents to the apical dendrite and cell body of the pyramidal cells. The synaptic transmembrane currents are the result of the action potentials (AP) of afferent pre-synaptic neurons, which are triggered only if the cell membrane reaches a certain depolarization threshold. As a result of AP, neurotransmitters are released into the synapse and bind to the receptors of the postsynaptic neuron creating postsynaptic potentials (PSPs). The direction of the resulting intracellular postsynaptic current (i.e. primary current) in the cortex is from the surface to the deeper layers of the grey matter (FIGURE 5). The PSP is the main source of electric currents measured with EEG, as well as the magnetic field measured with MEG. However, the measured signals are also affected by returning currents (i.e. volume currents), which spreads in the surrounding conducting volume. EEG is especially sensitive to these volume currents as they induce voltage differences in the scalp, but they may also affect the

magnetic fields, either amplifying or weakening them. (Hämäläinen et al., 1993; Hari & Puce, 2017)

2.5.2 MEG instrumentation

MEG detects very weak magnetic fields from outside of the head. The strength of the magnetic fields measured with MEG are typically in the range of 100 to 500 fT, while the Earth's steady magnetic field is significantly stronger at around 50 to 100 μT. The MEG device operation is based on highly sensitive SQUID (Superconducting Quantum Interference Device) sensors that consist of a superconducting loop interrupted by weak Josephson junctions that are embedded in liquid helium at -269 °C to achieve superconductivity. SQUIDs are coupled with a pickup coil (i.e. flux transformer) that converts magnetic signals into electrical currents. These currents are further transferred to the electronics of the device such as electric signal amplifiers. MEG instruments can have different configurations of sensors, which can detect different components of the magnetic field. The MEG device used in this dissertation is a whole-head coverage device with 102 sensor units mounted in a helmet-shaped sensor array. Each sensor unit comprises two orthogonal planar gradiometers and one magnetometer. The gradiometers consist of two oppositely wounded detector coil loops in the same plane. They detect the magnetic fields just beneath the loops, and thus the location of activation can roughly be determined at the sensor level. However, the ability of the gradiometers to detect deeper brain sources is limited as they are sensitive to nearby sources. The magnetometers have a single-loop structure, and they measure the magnetic field close to the loop. Their sensitivity to more distant brain sources also makes them sensitive to ambient interference. (Hämäläinen et al., 1993; Hari & Salmelin, 2012)

During MEG measurement, the subject is sitting or lying comfortably with their head placed inside the helmet of the MEG the device. Since MEG is sensitive to various ambient noise, measurements are typically performed in a magnetically shielded room (MSR). The MSR consists of several layers of aluminum and mu metal, providing passive magnetic shielding, nevertheless, additional active shielding can be combined if the passive shielding does not provide adequate protection from the ambient noises. MEG registrations are easy and quick to start and do not require long preparation. (Hari & Puce, 2017)

MEG is a reference-free method, which simplifies the analysis since the choice of reference is not relevant to the results. MEG is sensitive mainly for tangentially oriented sources, which means that it is unable to detect radial cortical sources located strictly parallel to the skull surface. This is because the volume currents also generate a magnetic field around them which cancels out the

magnetic field caused by the radial intracellular primary current. Hence, MEG detects cortical activations primarily from the fissural cortex (Hämäläinen et al. 1993). In practice, this limitation is restricted as the cortical surface is heavily folded and about two-thirds of the cortex (primary motor, sensory, auditory, and visual cortex) and located in the walls of cortical fissures. The location of the primary sensorimotor areas is excellent in this sense and exploring these areas with MEG is particularly profitable. (Hari & Puce, 2017)

2.5.3 EEG instrumentation

The EEG signal is usually measured from the scalp with surface electrodes, but it can also be measured with intracranial subdural grids and depth electrodes. EEG detects voltage differences (i.e., electric potentials) in microvolts (μV) between two points. The measured signal is conducted through an electrode selector to serially connected pre- and power amplifiers and then transmitted to the computer via an analogue-to-digital converter. EEG electrodes are commonly placed on the scalp according to the standard international 10–20 (or denser 10–10) system, which means that the percentual distances and locations of the electrodes are determined with respect to certain head landmarks (nasion-inion and preauricular points). The number of electrodes and the electrode montage may vary as preferred. The electrode preparation can be quite time-consuming, and it should be done carefully as it significantly affects the quality of the recorded signal. EEG always requires a reference electrode that is typically placed in an inactive location, such as the mastoids behind the ear or earlobes. The potential difference of the reference electrodes is compared to all other EEG electrodes. However, the reference electrode attached to the body is never completely silent, and its placement also affects the EEG signals and waveforms. The recorded EEG signals can afterward be digitally re-referenced, for example to the commonly used bipolar double banana montage, local average reference of the Laplacian derivation, and common averaged reference of all electrodes. (Hari & Puce, 2017)

Electrical disturbances can interfere with EEG measurements, but in noisy environments an electrically shielded environment can be formed by surrounding the room with a mesh of conducting material. This so-called Faraday cage protects the inside of the room from external high-frequency electromagnetic disturbances (Hari & Puce, 2017).

2.5.4 Advantages and disadvantages of MEG and EEG

Both MEG and EEG have advantages and disadvantages. MEG provides better spatial resolution than EEG, as the magnetic fields propagate almost unchanged

through the head structures (skull, scalp membranes, and cerebrospinal fluid), unlike electrical currents that alter as they pass through tissues. Tissue inhomogeneity attenuates and smears the potential distribution over a wider area, which hampers accurate source localization, and therefore, especially the separation of simultaneously active brain sources is challenging in EEG (Hari & Puce, 2017; Hari & Salmelin, 2012; Wolters et al., 2006). However, the advantage of EEG compared to MEG is its sensitivity to all source orientations, while MEG is insensitive to strictly radially oriented sources (Baillet et al., 2001). Moreover, MEG's ability to detect deep sources is decreased but not completely blocked (Hillebrand & Barnes, 2002; Riggs et al., 2009).

MEG measurements require the shielding of the MSR, which increases installation costs in addition to the already expensive MEG equipment. MEG measurements are quick and easy to start because they do not require long preparation, unlike EEG. EEG is commonly used in hospitals and research institutes mainly because the devices are small, easy to move for bedside recordings, inexpensive to obtain, and has low operating costs. EEG caps are also available in different sizes and configurations compared to MEG. In addition, EEG provides the possibility to do measurements lasting several days, because the subject can move during the EEG registration. However, MEG offers a better signal-to-noise ratio (SNR) than EEG, and MEG is also less sensitive to various environmental disturbances, movements, and muscular activity (Hari & Puce, 2017). The EEG signal is affected by the quality of the reference electrode(s), in contrast with the MEG signal, which is a reference-free method that shows brain activation at the location indicated by the sensors. The choice of EEG montage has a substantial effect on the signals obtained. The simultaneous use of EEG and MEG has been found to be beneficial in the detection of epileptic activity (Ebersole & Ebersole, 2010). Combining these two methods can also improve the localization of activated source areas (Antonakakis et al., 2019).

3 AIMS OF THE STUDY

This dissertation aimed to demonstrate the usability of beta modulation as a clinical tool. To achieve this goal, the stability of beta modulation was evaluated by studying the replicability of beta suppression and rebound in the same subjects and evaluating the effect of alertness on beta modulation. For potential clinical applications, the ability to detect beta suppression and rebound was compared between MEG and EEG. Furthermore, beta modulation was applied as a measure of SM1 cortical excitation and inhibition in adolescents with CP. The specific objectives of the studies were the following:

1. To evaluate whether the modulation of the beta rhythm can be quantified equally with MEG and EEG methods. That is, could EEG be used as an equivalent tool to assess SM1 cortical function (Study I)?
2. To define whether the state of alertness (drowsiness or active attention) affects the beta rhythm modulation in healthy subjects, since a change in vigilance may be an issue especially in clinical studies (Study II).
3. To clarify the reproducibility of beta rhythm modulation, which is a prerequisite for follow-up studies (Study III).
4. To elucidate changes in the cortical excitation–inhibition balance that may underlie motor deficits in CP by determining the SM1 cortex beta suppression and rebound strengths (i.e. level of excitation and inhibition) in adolescents with hemiplegic and diplegic CP (Study IV).

4 MATERIALS AND METHODS

4.1 Subjects

All subjects participated in the study voluntarily and gave written informed consent prior to MEG/EEG measurements. The studies were conducted with the standards of the Declaration of Helsinki, and the protocol was approved by the ethics committee of Aalto University and/or the Hospital District of Helsinki and Uusimaa (HUS).

4.1.1 Healthy adults (studies I, II, III)

In total, twenty-five healthy young adults (12 females, age 19–35, mean 23 ± 4yrs) participated in studies I, II, and III. Twenty-three of them were right-handed, one was left-handed, and one was ambidextrous. Not all participants were able to participate in all the studies, hence the number of subjects varied slightly between the studies.

4.1.2 Children/adolescents with CP and healthy controls (Study IV)

Twenty-eight CP children and adolescents (17 females, age 13.2 ± 2.3 years) participated in the study. Sixteen of them had a diagnosis of hemiplegia (five right-handed) and twelve had diplegia (nine right-handed). Between-group differences were defined for the dominant and non-dominant hand. All the CP participants had mild symptoms, that is, GMFCS scale of 1–2 and MACS 1–3.

Thirty-two age-matched, typically developed, and neurologically normal children and adolescents (19 females, age 14.0 ± 2.4 years) attended the study as a control group. Thirty of them were right-handed and two left-handed.

4.2 Instrumentation and stimulation

4.2.1 MEG/EEG recordings

An Elekta Neuromag Vectorview™ (Elekta Oy, Helsinki, Finland) 306-channel whole-head MEG system (204 planar gradiometers and 102 magnetometers) was used to measure MEG (FIGURE 6). EEG was recorded simultaneously with a 60 channel MEG-compatible EEG cap (ANT Neuro waveguard™original), where the surface electrodes (Ag-AgCl) were mounted according to the international 10–10 system. The impedance of the EEG electrodes was less than 5 to 10 kΩ at the beginning of the measurement. In addition, two vertical electrooculogram electrodes (EOG) were attached to detect eye blinks. The measurements were conducted in a magnetically shielded room (Imedco AG, Hägendorf, Switzerland) at the MEG Core, Aalto NeuroImaging, Aalto University.

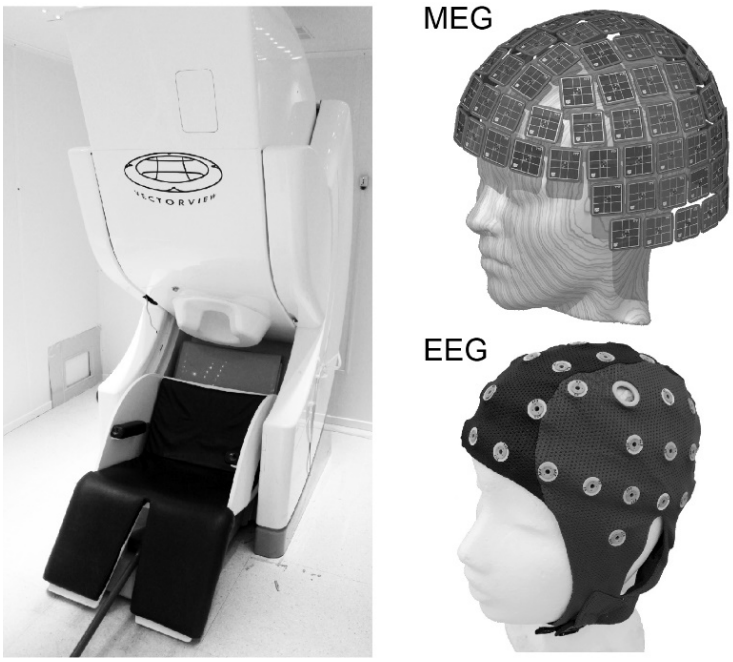

FIGURE 6 Elekta Vectorview™ MEG device at Aalto University MEG Core. The layout of MEG sensors is shown at the top right (figure courtesy of Mika Seppä), and the 60-channel ANT EEG cap at the bottom right.

The position of the participant's head in relation to the MEG sensors was determined by five indicator coils of which three were attached to the forehead and one above each ear at the beginning of each measurement session. In addition, head position was also measured continuously during the sessions. The location of the coils together with three anatomical landmarks (left and right preauricular points and nasion), EEG electrodes, and 100–200 additional points from the scalp

surface, were determined with a 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA).

MEG and EEG signals were recorded at a sampling frequency of 1000 Hz and band-pass filtered from 0.1 to 330 Hz.

4.2.2 Proprioceptive stimulation (studies I, III, IV)

The proprioceptive stimulus, that is, passive movement, was induced with a custom-made pneumatic movement actuator to move the index fingers (Piitulainen et al., 2015a). The participant's hand was laid comfortably on the table plates of the movement actuator and the stimulated finger was lightly fastened with tapes on the artificial muscle of the movement actuator (FIGURE 7). The kinematics of the movement was detected with a 3-axis accelerometer, which was attached to the finger.

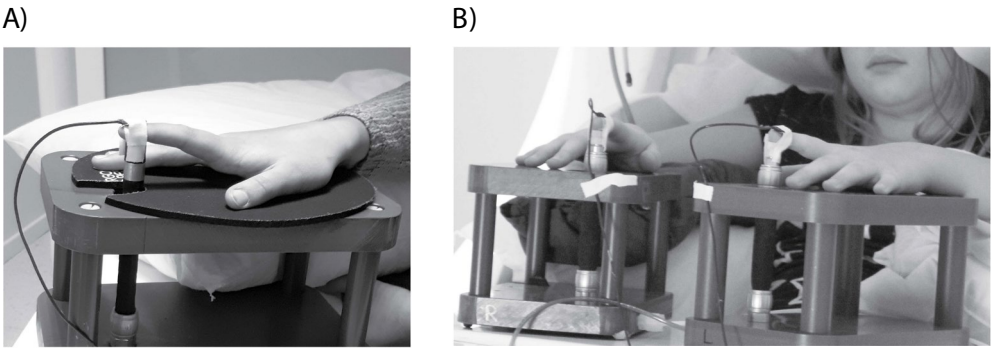

FIGURE 7 The experimental setup to proprioceptive stimulation: A) in studies I and III, and B) in Study VI.

In studies I and III, the index finger of the right and left hand was stimulated with extension–flexion movement in separate sessions with a 5-second interstimulus interval (ISI). The stimulus (130 ms duration, air pressure of 4 bar) generated a fast extension–flexion movement of the index finger in a range of ~5 mm.

In Study IV, the left and right index fingers were stimulated alternately in the same measurement session with two movement actuators. The devices first generated the prompt flexion of the finger, followed by a consistent finger extension after 2 seconds of the flexion onset. The ISI of the finger flexion was 4 seconds. The range of the movement was ~9.5 mm with an air pressure of 5 bar.

4.2.3 Tactile stimulation (studies I, II, III)

The tactile stimuli were applied to the tips of index fingers with pneumatic balloon diaphragms driven by compressed air, while the participants held their

hands relaxed on a pillow (FIGURE 8). Tactile stimuli were given alternately in the same session to both fingers with a 6-second ISI for one hand.

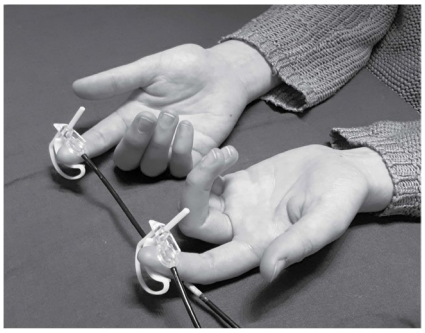

FIGURE 8 The experimental setup for tactile stimulation in studies I, II, and III.

4.3 Experimental procedures

During the MEG/EEG experiments, the participants sat comfortably in the MSR with their eyes open and head placed inside the helmet-shaped MEG sensor array. The participants were asked to direct their gaze on a small image in front of them (or scenery video in Study IV) and not pay attention to the stimulus, while their index fingers were alternately stimulated with either tactile or proprioceptive stimulation. To prevent the perception of noise artefact from the stimulus devices, the participants used earplugs throughout the MEG/EEG measurements, and in addition, white noise was played to mask the noise in Study IV. A visual barrier was used to prevent visual contamination caused by the movement.

In studies I, II, and III, the SM1 cortex beta rhythm in healthy adults was modulated with tactile and/or proprioceptive stimuli, which were delivered to the index fingers in separate sessions. Both MEG and EEG were recorded simultaneously, and around 90 trials for each hand were collected for each stimulus session, with one stimulus session lasting about 9 to 10 minutes. The measurement sessions were repeated identically after one year to define the reproducibility of beta suppression and rebound (Study III). In Study II, only tactile stimulation was used, in which a neutral eyes-open condition was compared with active attention (quiet counting of the number of received stimuli) and snooze (eyes closed allowing to fall asleep) conditions to clarify the effect of alertness on beta modulation. Different stimulus sessions and/or conditions were recorded in randomized order.

In study IV, proprioceptive stimulation was used to modulate the rhythmic activity of the SM1 cortex in CP and typically developed children/adolescents.

The stimulus was delivered randomly to the left and right index fingers in the same stimulus session (ankle movements were delivered in the same session but were not analyzed in this context), and about 60 trials were collected for each hand.

4.4 Evaluation of alertness state (Study II)

Study II explored the effect of alertness on beta rhythm modulation. The participant's alertness was evaluated with two methods (a questionnaire and sleep stage scorings) to study how reduced (snoozing) or enhanced (active attention to tactile stimulus) alertness affects the beta rhythm modulation compared with the neutral condition.

In the questionnaire, the participants assessed their overall alertness subjectively during the three different conditions: neutral, attention, and snooze. The evaluation was done on a seven-step Likert scale; 0 = Fell asleep, 1 = Fully tired, 2 = Moderately tired, 3 = Slightly tired, 4 = Slightly alert, 5 = Moderately alert, and 6 = Fully alert.

The sleep stage scoring was done according to the AASM manual (American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events; (Richard B. Berry et al., 2012), for the snooze condition data. The sleep stages were estimated from EEG channels over the central, frontal, and occipital regions, and in addition, EOG channels were used. The sleep stage was evaluated in steps of 30-second analysis windows. During the snooze condition, only stages of wakefulness (Stage W), drowsiness (Stage N1), and light sleep (Stage N2) were observed due to the short recording time. According to the ASSM manual, Stage W represents wakefulness and includes over 50% of alpha rhythm and visible eye blinks. Stage N1 indicates drowsiness to falling asleep, showing vertex sharp waves, slow eye movements, and over 50% of low voltage mixed frequency (LVMF). Stage N2 indicates light sleep with LVMF, K-complexes, and sleep spindles. The prevalence of sleep stages W, N1, and N2 are presented in percentages.

4.5 Data analysis of MEG/EEG

4.5.1 Preprocessing of the raw data

The MEG data were preprocessed with Maxfilter software (v2.2; Elekta Oy, Helsinki, Finland), using the signal-space separation method with temporal

extension (tSSS), including head movement compensation (Taulu & Simola, 2006). In addition, the head coordinates of different stimulation sessions within one subject were transformed to the same average head coordinate. From here on, MNE Python was used to conduct the raw data analysis (Gramfort et al., 2013). The EEG data were re-referenced using the average reference. Stimulus-related somatosensory and motor-evoked responses were subtracted from the MEG/EEG raw data as they may interfere with beta modulation analysis. Eye movement artefacts were removed using a principal component analysis (PCA) (Uusitalo & Ilmoniemi, 1997).

4.5.2 Time–frequency representation (TFR)

The modulation of the beta rhythm was computed in time–frequency representation (TFR) with the Morlet wavelet transformation, with the frequency range varying in different sub-studies between 2 and 40 Hz and the time window from –700 to 4000 ms with respect to stimulus onset (Tallon-Baudry et al., 1997). TFRs were used to determine the individual frequency band of beta modulation and to visualize group-level results.

4.5.3 Temporal spectral evolution (TSE)

The TSE method was used to quantify the amplitude and temporal occurrence of beta suppression and rebound (Salmelin & Hari, 1994). In TSE, the MEG/EEG raw data were first bandpass filtered to a suitable beta frequency between 13 and 26 Hz with a bandwidth of 10 to 12 Hz. After filtering, a Hilbert transform was utilized to achieve the envelope signal, and the data were averaged with a time window of around -700 to 4000 ms (varied in different sub-studies) with respect to stimulus trigger onset. The MEG/EEG channels showing maximal amplitude from the left and the right SM1 cortex hand region were selected to quantify the peak amplitudes and latencies of beta rebound and suppression with 1 ms resolution. For the final analysis, the peak values were converted into relative percentage values with respect to the pre-stimulus baseline.

4.5.4 Spectra analyses

Power spectral densities (PSD) were calculated from the eyes-open resting state MEG/EEG data to determine the individual frequencies and amplitudes of spontaneous beta activity (Study I) and to detect alterations in the SM1 cortex rhythmic activity regarding changes in alertness (Study II). The Welch method, with a sliding 2048-point fast Fourier transform (FFT) with no overlap and a Hann window function, was used to determine the PSDs.

4.5.5 Statistical analysis

Statistical tests were performed with IBM SPSS Statistics or with R statistical software. In studies I, II and III with healthy adults, the non-parametric Wilcoxon signed-rank test was used to test for differences in latency and amplitude of beta suppression and rebound between MEG and EEG (Study I), between different conditions of alertness (Study II), and between follow-up sessions (Study III). The Wilcoxon test was chosen since, based on the Shapiro-Wilk test the data turned out non-normally distributed. Correlations were tested with the Spearman's correlation coefficient test. Additionally in Study II, the correlations between follow-up recordings were evaluated with the intraclass correlation coefficient (ICC) test, and inter-individual variability was defined with coefficient variation (CV). In Study IV, the Kruskal-Wallis H test (one-way analysis of variance, ANOVA) and the Conover post hoc test were used to determine significant differences between the groups.

All the statistical tests were corrected for multiple comparisons with Bonferroni or FDR correction (except in Study I). A p-value of 0.05 or less was accepted as statistically significant.

4.6 Ethical considerations

The local Ethics Committees of Aalto University (studies I, II, and III) and Helsinki and Uusimaa Hospital district (Study IV) approved the experiments according to the Declaration of Helsinki. The recruitment of participants was carried out following good ethical principles. The voluntary participants were informed about the study and its purposes, and they were asked to give written informed consent prior to the MEG/EEG experiment. All participants were able to quit at any point.

MEG and EEG are well-known brain imaging methods. They are noninvasive, safe, and convenient, and do not cause any harm to the subjects. The MEG/EEG data was processed confidentially and anonymously from the beginning of the studies, and the results were reported at the group level.

5 RESULTS

5.1 Study I: Comparing MEG and EEG in detecting the 20-Hz rhythm modulation to tactile and proprioceptive stimulation

The 20 Hz suppression and rebound were seen bilaterally over the SM1 cortex for unilateral stimulation for both tactile and proprioceptive stimulation in MEG and EEG. Peak latencies of beta suppression (at around 330 ms) and rebound (at around 820 ms) measured with MEG and EEG did not differ between MEG and EEG methods (FIGURE 9).

The relative peak strengths of suppression and rebound in the contralateral hemisphere with respect to the stimulated hand are shown in TABLE 1 and FIGURE 10. The strengths of suppression and rebound were significantly stronger in MEG than in EEG, except for the rebound to the right-hand tactile stimulation. Despite differences in the suppression and rebound strengths between MEG and EEG, the results correlated well with each other ($r = 0.62 – 0.84$, $p < 0.01$).

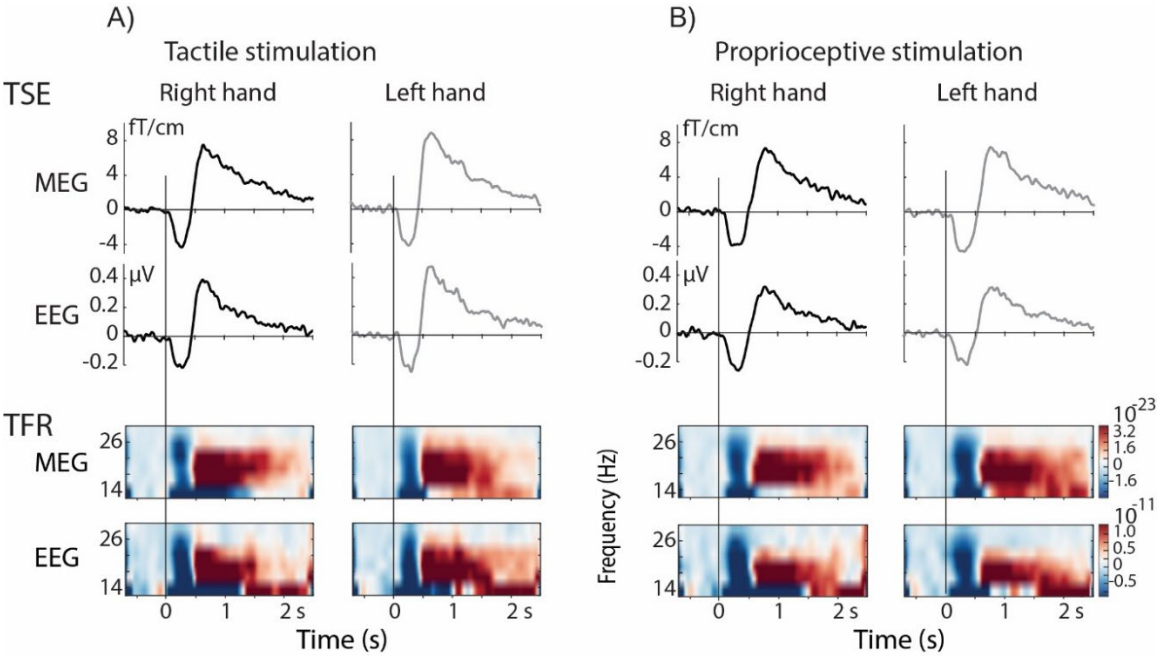

FIGURE 9 Beta rhythm modulation to (A) tactile and (B) proprioceptive stimulation. Grand averaged (N=24) temporal spectral evolution curves (TSE) and time–frequency representations (TRF) over the left and right sensorimotor regions are shown for contralateral hand stimulation in MEG and EEG.

TABLE 1 The relative (%) beta modulation strengths (mean ± SEM) to index finger stimulations

	MEG		**EEG**	
	Right hand	Left hand	Right hand	Left hand
Tactile stimulation				
Suppression	-25 ± 2%	-28 ± 2%	-20 ± 2% **	-22 ± 2% **
Rebound	53 ± 8%	63 ± 9%	41 ± 5%	48 ± 6% *
Proprioceptive stimulation				
Suppression	-25 ± 2%	-27 ± 2%	-21 ± 2% *	-21 ± 2% **
Rebound	53 ± 9%	53 ± 9%	39 ± 5% *	39 ± 5% *

Statistically significant differences between MEG and EEG results are marked with asterisks as follows; ** $p < 0.01$, * $p < 0.05$

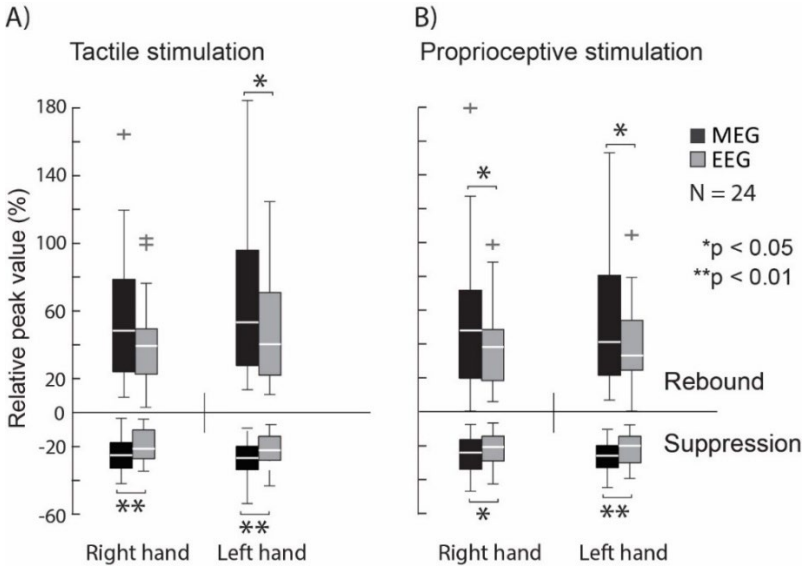

FIGURE 10 Relative peak strengths of beta suppression and rebound to (A) tactile and (B) proprioceptive stimulation in MEG and EEG. 50% of beta suppression and rebound strengths are represented inside the boxes. Statistical differences in suppression/rebound strengths between MEG and EEG are denoted as * $p < 0.05$ and ** $p < 0.01$.

5.2 Study II: The effect of alertness and attention on the modulation of the beta rhythm to tactile stimulation

The healthy subjects' alertness was diminished during the snooze condition based on the questionnaire (neutral 1.6 ± 0.4 vs snooze 3.8 ± 0.4 condition, $p < 0.01$). Sleep state N1 (26 ± 6%) and N2 (4 ± 2%) were detected during the snooze condition in the EEG. The decreased alertness (*neutral versus snooze condition*) at the group level did not significantly reduce the relative (%) strength of the contralateral suppression for the left- (-31 ± 2% vs -26 ± 2% in MEG; -18 ± 2% vs -15 ± 2% in EEG) or right-hand stimulation (-25 ± 2% vs -20 ± 2% in MEG; -20 ± 2% vs -17 ± 2% in EEG). Respectively, no significant changes were observed in rebound strengths for the left- (59 ± 8% vs 50 ± 7% in MEG; 37 ± 5% vs 35 ± 4% in EEG) or right-hand stimulation (44 ± 7% vs 34 ± 5% in MEG; 35 ± 4% vs 30 ± 4% in EEG) (FIGURE 11).

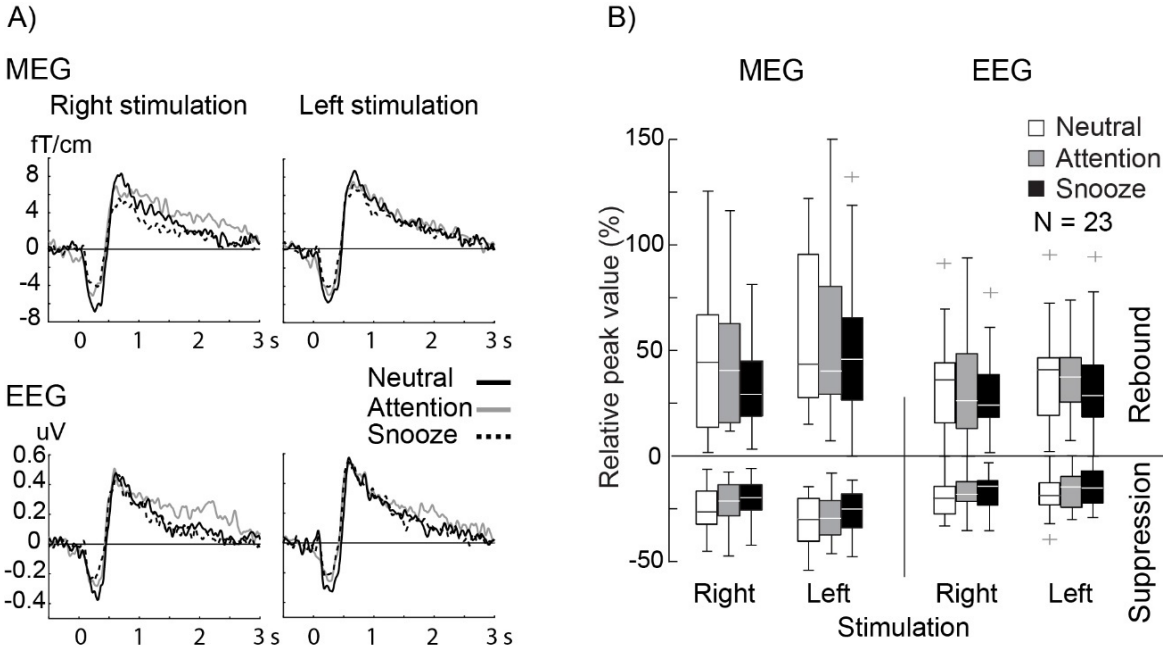

FIGURE 11 Beta rhythm modulation in the contralateral hemisphere to tactile stimulation during the neutral, snooze, and attention conditions. A) Temporal spectral evolution (TSE) curves grand averaged (N = 23) from the most representative channels of the SM1 cortex area. B) Relative peak strengths of beta suppression and rebound.

In addition to the results presented above, some individual subjects with clearly decreased alertness (i.e. those with more N1/N2 sleep) had tendency for more reduced beta modulation strengths, although the group results were not significant. In particularly, weaker suppression strengths correlated with the amount of N1/N2 sleep. Attention to the tactile stimulus, on the other hand, did not affect the strength of suppression or rebound.

5.3 Study III: Reproducibility of Rolandic beta rhythm modulation in MEG and EEG

The reproducibility of relative beta suppression and rebound strengths was good during the one-year follow-up period for both tactile and proprioceptive stimulation at the group level, and no significant differences were seen between T_0 and $T_{1\text{-year}}$ measurements (FIGURE 12A). The suppression and rebound strengths between T_0 and $T_{1\text{-year}}$ measurements also correlated well with each other both in MEG and EEG (ICC = 0.70 – 0.96 and Spearman's r = 0.47 – 0.94) (FIGURE 12B)

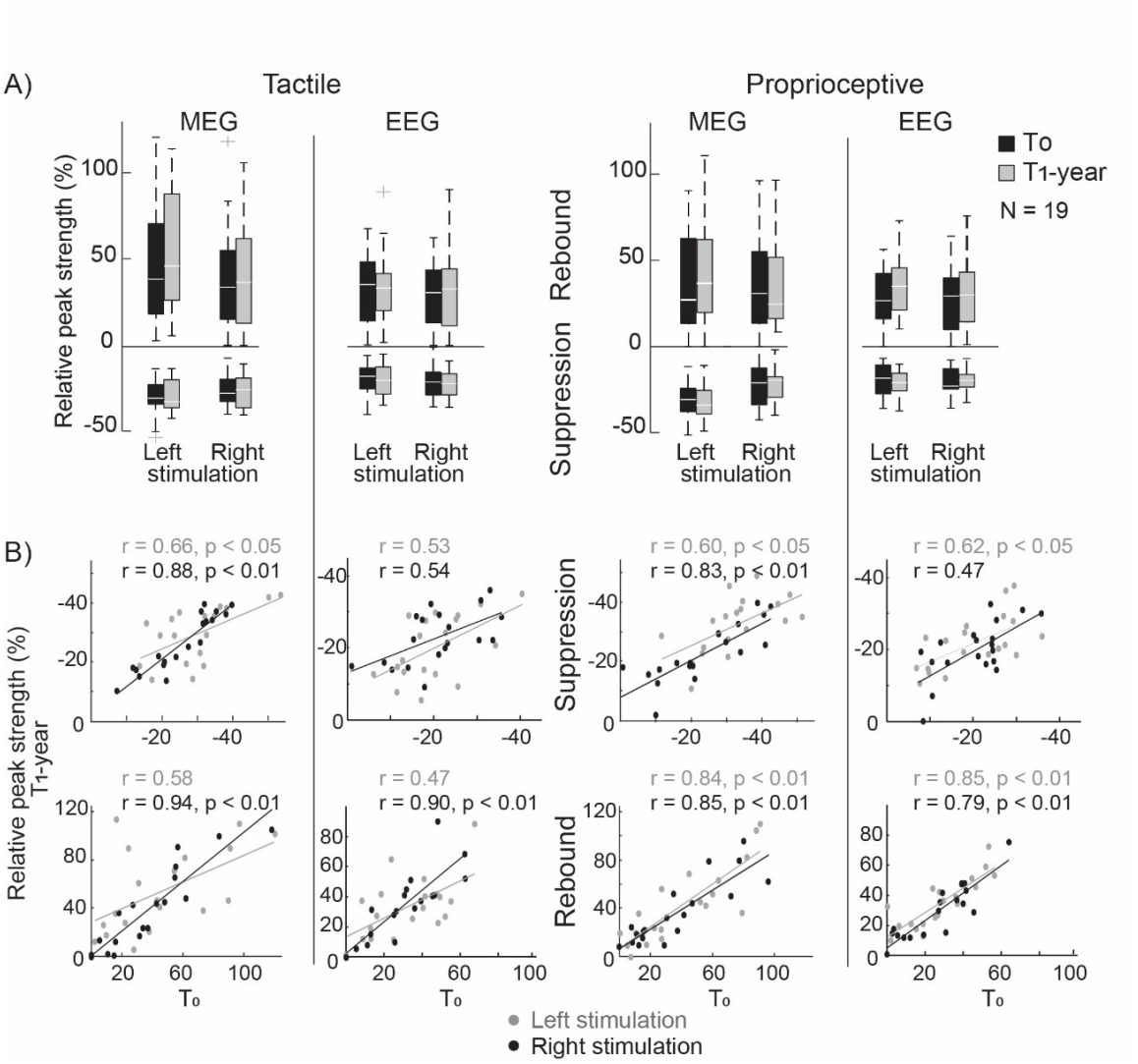

FIGURE 12 Reproducibility of beta suppression and rebound to tactile and proprioceptive stimulation between T_0 and $T_{1\text{-year}}$ measurements in MEG and EEG. A) Peak strengths of relative suppression and rebound strengths. B) Spearman's correlation coefficients of the relative peak strengths.

The baseline power of beta rhythm remained fully reproducible during the one-year follow-up period (ICC = 0.72 – 0.99 and Spearman's r = 0.57 – 0.99). The strengths of beta modulation, especially beta rebound, varied between individuals, being weak or even undetectable in some individuals (coefficient of variation for suppression 30% – 70% and rebound 46% – 96%).

5.4 Study IV: Altered excitation–inhibition balance in the primary sensorimotor cortex to proprioceptive hand stimulation in cerebral palsy

Alterations in the SM1 cortex beta modulation strengths were observed in adolescents with diplegic cerebral palsy (DP) compared to typically developed controls (TD), however no similar alterations were observed in adolescents with hemiplegic cerebral palsy (HP) (FIGURE 13). Beta suppression, that is, excitation of the SM1 cortex, was significantly stronger in the contralateral hemisphere for the dominant hand finger flexion in DP than in TD participants (-30 ± 1.9% vs. -24 ± 1.5%, P = 0.03). In addition, the strengths of beta rebound were significantly decreased in DP compared to TD in the ipsilateral hemisphere for the dominant (9 ± 1.8% vs. 22 ± 2.9%, P = 0.008) and non-dominant (12 ± 3.3% vs. 20 ± 2.1%, P = 0.02) hand finger flexion, reflecting alteration of the ipsilateral SM1 cortex inhibition in adolescents with DP.

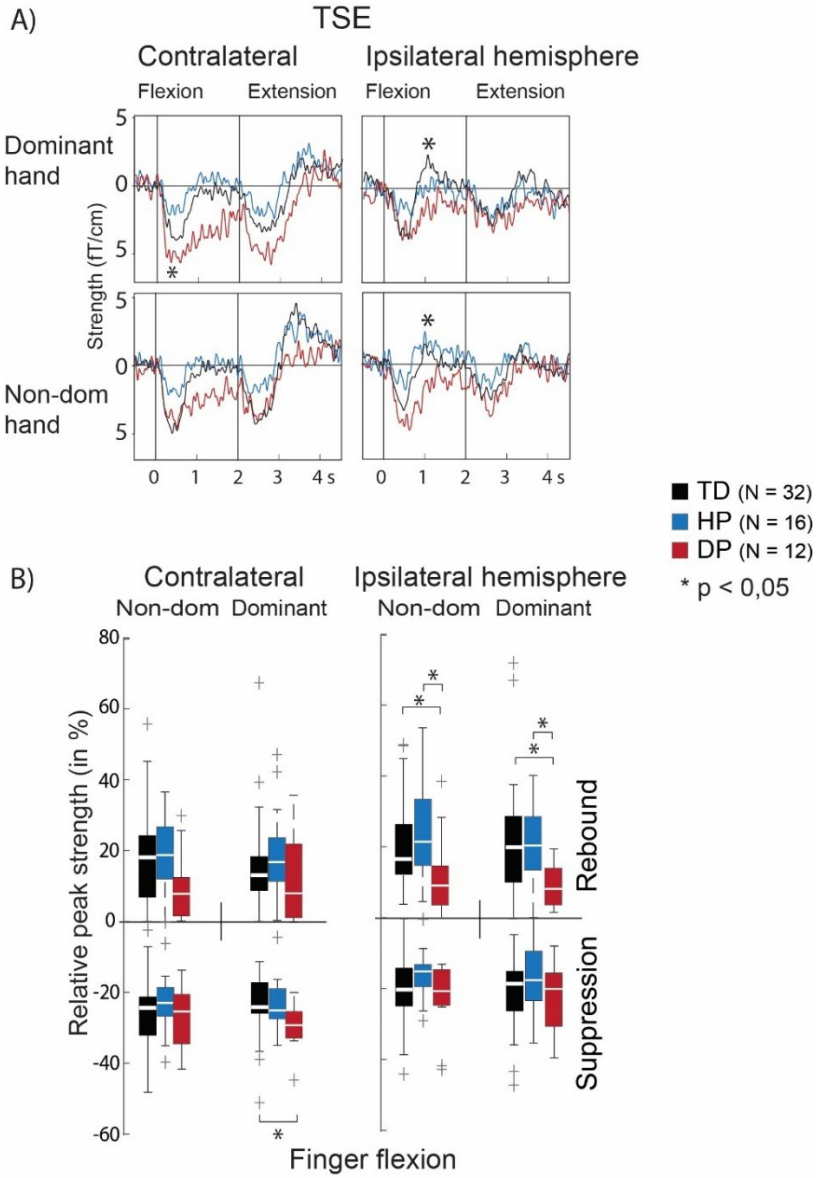

FIGURE 13 Strength of beta suppression and rebound to proprioceptive stimulation in CP and TD participants measured with MEG. A) Grand averaged TSE curves from the most representative channel of the SM1 region for the finger flexion and extension in DP (n = 12), HP (n = 16), and TD (n = 32) groups. B) Relative peak strengths of beta suppression and rebound to the finger flexion in DP, HP, and TD.

6 DISCUSSION

This dissertation focused on investigating the modulation of the cortical beta rhythm with MEG and EEG from a clinical perspective since new suitable biomarkers are required for clinical studies to explore the human brain function non-invasively. Rolandic beta rhythm modulation has been proposed as a neurophysiological biomarker that reflects the SM1 cortex functional state (excitation and inhibition), which has been shown to be altered in various neurological and psychiatric diseases. The measurability of beta modulation fulfils several requirements for clinical applications, such as easy accessibility and inexpensiveness to measure and analyze. However, information on the essential features of a good biomarker, such as reliability and reproducibility, were lacking in the beta rhythm modulation. To improve this, the objectives of this dissertation were to assess (1) whether the strength of beta suppression and rebound is comparable between MEG and EEG recordings, (2) whether the state of alertness influences the strength of beta modulation and, (3) are beta suppression and rebound strengths reproducible within one year and, (4) to clarify alterations in the SM1 cortex excitation–inhibition balance in hemiplegic and diplegic CP adolescents.

The results showed that beta modulation is readily detected both with MEG and EEG. Alteration in alertness did not significantly change the strength of beta modulation in healthy adults, and reproducibility of the beta modulation was good within a one-year time span. These results encourage the use of beta modulation as a biomarker of the functional state of the SM1 cortex in clinical follow-up studies. The present results also provided novel information about the excitatory and inhibitory changes in the SM1 cortex in adolescents with diplegic CP.

6.1 Detecting sensorimotor cortex beta rhythm modulation using MEG and EEG

Beta modulation has been studied with both MEG and EEG in healthy subjects and various movement disorders such as stroke, PD, and CP (Degardin et al., 2009; Parkkonen et al., 2018; Pihko et al., 2014). As MEG measurements demand considerable investments in MEG recording systems, as well as MSR and expertise in analysis methods, this method is less often available and more frequently used in basic research, while EEG is relatively cheap and routinely used in a clinical environment. The aim of the Study I was to compare the modulation of the beta rhythm between simultaneously measured MEG and EEG, and to evaluate the possibility to detect this neurophysiological biomarker with more readily available EEG in clinical research.

MEG and EEG are both excellent methods for detecting cortical brain signals, providing a valid method to increase the knowledge between cellular-level animal models and human neuroimaging studies. However, a comparison between these methods was completely lacking in the context of the beta modulation strength. Study I confirmed that both MEG and EEG detect beta rhythm modulation, but our finding also showed that beta suppression and rebound strengths were stronger when measured with MEG. This result is not surprising, since SNR in MEG has been shown to be better than in EEG (Goldenholz et al., 2009; Hillebrand & Barnes, 2002). However, it is good to note that the SNR of the EEG also benefited from the low interference environment provided by the MSR. Thus, the effect of SNR on the beta suppression and rebound strengths in EEG could be even larger, for example in hospital recordings. Moreover, the SNR can even vary between EEG measurement environments. On the other hand, the new MEG Triux™ neo device offers more advanced sensor technology with better SNR, in which case the difference between the beta modulation strengths measured by MEG and EEG could have been even more pronounced. However, since the differences in the strengths of beta suppression and rebound were not remarkable between MEG and EEG in our study, they both proved to be valid methods for the present research purposes, but the use of MEG can be recommended to study the 20-Hz rhythm modulation whenever possible. Since EEG is easily available and enables larger clinical trials in hospitalized patients, it allows more extensive use of beta modulation as a biomarker in hospitals and rehabilitation centres. The advantage of beta modulation as a potential biomarker is that it can be readily and non-invasively measured both with MEG and EEG, which are easy and safe methods for different patient and subject groups.

6.2 Reproducibility of beta suppression and rebound

A prerequisite for a good biomarker is the stability and reproducibility of the results. The reproducibility of a biomarker can be purely due to the properties of the biomarker or due to external factors that can be influenced during the study. The individual variability of a biomarker cannot be influenced, thus, all possible external distractions should be minimized during the experiments. However, studies in which patients are acutely ill or suffer from movement disorders such as tremors are particularly vulnerable to these external factors in beta modulation studies.

6.2.1 Individual variability of beta modulation

The long-term reproducibility of beta modulation is a prerequisite for its use as a biomarker in longitudinal follow-up studies. In Study III, the strengths of beta suppression and rebound showed good reproducibility within the one-year follow-up period, supporting previous findings of a shorter follow-up study (a few weeks; Espenhahn et al., 2017). Since good reproducibility is an essential feature of a biomarker used in longitudinal follow-up studies, this study supports the use of beta modulation as a biomarker of SM1 functional state for up to one-year follow-up studies. However, the strength of beta suppression and rebound varies considerably between individuals, and sometimes a subject may have weak beta suppression but a strong rebound, or vice versa. The beta modulation can be weak or even undetectable from the noise level even in some healthy subjects, but this is most often the case for ipsilateral beta modulation. In MEG studies, individual variability of the beta modulation strengths can at least partly be due to variation in source depth and orientation, which can affect the strength of the magnetic fields measured outside the skull (Hillebrand & Barnes, 2002).

Study I found that the inclusion of lower frequencies from 13 to 15 Hz to the TSE analysis increased the strength of the rebound in part of the subjects, without affecting the suppression strengths. Previous studies have demonstrated that the beta rebound appears at a lower frequency band than the suppression (Pfurtscheller et al., 1997; Pihko et al., 2014). Including lower beta frequencies in the analysis can thus increase beta rebound strengths in part of the subjects. It is also advisable to check the suppression and rebound frequencies individually, whenever new types of stimulation are used or different subject groups are investigated. Beta power has also been shown to be stronger in the afternoon than in the morning (Toth et al., 2007; Wilson et al., 2014), which may also affect the detected beta modulation strengths. Therefore, it is advisable to measure beta modulation at the same time of day, especially in follow-up studies. Background

beta power level has been shown to increase with age, while children have lower beta levels than adults do (Gaetz et al., 2010; Rossiter et al., 2014; Xifra-Porxas et al., 2019). Older people have also been found to have stronger baseline beta power and stronger beta suppression amplitudes (Bardouille & Bailey, 2019; Walker et al., 2020). For this reason, the comparability of beta modulation studies performed in different age groups may be dubious. The good reproducibility of beta modulation enables its use as a biomarker, meaning these issues are important to take account when planning the studies.

6.2.2 Effect of stimulus modality to beta rhythm modulation

Beta rhythm modulation has been extensively studied in relation to voluntary movement. Different aspects of movement (e.g. range of movement, speed, duration, force, and muscle mass used for movement), have been shown to affect especially the amplitude and temporal occurrence of beta rebound (Cassim et al., 2000; Fry et al., 2016; Stančák et al., 1997; Toma et al., 2002; Zhang et al., 2020). Movements of different limbs, such as the finger, wrist, or ankle, can therefore generate different strengths of beta modulation, and the dynamics of the movement can influence both the strength and duration of the modulation. In addition, the initiation of movement is often controlled by a visual or auditory stimulus, which may affect the M1 cortex beta power (Piitulainen et al., 2015b). Since beta modulation is relatively sensitive to changes in movement, active movement may not be the best way to modulate beta rhythm in the sense of a biomarker. The use of voluntary movement is particularly challenging in patients suffering from movement disorders, as it may be difficult for them to maintain stable movement throughout the experiment. An uncontrolled movement, such as in PD, may also interfere with beta modulation (Vinding et al., 2019). Movement and task complexity have also been shown affect to the intensity of beta power, so it is important to keep the movement as simple as possible, at least in clinical beta modulation studies (Kilavik et al., 2013; Manganotti et al., 1998).

The easy-to-implement, well-repeatable, and subject-friendly tactile and proprioceptive stimuli used in our study produced clear modulation of the beta rhythm. Somatosensory stimulation, such as tactile and electrical stimulus, typically generates stable and repeatable stimulation. However, in studies I and III, novel proprioceptive stimulation was used in parallel with the tactile stimulus. The results showed that the proprioceptive stimulation produced similar beta suppression and rebound strengths and latencies compared to tactile stimulation. Study III also confirmed that beta modulation is highly repeatable over a long period with both stimulus modalities, thus supporting the use of tactile and proprioceptive stimuli when exploring somatosensory beta modulation in follow-up

studies. However, as stimulus kinematics may affect the beta suppression and rebound latencies and the strength of rebound (Fry et al., 2016), the effect of these properties should be tested when using a proprioceptive stimulus. In Study IV, the duration of the proprioceptive stimulus was slightly longer (~250 ms) than in studies I and III, which most likely contribute to the later appearance of beta suppression (~100 ms) and rebound (~300 ms). The slower movement, as well as the finger extension that began quickly after the finger flexion, may also have affected the strength of the rebound. Thus, the effect of proprioceptive stimulus kinematics for induced beta responses should be clarified and optimized in future studies.

6.2.3 Effect of alertness and attention to the beta modulation

A low alertness state is known to alter oscillatory brain activity when low-frequency activity typically becomes more common and parieto-occipital alpha frequency increases (Kelly, 1991). The effect of changes in alertness on beta rhythm is not well known. However, this information is essential, especially since beta modulation has been suggested as a biomarker of the SM1 cortex function in different groups of patients who may have challenges to maintain their alertness. Study II in healthy participants showed a trend of diminished beta modulation in relation to decreased alertness in healthy participants, but the reduction was not significant. However, a clear reduction of beta suppression and rebound was observed in some subjects whose alertness was remarkably reduced during recordings, being more pronounced for beta suppression than rebound. The same study also demonstrated that an increase in alertness related to the attention task did not significantly change the beta modulation strength, although previous studies have shown that enhanced attention to the somatosensory event increases beta rhythm synchronization (Bardouille et al., 2010; Dockstader et al., 2010). For these reasons, it is advisable to avoid both extra attention to the stimulus and reduced vigilance during beta modulation recordings. To maintain the subject's alertness, it is suggested to show, for example, a slowly changing landscape video. Subjects should be monitored during registration and efforts should be made to maintain their good alertness to avoid possible bias in group-level results due to decreased alertness. This is especially important when considering studying patients whose conditions, such as acute stroke, may impair their alertness.

6.3 Beta rhythm modulation as a neurophysiological biomarker of SM1 cortical function in neurological and psychiatric conditions

Beta rhythm modulation is altered in many neurological and psychiatric disorders, such as CP, stroke, Parkinson's Disease and schizophrenia (Gascoyne et al., 2021; Hunt et al., 2019). There is also indication that beta modulation may be altered in multiple sclerosis (Barratt et al., 2017) and autism (Gaetz et al., 2020).

Changes in cortical inhibition after acute stroke are suggested to enable the reorganization of the motor cortex and thus recovery after stroke (Butefisch, 2003; Ward, 2017). MEG studies have shown that especially the strength of beta rebound correlates with motor recovery after acute stroke (Laaksonen et al., 2012; Parkkonen et al., 2017; Tang et al., 2020). Beta rebound has also been shown to predict motor performance in chronic stroke (Espenhahn et al., 2020). These suggests that the excitatory and inhibitory regulation of the SM1 cortex can be essential for brain plasticity and recovery after a stroke. Furthermore, with such a biomarker it could be possible to evaluate the individual length of the so-called sensitive period during which the brain's capacity for reorganization is strongest (Krakauer et al., 2012; Ward, 2017). Hence, beta modulation could be a useful biomarker to objectively assess the effect of various interventions, such as medical therapies and rehabilitation methods on the recovery of stroke patients.

Beta rebound is decreased in PD compared to healthy individuals (Degardin et al., 2009; Vinding et al., 2019). Levodopa medication (Degardin et al., 2009) and deep brain stimulation (Devos & Defebvre, 2006) have been shown to normalises the strength of modulation in PD. The strength of beta rebound has also been shown to be reduced in schizophrenia (Uhlhaas & Singer, 2010). In addition, the severity of schizophrenia symptoms has been demonstrated to correlate with the strength of beta rebound (Gascoyne et al., 2021). These examples indicate that beta rebound may be a promising tool for clinical use in the future.

6.4 Evidence about alteration of SM1 cortical excitation and inhibition in CP

Cerebral palsy (CP) is a lifelong disability that can make it difficult to cope in everyday life (Rosenbaum et al., 2007). Therefore, investment in CP rehabilitation as early as possible after the diagnosis is particularly important. However, more knowledge is needed about the functional mechanisms underlying early developmental brain injury in CP. Beta rhythm modulation has been proposed as a

biomarker that reflects the excitatory and inhibitory function of the SM1 cortex (Cheyne, 2013). In Study IV we investigated possible impairments of the cortical SM1 excitatory and inhibitory function in different types of CP (spastic diplegic and hemiplegic) by measuring the strength of beta modulation. The study showed that the SM1 cortex excitation–inhibition balance is altered particularly in adolescents with diplegic CP compared to the typically developed adolescents, but no similar changes were observed in adolescents with hemiplegic CP. More pronounced disturbances in the SM1 cortex excitation–inhibition balance in diplegics can be due to larger white matter lesions in somatosensory afference pathways, which are more common in preterm diplegics (Back, 2017; Reddihough & Collins, 2003). CP population is a very heterogeneous group with varying degrees of motor and postural balance problems, as well as impairments of somatosensory and proprioceptive function (Clayton et al., 2003; Poitras et al., 2021; Wingert et al., 2009). These impairments are the result of early developmental brain injury with varying timing and mechanisms, and thus a great variability in the location and extent of the lesions (Jaspers et al., 2016; Krägeloh-Mann, 2004; Krägeloh-Mann & Horber, 2007). These may at least partially explain the differences in beta modulation between CP subgroups revealed in our study. Due to the high individual variability, even dividing into hemiplegics and diplegics can be a rather rough way to classify CPs for neuroimaging studies.

The SM1 cortex oscillatory beta activity was found to be altered both in the contra- and ipsilateral hemispheres to the stimulated hand in adolescents with DP compared to heathy controls. Increased excitation of the contralateral hemisphere and decreased inhibition of the ipsilateral hemisphere can reflect widespread brain dysfunction that is more pronounced in DP than HP. The increased contralateral excitation may reflect the extent of white matter damage in the thalamocortical sensory pathways (Back, 2017; Reddihough & Collins, 2003¸ Jaatela et al., unpublished observation), which may also lead to inhibitory changes in the ipsilateral hemisphere. However, the cause-and-effect relationship can also be reversed, in which case increased excitation would be the result of decreased interhemispheric inhibition. The latter option is supported by study in which transcallosal inhibitory connections have been proposed to be impaired in CP (Mackey et al., 2014). Since the excitation–inhibition balance seems to be disturbed in both hemispheres simultaneously, it can be suggested that the disturbances are the result of more general interhemispheric dysfunction rather than alterations separately in the intra-hemispheric excitation and inhibition.

The proprioceptive stimulus used in Study IV had a different timing and duration of finger flexion and extension movements, which resulted in a different suppression–rebound pattern than in earlier studies with healthy adults. The most prominent difference in healthy adolescents was a stronger ipsilateral beta

rebound for finger flexion, which can suggest reflecting normal inhibitory regulation of the contralateral hand movement. Strong ipsilateral motor cortex activation has also been shown to correlate with accuracy and precision of hand movement in fMRI (Buetefisch et al., 2014). The decreased ipsilateral beta rebound seen in our study in individuals with DP may thus reflect poorer balance control and fine movements skills.

Due to the individual variability of CP, it is quite demanding to make a coherent therapy and rehabilitation plan that would serve everyone equally well (Nardone et al., 2021). Both somatosensation and proprioception are crucial for motor control and balance, and thus effective CP rehabilitation can require parallel activation of both the somatosensory and motor system. Moreover, the somatosensory system could be an excellent target for early rehabilitation, especially because it can be stimulated already in very young children without their own activity. However, more detailed information about beta modulation alterations in different types of CP is still needed. Detecting the strength of beta modulation may help to plan more effective and individualized therapies and rehabilitation in the future, and thus facilitate lifelong mobility difficulties.

6.5 Future perspectives and limitations for beta modulation studies

Beta rhythm modulation enables an inexpensive and safe method to detect the excitation and inhibition of the human SM1 cortex in healthy subjects as well as in a variety of diseases, thus it could be utilized more readily as a biomarker of SM1 cortical function in the future. However, it is important to standardize the stimulus for clinical studies, which would guarantee better comparability of the beta modulation studies. Individual variation in the strength of beta modulation also brings challenges, as it is not detectable in some individuals. An up-and-coming MEG technology, with an optically pumped magnetometer (OPM), could enable even better detectability of the SM1 cortex beta modulation since the sensors can be placed closer to the cortex to detect the magnetic fields more strongly (Boto et al., 2018; Iivanainen et al., 2017).

In this dissertation, the sensor-level TSE method was used to analyze the modulation of beta rhythm. This method was chosen because it provides sufficient information about the strength of the beta modulation. It also provides suitable analysis method for clinical environments, since it is easy to implement, quick to use, and possible to partially automate. Another commonly used analysis method is a beamformer, in which spatial filtering is used to compute the

amount of beta activity at the source space of the brain (Hillebrand & Barnes, 2005; Westner et al., 2022). However, the exact comparability of these methods for detecting the strength of beta modulation is not yet complete and should be clarified in the future.

Revival of beta rebound strength has been shown to correlate with recovery from stroke (Laaksonen et al., 2012; Parkkonen et al., 2017; Tang et al., 2020), thus it may be utilized as a biomarker to indicate the effectiveness of different stroke rehabilitation methods in hospital environments. Of particular interest would be to study the effect of selective serotonin reuptake inhibitors (SSRIs) drugs, such as fluoxetine and paroxetine, on the beta rebound during stroke recovery, since the SSRIs have been demonstrated to improve stroke recovery, most likely by reopening the plastic window of stroke recovery through changes in cortical excitability (Pinto et al., 2017; Yeo et al., 2017). Earlier studies have indicated that stroke patients respond differently to transcranial magnetic stimulation therapy: some patients show remarkable improvement, whereas in some studies practically no effect is observed (Chen et al., 2022; Xue et al., 2022). It is likely that despite similar symptoms, the patients' various brain lesions affect the cortical excitation–inhibition circuits differently. Therefore, the same treatment may not work for all stroke patients either.

7 CONCLUSIONS

Our results confirmed that beta rhythm modulation provides a potential neurophysiological biomarker to evaluate the SM1 cortical function in both healthy subjects and patients with various neurological conditions. In this dissertation, beta modulation was found to be detectable both when using MEG or EEG, which will likely facilitate the clinical use of beta modulation in future clinical studies or applications. In addition, the mechanically induced tactile and proprioceptive stimuli used in the previously mentioned studies are both easily implementable in research labs and hospitals. The strengths of beta suppression and rebound proved to be highly reproducible during a one-year follow-up period in healthy adults. The importance of good individual reproducibility of beta modulation is particularly emphasized in longitudinal studies or when monitoring the effectiveness of treatment and rehabilitation in patients. Since patient recordings can be more sensitive to various distractions, the effect of altered vigilance on beta modulation was also investigated. Reduced alertness did not affect the strength of beta modulation at the group level, but the strength of beta suppression did correlate with the level of alertness. Therefore, it is recommended to maintain similar alertness during recordings, since reduction in the alertness may lead to decreased beta modulation strengths during the MEG and EEG recordings. These results obtained in healthy subjects confirmed that beta suppression and rebound strength can enable reliable detection of the SM1 cortex excitation–inhibition balance, which may be used as a biomarker to monitor functional changes in the SM1 cortex.

In addition, the dissertation demonstrated that the SM1 cortex excitation and inhibition are altered in diplegic CP, yet similar results were not observed in hemiplegic CP. Alterations were seen in both the contra- and ipsilateral hemispheres in relation to proprioceptive stimulus, with increased excitation on the contralateral and decreased inhibition on the ipsilateral SM1 cortex. The

unbalanced excitation and inhibition in the SM1 cortex may reflect more severe white matter damage of thalamocortical pathways and/or alteration in the interhemispheric inhibitory regulation in diplegic CP. This finding further emphasizes the importance of intact proprioceptive afference for maintaining SM1 cortex excitation–inhibition balance. These results suggests that individuals with different types of CP may thus benefit differently from rehabilitation methods, and that proprioceptive and somatosensory rehabilitation could be especially effective in diplegic CP.

YHTEENVETO (SUMMARY IN FINNISH)

Väitöskirjassa tutkittiin tunto- ja liikeaivokuoren (SM1) alueen beta-rytmin moduloitumista tunto- ja liikeaistiärsykkeille, ja sen soveltuvuutta kliiniseksi biomarkkeriksi kuvastamaan aivokuoren toiminnallista tilaa, tarkemmin sanottuna aivokuoren eksitaation ja inhibition tasapainoa. Ensimmäisessä osatutkimuksessa beta-modulaation voimakkuuksia verrattiin kahden eri menetelmän MEG:n ja EEG:n välillä. Tutkimuksen tarkoituksena oli selvittää näiden menetelmien soveltuvuutta beta-rytmin modulaation tutkimiseen ja arvioida olisiko helpommin kliinisissä ympäristöissä toteutettava EEG yhtä herkkä menetelmä beta-rytmin modulaation mittaamiseen kuin MEG. Toisessa osatutkimuksessa tutkittiin vireystilan vaihtelun vaikutuksia beta-rytmin modulaation voimakkuuteen. Tätä oli tärkeä selvittää, koska hyvän vireystilan ylläpitäminen mittauksen aikana voi olla haastavaa etenkin osalla potilaista, kuten aivohalvauksen akuuttivaiheessa. Kolmannessa osatutkimuksessa selvitettiin beta-rytmin modulaation pitkän aikavälin toistettavuutta. Hyvä toistettavuus on olennaista beta-rytmin modulaation luotettavalle käytölle biomarkkerina seurantatutkimuksissa, kuten esimerkiksi aivoinfarktista toipumisen seurannassa ja kuntoutuksen vaikuttavuuden arvioinnissa. Neljännessä osatyössä beta-rytmin modulaatiota käytettiin tunto- ja liikeaivokuoren eksitaation ja inhibition muutosten tutkimiseen nuorilla, joilla on CP-vamma.

Tulokset osoittivat, että beta-rytmin modulaatio on voimakkaampaa MEG:llä kuin EEG:llä mitattuna, mutta erot suhteellisissa voimakkuuksissa eivät kuitenkaan olleet suuria. Siten paremmin saatavilla olevan EEG:n voidaan todeta olevan käyttökelpoinen menetelmä beta-rytmin modulaation tutkimiseen etenkin kliinisissä ympäristöissä. Vireystilan laskulla ei havaittu olevan merkitsevää vaikutusta beta-rytmin modulaation voimakkuuteen ryhmätasolla. Lisäksi beta-vaimenemisen ja -voimistumisen voimakkuudet osoittautuivat hyvin toistettavaksi vuoden seurantajakson aikana. Nämä löydökset tukevat beta-rytmin modulaation luotettavuutta ja käyttökelpoisuutta biomarkkerina. Beta-rytmin modulaatiota mittaamalla saatiin myös mielenkiintoisia tuloksia nuorilla, joilla on hemi- tai dipleginen CP-vamma. SM1-aivokuoren eksitaatio-inhibitio-tasapainon havaittiin muuttuneen molemmissa aivopuoliskoissa diplegisessä CP-vammassa, kun taas hemiplegisessä CP-vammassa tulokset vastasivat enemmän terveiden kontrollien tuloksia. Nämä tulokset saattavat olla seurausta diplegiselle CP-vammalle tyypillisestä varhaisemmasta aivovaurion syntyhetkestä ja sen seurauksena syntyneistä laajemmista aivojen valkean aineen vaurioista.

Väitöskirjassa esitetyt tulokset osoittavat, että beta-rytmin modulaation mittaaminen MEG:llä ja EEG:llä soveltuu hyvin neurofysiologiseksi

biomarkkeriksi, jonka avulla voidaan havaita SM1-aivokuoren eksitaation ja inhibition muutoksia. Hyvän toistettavuuden sekä sen suhteellisen helpon mitattavuuden ja analysoitavuuden ansiosta beta-rytmin modulaatiota voidaan tulevaisuudessa mahdollisesti käyttää SM1-aivokuoren toiminnan muutosten tutkimiseen liikehäiriöitä aiheuttavissa neurologisissa sairauksissa, niistä toipumisessa sekä kuntoutusmenetelmien vaikuttavuuden arvioinnissa.

REFERENCES

Aboitiz, F. (1992). Brain connections: Interhemispheric fiber systems and anatomical brain asymmetries in humans. *Biological Research*, *25*(2), 51–61.

Alegre, M., Labarga, A., Gurtubay, I. G., Iriarte, J., Malanda, A., & Artieda, J. (2002). Beta electroencephalograph changes during passive movements: Sensory afferences contribute to beta event-related desynchronization in humans. *Neuroscience Letters*, *331*(1), 29–32. https://doi.org/10.1016/S0304-3940(02)00825-X

Andersen, R. A., & Buneo, C. A. (2002). Intentional Maps in Posterior Parietal Cortex. *Annual Review of Neuroscience*, *25*(1), 189–220. https://doi.org/10.1146/annurev.neuro.25.112701.142922

Antonakakis, M., Schrader, S., Wollbrink, A., Oostenveld, R., Rampp, S., Haueisen, J., & Wolters, C. H. (2019). The effect of stimulation type, head modeling, and combined EEG and MEG on the source reconstruction of the somatosensory P20/N20 component. *Human Brain Mapping*, *40*(17), 5011–5028. https://doi.org/10.1002/hbm.24754

Aronson, J. K., & Ferner, R. E. (2017). Biomarkers—A General Review. *Current Protocols in Pharmacology*, *76*(1). https://doi.org/10.1002/cpph.19

Back, S. A. (2017). White matter injury in the preterm infant: Pathology and mechanisms. *Acta Neuropathologica*, *134*(3), 331–349. https://doi.org/10.1007/s00401-017-1718-6

Baillet, S., Mosher, J. C., & Leahy, R. M. (2001). Electromagnetic brain mapping. *IEEE Signal Processing Magazine*, *18*(6), 14–30. https://doi.org/10.1109/79.962275

Baker, S. N. (2007). Oscillatory interactions between sensorimotor cortex and the periphery. *Current Opinion in Neurobiology*, *17*(6), 649–655. https://doi.org/10.1016/j.conb.2008.01.007

Bardouille, T., & Bailey, L. (2019). Evidence for age-related changes in sensorimotor neuromagnetic responses during cued button pressing in a large open-access dataset. *NeuroImage*, *193*, 25–34. https://doi.org/10.1016/j.neuroimage.2019.02.065

Bardouille, T., Picton, T. W., & Ross, B. (2010). Attention modulates beta oscillations during prolonged tactile stimulation. *The European Journal of Neuroscience*, *31*(4), 761–769. https://doi.org/10.1111/j.1460-9568.2010.07094.x

Barratt, E. L., Tewarie, P. K., Clarke, M. A., Hall, E. L., Gowland, P. A., Morris, P. G., Francis, S. T., Evangelou, N., & Brookes, M. J. (2017). Abnormal task driven neural oscillations in multiple sclerosis: A visuomotor MEG study: Neural Oscillations in Multiple Sclerosis. *Human Brain Mapping*, *38*(5), 2441–2453. https://doi.org/10.1002/hbm.23531

Berry, R.B., Brooks, R., Gamaldo, C.E., Harding, S.M., Lloyd, R.M., Mbbc. M., & and Vaughn, B. V. (2012). *The AASM Manual for the Scoring of Sleep and Associated Events: RULES, TERMINOLOGY AND TECHNICAL*

SPECIFICATIONS VERSION 2.2: American Academy of Sleep Medicine; 2012. http://www.aasmnet.org/resources/pdf/scoring-manual-preface.pdf

Boonstra, T. W., Daffertshofer, A., Breakspear, M., & Beek, P. J. (2007). Multivariate time–frequency analysis of electromagnetic brain activity during bimanual motor learning. *NeuroImage*, *36*(2), 370–377. https://doi.org/10.1016/j.neuroimage.2007.03.012

Boto, E., Holmes, N., Leggett, J., Roberts, G., Shah, V., Meyer, S. S., Muñoz, L. D., Mullinger, K. J., Tierney, T. M., Bestmann, S., Barnes, G. R., Bowtell, R., & Brookes, M. J. (2018). Moving magnetoencephalography towards real-world applications with a wearable system. *Nature*, *555*(7698), 657–661. https://doi.org/10.1038/nature26147

Brun, C., Traverse, É., Granger, É., & Mercier, C. (2021). Somatosensory deficits and neural correlates in cerebral palsy: A scoping review. *Developmental Medicine & Child Neurology*, *63*(12), 1382–1393. https://doi.org/10.1111/dmcn.14963

Buetefisch, C. M., Revill, K. P., Shuster, L., Hines, B., & Parsons, M. (2014). Motor demand-dependent activation of ipsilateral motor cortex. *Journal of Neurophysiology*, *112*(4), 999–1009. https://doi.org/10.1152/jn.00110.2014

Butefisch, C. M. (2003). Remote changes in cortical excitability after stroke. *Brain*, *126*(2), 470–481. https://doi.org/10.1093/brain/awg044

Carcea, I., & Froemke, R. C. (2013). Cortical Plasticity, Excitatory–Inhibitory Balance, and Sensory Perception. In *Progress in Brain Research* (Vol. 207, pp. 65–90). Elsevier. https://doi.org/10.1016/B978-0-444-63327-9.00003-5

Carson, R. G. (2005). Neural pathways mediating bilateral interactions between the upper limbs. *Brain Research Reviews*, *49*(3), 641–662. https://doi.org/10.1016/j.brainresrev.2005.03.005

Cassim, F., Monaca, C., Szurhaj, W., Bourriez, J.-L., Defebvre, L., Derambure, P., & Guieu, J.-D. (2001). Does post-movement beta synchronization reflect an idling motor cortex? *Neuroreport*, *12*(17), 3859–3863. https://doi.org/10.1097/00001756-200112040-00051

Cassim, F., Szurhaj, W., Sediri, H., Devos, D., Bourriez, J.-L., Poirot, I., Derambure, P., Defebvre, L., & Guieu, J.-D. (2000). Brief and sustained movements: Differences in event-related (de)synchronization (ERD/ERS) patterns. *Clinical Neurophysiology*, *111*(11), 2032–2039. https://doi.org/10.1016/S1388-2457(00)00455-7

Chen, G., Lin, T., Wu, M., Cai, G., Ding, Q., Xu, J., Li, W., Wu, C., Chen, H., & Lan, Y. (2022). Effects of repetitive transcranial magnetic stimulation on upper-limb and finger function in stroke patients: A systematic review and meta-analysis of randomized controlled trials. *Frontiers in Neurology*, *13*, 940467. https://doi.org/10.3389/fneur.2022.940467

Chen, R., Corwell, B., & Hallett, M. (1999). Modulation of motor cortex excitability by median nerve and digit stimulation. *Experimental Brain Research*, *129*(1), 77–86. https://doi.org/91290077.221

Cheyne, D., Gaetz, W., Garnero, L., Lachaux, J.-P., Ducorps, A., Schwartz, D., & Varela, F. J. (2003). Neuromagnetic imaging of cortical oscillations

accompanying tactile stimulation. *Cognitive Brain Research*, *17*(3), 599–611. https://doi.org/10.1016/S0926-6410(03)00173-3
Cheyne, D. O. (2013). MEG studies of sensorimotor rhythms: A review. *Experimental Neurology*, *245*, 27–39. https://doi.org/10.1016/j.expneurol.2012.08.030
Clayton, K., Fleming, J. M., & Copley, J. (2003). Behavioral responses to tactile stimuli in children with cerebral palsy. *Physical & Occupational Therapy in Pediatrics*, *23*(1), 43–62.
Danker-Hopfe, H., Anderer, P., Zeitlhofer, J., Boeck, M., Dorn, H., Gruber, G., Heller, E., Loretz, E., Moser, D., Parapatics, S., Saletu, B., Schmidt, A., & Dorffner, G. (2009). Interrater reliability for sleep scoring according to the Rechtschaffen & Kales and the new AASM standard. *Journal of Sleep Research*, *18*(1), 74–84. https://doi.org/10.1111/j.1365-2869.2008.00700.x
Degardin, A., Houdayer, E., Bourriez, J.-L., Destée, A., Defebvre, L., Derambure, P., & Devos, D. (2009). Deficient "sensory" beta synchronization in Parkinson's disease. *Clinical Neurophysiology*, *120*(3), 636–642. https://doi.org/10.1016/j.clinph.2009.01.001
Devos, D., & Defebvre, L. (2006). Effect of deep brain stimulation and l-Dopa on electrocortical rhythms related to movement in Parkinson's disease. In *Progress in Brain Research* (Vol. 159, pp. 331–349). Elsevier. https://doi.org/10.1016/S0079-6123(06)59022-3
Diesburg, D. A., Greenlee, J. D., & Wessel, J. R. (2021). Cortico-subcortical β burst dynamics underlying movement cancellation in humans. *ELife*, *10*, e70270. https://doi.org/10.7554/eLife.70270
Disbrow, E., Roberts, T., & Krubitzer, L. (2000). Somatotopic organization of cortical fields in the lateral sulcus ofHomo sapiens: Evidence for SII and PV. *The Journal of Comparative Neurology*, *418*(1), 1–21. https://doi.org/10.1002/(SICI)1096-9861(20000228)418:1<1::AID-CNE1>3.0.CO;2-P
Dockstader, C., Cheyne, D., & Tannock, R. (2010). Cortical dynamics of selective attention to somatosensory events. *NeuroImage*, *49*(2), 1777–1785. https://doi.org/10.1016/j.neuroimage.2009.09.035
Ebersole, J. S., & Ebersole, S. M. (2010). Combining MEG and EEG Source Modeling in Epilepsy Evaluations. *Journal of Clinical Neurophysiology*, *27*(6), 360–371. https://doi.org/10.1097/WNP.0b013e318201ffc4
Eliasson, A.-C., Krumlinde-Sundholm, L., Rösblad, B., Beckung, E., Arner, M., Öhrvall, A.-M., & Rosenbaum, P. (2006). The Manual Ability Classification System (MACS) for children with cerebral palsy: Scale development and evidence of validity and reliability. *Developmental Medicine & Child Neurology*, *48*(07), 549. https://doi.org/10.1017/S0012162206001162
Engel, A. K., & Fries, P. (2010). Beta-band oscillations—Signalling the status quo? *Current Opinion in Neurobiology*, *20*(2), 156–165. https://doi.org/10.1016/j.conb.2010.02.015
Espenhahn, S., de Berker, A. O., van Wijk, B. C. M., Rossiter, H. E., & Ward, N. S. (2017). Movement-related beta oscillations show high intra-individual

reliability. *NeuroImage*, *147*, 175–185. https://doi.org/10.1016/j.neuroimage.2016.12.025
Espenhahn, S., Rossiter, H. E., van Wijk, B. C. M., Redman, N., Rondina, J. M., Diedrichsen, J., & Ward, N. S. (2020). Sensorimotor cortex beta oscillations reflect motor skill learning ability after stroke. *Brain Communications*, *2*(2), fcaa161. https://doi.org/10.1093/braincomms/fcaa161
Eyre, J. (2007). Corticospinal tract development and its plasticity after perinatal injury. *Neuroscience & Biobehavioral Reviews*, *31*(8), 1136–1149. https://doi.org/10.1016/j.neubiorev.2007.05.011
Feige, B., Kristeva-Feige, R., Rossi, S., Pizzella, V., & Rossini, P. M. (1996). Neuromagnetic study of movement-related changes in rhythmic brain activity. *Brain Research*, *734*(1–2), 252–260.
Feingold, J., Gibson, D. J., DePasquale, B., & Graybiel, A. M. (2015). Bursts of beta oscillation differentiate postperformance activity in the striatum and motor cortex of monkeys performing movement tasks. *Proceedings of the National Academy of Sciences*, *112*(44), 13687–13692. https://doi.org/10.1073/pnas.1517629112
Florin, E., & Baillet, S. (2015). The brain's resting-state activity is shaped by synchronized cross-frequency coupling of neural oscillations. *NeuroImage*, *111*, 26–35. https://doi.org/10.1016/j.neuroimage.2015.01.054
Forss, N., & Jousmäki, V. (1998). Sensorimotor integration in human primary and secondary somatosensory cortices. *Brain Research*, *781*(1–2), 259–267. https://doi.org/S0006-8993(97)01240-7
Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, *9*(10), 474–480. https://doi.org/10.1016/j.tics.2005.08.011
Fry, A., Mullinger, K. J., O'Neill, G. C., Barratt, E. L., Morris, P. G., Bauer, M., Folland, J. P., & Brookes, M. J. (2016). Modulation of post-movement beta rebound by contraction force and rate of force development: Modulation of PMBR by force & RFD. *Human Brain Mapping*, *37*(7), 2493–2511. https://doi.org/10.1002/hbm.23189
Gaetz, W., & Cheyne, D. (2006). Localization of sensorimotor cortical rhythms induced by tactile stimulation using spatially filtered MEG. *NeuroImage*, *30*(3), 899–908. https://doi.org/10.1016/j.neuroimage.2005.10.009
Gaetz, W., Edgar, J. C., Wang, D. J., & Roberts, T. P. (2011). Relating MEG measured motor cortical oscillations to resting gamma-aminobutyric acid (GABA) concentration. *NeuroImage*, *55*(2), 616–621. https://doi.org/10.1016/j.neuroimage.2010.12.077
Gaetz, W., Macdonald, M., Cheyne, D., & Snead, O. C. (2010). Neuromagnetic imaging of movement-related cortical oscillations in children and adults: Age predicts post-movement beta rebound. *NeuroImage*, *51*(2), 792–807. https://doi.org/10.1016/j.neuroimage.2010.01.077
Gaetz, W., Rhodes, E., Bloy, L., Blaskey, L., Jackel, C. R., Brodkin, E. S., Waldman, A., Embick, D., Hall, S., & Roberts, T. P. L. (2020). Evaluating motor cortical oscillations and age-related change in autism spectrum

disorder. *NeuroImage*, *207*, 116349. https://doi.org/10.1016/j.neuroimage.2019.116349
Gascoyne, L. E., Brookes, M. J., Rathnaiah, M., Katshu, M. Z. U. H., Koelewijn, L., Williams, G., Kumar, J., Walters, J. T. R., Seedat, Z. A., Palaniyappan, L., Deakin, J. F. W., Singh, K. D., Liddle, P. F., & Morris, P. G. (2021). Motor-related oscillatory activity in schizophrenia according to phase of illness and clinical symptom severity. *NeuroImage: Clinical*, *29*, 102524. https://doi.org/10.1016/j.nicl.2020.102524
Gerloff, C. (1997). Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain*, *120*(9), 1587–1602. https://doi.org/10.1093/brain/120.9.1587
Ghez, C. (1991). Voluntary Movement. In Kandel, E.R., Schwartz, J.H. & Jessell, T.M., (Eds.), *Principles of Neural Science*, (4th ed., pp. 610–613). Appleton & Lange.
Ghilardi, M. F., Tatti, E., & Quartarone, A. (2021). Beta power and movement-related beta modulation as hallmarks of energy for plasticity induction: Implications for Parkinson's disease. *Parkinsonism & Related Disorders*, *88*, 136–139. https://doi.org/10.1016/j.parkreldis.2021.05.018
Goldenholz, D. M., Ahlfors, S. P., Hämäläinen, M. S., Sharon, D., Ishitobi, M., Vaina, L. M., & Stufflebeam, S. M. (2009). Mapping the signal-to-noise-ratios of cortical sources in magnetoencephalography and electroencephalography. *Human Brain Mapping*, *30*(4), 1077–1086. https://doi.org/10.1002/hbm.20571
Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., & Hamalainen, M. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience*, *7*, 267. https://doi.org/10.3389/fnins.2013.00267
Guye, M., Parker, G. J. M., Symms, M., Boulby, P., Wheeler-Kingshott, C. A. M., Salek-Haddadi, A., Barker, G. J., & Duncan, J. S. (2003). Combined functional MRI and tractography to demonstrate the connectivity of the human primary motor cortex in vivo. *NeuroImage*, *19*(4), 1349–1360. https://doi.org/10.1016/S1053-8119(03)00165-4
Hall, S. D., Barnes, G. R., Furlong, P. L., Seri, S., & Hillebrand, A. (2010). Neuronal network pharmacodynamics of GABAergic modulation in the human cortex determined using pharmaco-magnetoencephalography. *Human Brain Mapping*, *31*(4), 581–594. https://doi.org/10.1002/hbm.20889
Hall, S. D., Prokic, E. J., McAllister, C. J., Ronnqvist, K. C., Williams, A. C., Yamawaki, N., Witton, C., Woodhall, G. L., & Stanford, I. M. (2014). GABA-mediated changes in inter-hemispheric beta frequency activity in early-stage Parkinson's disease. *Neuroscience*, *281*, 68–76. https://doi.org/10.1016/j.neuroscience.2014.09.037
Hall, S. D., Stanford, I. M., Yamawaki, N., McAllister, C. J., Ronnqvist, K. C., Woodhall, G. L., & Furlong, P. L. (2011). The role of GABAergic modulation in motor function related neuronal network activity.

NeuroImage, *56*(3), 1506–1510. https://doi.org/10.1016/j.neuroimage.2011.02.025
Halsband, U., Ito, N., Tanji, J., & Freund, H.-J. (1993). The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain*, *116*(1), 243–266. https://doi.org/10.1093/brain/116.1.243
Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography—Theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics*, *65*(2), 34. https://doi.org/10.1103/revmodphys.65.413
Hari, R. (1997). Human cortical oscillations: A neuromagnetic view through the skull. *Trends in Neurosciences*, *20*(1), 44–49. https://doi.org/10.1016/S0166-2236(96)10065-5
Hari, R. (2006). Action–perception connection and the cortical mu rhythm. In *Progress in Brain Research* (Vol. 159, pp. 253–260). Elsevier. https://doi.org/10.1016/S0079-6123(06)59017-X
Hari, R., Forss, N., Avikainen, S., Kirveskari, E., Salenius, S., & Rizzolatti, G. (1998). Activation of human primary motor cortex during action observation: A neuromagnetic study. *Proceedings of the National Academy of Sciences*, *95*(25), 15061–15065. https://doi.org/10.1073/pnas.95.25.15061
Hari, R., & Puce, A. (2017). *MEG-EEG primer*, (pp. 6–11, 25–35, 47–65, 304, 305). Oxford University Press.
Hari, R., & Salmelin, R. (1997). Human cortical oscillations: A neuromagnetic view through the skull. *Trends in Neurosciences*, *20*(1), 44–49. https://doi.org/S0166-2236(96)10065-5
Hari, R., & Salmelin, R. (2012). Magnetoencephalography: From SQUIDs to neuroscience. Neuroimage 20th anniversary special edition. *NeuroImage*, *61*(2), 386–396. https://doi.org/10.1016/j.neuroimage.2011.11.074 [doi]
Heinrichs-Graham, E., & Wilson, T. W. (2016). Is an absolute level of cortical beta suppression required for proper movement? Magnetoencephalographic evidence from healthy aging. *NeuroImage*, *134*, 514–521. https://doi.org/S1053-8119(16)30072-6
Hétu, S., Grégoire, M., Saimpont, A., Coll, M.-P., Eugène, F., Michon, P.-E., & Jackson, P. L. (2013). The neural network of motor imagery: An ALE meta-analysis. *Neuroscience & Biobehavioral Reviews*, *37*(5), 930–949. https://doi.org/10.1016/j.neubiorev.2013.03.017
Hillebrand, A., & Barnes, G. R. (2002). A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. *NeuroImage*, *16*(3 Pt 1), 638–650. https://doi.org/S105381190291102X
Hillebrand, A., & Barnes, G. R. (2005). Beamformer Analysis of MEG Data. In *International Review of Neurobiology* (Vol. 68, pp. 149–171). Elsevier. https://doi.org/10.1016/S0074-7742(05)68006-3
Hinkley, L. B., Krubitzer, L. A., Nagarajan, S. S., & Disbrow, E. A. (2007). Sensorimotor Integration in S2, PV, and Parietal Rostroventral Areas of the

Human Sylvian Fissure. *Journal of Neurophysiology*, *97*(2), 1288–1297. https://doi.org/10.1152/jn.00733.2006
Hoffman, R. M., Wilson, T. W., & Kurz, M. J. (2019). Hand Motor Actions of Children With Cerebral Palsy Are Associated With Abnormal Sensorimotor Cortical Oscillations. *Neurorehabilitation and Neural Repair*, *33*(12), 1018–1028. https://doi.org/10.1177/1545968319883880
Holgado, A. J. N., Terry, J. R., & Bogacz, R. (2010). Conditions for the Generation of Beta Oscillations in the Subthalamic Nucleus-Globus Pallidus Network. *Journal of Neuroscience*, *30*(37), 12340–12352. https://doi.org/10.1523/JNEUROSCI.0817-10.2010
Horton, J. C., Fahle, M., Mulder, T., & Trauzettel-Klosinski, S. (2017). Adaptation, perceptual learning, and plasticity of brain functions. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *255*(3), 435–447. https://doi.org/10.1007/s00417-016-3580-y
Houdayer, E., Labyt, E., Cassim, F., Bourriez, J. L., & Derambure, P. (2006). Relationship between event-related beta synchronization and afferent inputs: Analysis of finger movement and peripheral nerve stimulations. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *117*(3), 628–636. https://doi.org/S1388-2457(05)00480-3
Houweling, S., van Dijk, B. W., Beek, P. J., & Daffertshofer, A. (2010). Cortico-spinal synchronization reflects changes in performance when learning a complex bimanual task. *NeuroImage*, *49*(4), 3269–3275. https://doi.org/10.1016/j.neuroimage.2009.11.017
Hsiao, S. (2008). Central mechanisms of tactile shape perception. *Current Opinion in Neurobiology*, *18*(4), 418–424. https://doi.org/10.1016/j.conb.2008.09.001
Hunt, B. A. E., Liddle, E. B., Gascoyne, L. E., Magazzini, L., Routley, B. C., Singh, K. D., Morris, P. G., Brookes, M. J., & Liddle, P. F. (2019). Attenuated Post-Movement Beta Rebound Associated With Schizotypal Features in Healthy People. *Schizophrenia Bulletin*, *45*(4), 883–891. https://doi.org/10.1093/schbul/sby117
Hussain, S. J., Cohen, L. G., & Bönstrup, M. (2019). Beta rhythm events predict corticospinal motor output. *Scientific Reports*, *9*(1), 18305. https://doi.org/10.1038/s41598-019-54706-w
Iivanainen, J., Stenroos, M., & Parkkonen, L. (2017). Measuring MEG closer to the brain: Performance of on-scalp sensor arrays. *NeuroImage*, *147*, 542–553. https://doi.org/10.1016/j.neuroimage.2016.12.048
Jaspers, E., Byblow, W. D., Feys, H., & Wenderoth, N. (2016). The Corticospinal Tract: A Biomarker to Categorize Upper Limb Functional Potential in Unilateral Cerebral Palsy. *Frontiers in Pediatrics*, *3*. https://doi.org/10.3389/fped.2015.00112
Jensen, O., Goel, P., Kopell, N., Pohja, M., Hari, R., & Ermentrout, B. (2005). On the human sensorimotor-cortex beta rhythm: Sources and modeling. *NeuroImage*, *26*(2), 347–355. https://doi.org/S1053-8119(05)00106-0

Jensen, O., Kaiser, J., & Lachaux, J. P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences*, *30*(7), 317–324. https://doi.org/S0166-2236(07)00105-1

Jones, S. R. (2016). When brain rhythms aren't 'rhythmic': Implication for their mechanisms and meaning. *Current Opinion in Neurobiology*, *40*, 72–80. https://doi.org/10.1016/j.conb.2016.06.010

Jurkiewicz, M. T., Gaetz, W. C., Bostan, A. C., & Cheyne, D. (2006). Post-movement beta rebound is generated in motor cortex: Evidence from neuromagnetic recordings. *NeuroImage*, *32*(3), 1281–1289. https://doi.org/S1053-8119(06)00661-6

Kandel, E. R., & Jessell, T. M. (1991). Touch. In Kandel, E.R., Schwartz, J.H. & Jessell, T.M., (eds.), *Principles of Neural Science*, (4th ed., pp. 367–372). Appleton & Lange.

Kelly, D. D. (1991). Sleep and Dreaming. In Kandel, E.R., Schwartz, J.H. & Jessell, T.M., (Eds.), *Principles of Neural Science*, (4th ed., pp. 794–795). Appleton & Lange.

Kelly, J. P., & Dodd, J. (1991). Anatomical Organization of the Nervous System. In Kandel, E.R., Schwartz, J.H. and Jessell, T.M., (Eds.), *Principles of Neural Science*, (4th ed., pp. 275–281). Appleton & Lange.

Kilavik, B. E., Zaepffel, M., Brovelli, A., MacKay, W. A., & Riehle, A. (2013). The ups and downs of beta oscillations in sensorimotor cortex. *Experimental Neurology*, *245*, 15–26. https://doi.org/10.1016/j.expneurol.2012.09.014

Kirveskari, E., Vartiainen, N. V., Gockel, M., & Forss, N. (2010). Motor cortex dysfunction in complex regional pain syndrome. *Clinical Neurophysiology*, *121*(7), 1085–1091. https://doi.org/10.1016/j.clinph.2010.01.032

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Koelewijn, L., Bompas, A., Tales, A., Brookes, M. J., Muthukumaraswamy, S. D., Bayer, A., & Singh, K. D. (2017). Alzheimer's disease disrupts alpha and beta-band resting-state oscillatory network connectivity. *Clinical Neurophysiology*, *128*(11), 2347–2357. https://doi.org/10.1016/j.clinph.2017.04.018

Kolasinski, J., Hinson, E. L., Zand, A. P. D., Rizov, A., Emir, U. E., & Stagg, C. J. (2019). The dynamics of cortical GABA in human motor learning. *The Journal of Physiology*, *597*(1), 271–282. https://doi.org/10.1113/JP276626

Krägeloh-Mann, I. (2004). Imaging of early brain injury and cortical plasticity. *Experimental Neurology*, *190*, 84–90. https://doi.org/10.1016/j.expneurol.2004.05.037

Krägeloh-Mann, I., & Horber, V. (2007). The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: A systematic review. *Developmental Medicine & Child Neurology*, *49*(2), 144–151. https://doi.org/10.1111/j.1469-8749.2007.00144.x

Krakauer, J. W., Carmichael, S. T., Corbett, D., & Wittenberg, G. F. (2012). Getting neurorehabilitation right: What can be learned from animal

models? *Neurorehabilitation and Neural Repair*, *26*(8), 923–931. https://doi.org/10.1177/1545968312440745
Krigger, K. W. (2006). Cerebral palsy: An overview. *American Family Physician*, *73*(1), 91–100.
Kurz, M. J., Becker, K. M., Heinrichs-Graham, E., & Wilson, T. W. (2015). Children with cerebral palsy have uncharacteristic somatosensory cortical oscillations after stimulation of the hand mechanoreceptors. *Neuroscience*, *305*, 67–75. https://doi.org/10.1016/j.neuroscience.2015.07.072
Kurz, M. J., & Wilson, T. W. (2011). Neuromagnetic activity in the somatosensory cortices of children with cerebral palsy. *Neuroscience Letters*, *490*(1), 1–5. https://doi.org/10.1016/j.neulet.2010.11.053
Laaksonen, K., Kirveskari, E., Mäkelä, J. P., Kaste, M., Mustanoja, S., Nummenmaa, L., Tatlisumak, T., & Forss, N. (2012). Effect of afferent input on motor cortex excitability during stroke recovery. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *123*(12), 2429–2436. https://doi.org/10.1016/j.clinph.2012.05.017
Liddle, E. B., Price, D., Palaniyappan, L., Brookes, M. J., Robson, S. E., Hall, E. L., Morris, P. G., & Liddle, P. F. (2016). Abnormal salience signaling in schizophrenia: The role of integrative beta oscillations: Salience Signaling in Schizophrenia. *Human Brain Mapping*, *37*(4), 1361–1374. https://doi.org/10.1002/hbm.23107
Mackey, A., Stinear, C., Stott, S., & Byblow, W. D. (2014). Upper limb function and cortical organization in youth with unilateral cerebral palsy. *Frontiers in Neurology*, *5*, 117. https://doi.org/10.3389/fneur.2014.00117
Mäkelä, J. P., Salmelin, R., Kotila, M., Salonen, O., Laaksonen, R., Hokkanen, L., & Hari, R. (1998). Modification of neuromagnetic cortical signals by thalamic infarctions. *Electroencephalography and Clinical Neurophysiology*, *106*(5), 433–443. https://doi.org/10.1016/S0013-4694(98)00005-4
Manganotti, P., Gerloff, C., Toro, C., Katsuta, H., Sadato, N., Zhuang, P., Leocani, L., & Hallett, M. (1998). Task-related coherence and task-related spectral power changes during sequential finger movements. *Electroencephalography and Clinical Neurophysiology*, *109*(1), 50–62.
Marcuse, L. V., Fields, M. C., & Yoo, J. (2016). The normal adult EEG. In *Rowan's Primer of EEG* (pp. 39–66). Elsevier. https://doi.org/10.1016/B978-0-323-35387-8.00002-0
Martin, J. H., & Jessell, T. M. (1991a). Anatomy of the Somatic Sensory System. In Kandel, E.R., Schwartz, J.H. & Jessell, T.M., (Eds.), *Principles of Neural Science*, (4th ed., pp. 359–362). Appleton & Lange.
Martin, J. H., & Jessell, T. M. (1991b). Modality Coding in the Somatic Sensory system. In Kandel, E.R., Schwartz, J.H. & Jessell, T.M., (Eds.), *Principles of Neural Science*, (4th ed., pp. 341–342). Appleton & Lange.
Mary, A., Bourguignon, M., Wens, V., Beeck, M. O. de, Leproult, R., Tiege, X. D., & Peigneux, P. (2015). Aging reduces experience-induced sensorimotor plasticity. A magnetoencephalographic study. *NeuroImage*, *104*, 59–68. https://doi.org/10.1016/j.neuroimage.2014.10.010

Mitz, A., & Wise, S. (1987). The somatotopic organization of the supplementary motor area: Intracortical microstimulation mapping. *The Journal of Neuroscience*, *7*(4), 1010–1021. https://doi.org/10.1523/JNEUROSCI.07-04-01010.1987

Moisello, C., Blanco, D., Lin, J., Panday, P., Kelly, S. P., Quartarone, A., Di Rocco, A., Cirelli, C., Tononi, G., & Ghilardi, M. F. (2015). Practice changes beta power at rest and its modulation during movement in healthy subjects but not in patients with P arkinson's disease. *Brain and Behavior*, *5*(10). https://doi.org/10.1002/brb3.374

Mujunen, T., Seipäjärvi, S., Nurminen, M., Parviainen, T., & Piitulainen, H. (2022). Reproducibility of evoked and induced MEG responses to proprioceptive stimulation of the ankle joint. *Neuroimage: Reports*, *2*(3), 100110. https://doi.org/10.1016/j.ynirp.2022.100110

Müller, G. R., Neuper, C., Rupp, R., Keinrath, C., Gerner, H. J., & Pfurtscheller, G. (2003). Event-related beta EEG changes during wrist movements induced by functional electrical stimulation of forearm muscles in man. *Neuroscience Letters*, *340*(2), 143–147. https://doi.org/10.1016/S0304-3940(03)00019-3

Muthukumaraswamy, S. D., Myers, J. F., Wilson, S. J., Nutt, D. J., Lingford-Hughes, A., Singh, K. D., & Hamandi, K. (2013). The effects of elevated endogenous GABA levels on movement-related network oscillations. *NeuroImage*, *66*, 36–41. https://doi.org/10.1016/j.neuroimage.2012.10.054

Nardone, R., Sebastianelli, L., Ferrazzoli, D., Brigo, F., Lochner, P., Saltuari, L., Trinka, E., & Versace, V. (2021). Brain functional reorganization in children with hemiplegic cerebral palsy: Assessment with TMS and therapeutic perspectives. *Neurophysiologie Clinique*, *51*(5), 391–408. https://doi.org/10.1016/j.neucli.2021.09.002

Nelson, A. B., Moisello, C., Lin, J., Panday, P., Ricci, S., Canessa, A., Di Rocco, A., Quartarone, A., Frazzitta, G., Isaias, I. U., Tononi, G., Cirelli, C., & Ghilardi, M. F. (2017). Beta Oscillatory Changes and Retention of Motor Skills during Practice in Healthy Subjects and in Patients with Parkinson's Disease. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00104

Neuper, C., & Pfurtscheller, G. (2001a). Evidence for distinct beta resonance frequencies in human EEG related to specific sensorimotor cortical areas. *Clinical Neurophysiology*, *112*(11), 2084–2097. https://doi.org/10.1016/S1388-2457(01)00661-7

Neuper, C., & Pfurtscheller, G. (2001b). Event-related dynamics of cortical rhythms: Frequency-specific features and functional correlates. *International Journal of Psychophysiology*, *43*(1), 41–58. https://doi.org/10.1016/S0167-8760(01)00178-7

Neuper, C., Scherer, R., Wriessnegger, S., & Pfurtscheller, G. (2009). Motor imagery and action observation: Modulation of sensorimotor brain rhythms during mental control of a brain-computer interface. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical*

Neurophysiology, *120*(2), 239–247. https://doi.org/10.1016/j.clinph.2008.11.015

Neuper, C., Wörtz, M., & Pfurtscheller, G. (2006). ERD/ERS patterns reflecting sensorimotor activation and deactivation. In *Progress in Brain Research* (Vol. 159, pp. 211–222). Elsevier. https://doi.org/10.1016/S0079-6123(06)59014-4

Nevalainen, P., Pihko, E., Mäenpää, H., Valanne, L., Nummenmaa, L., & Lauronen, L. (2012). Bilateral alterations in somatosensory cortical processing in hemiplegic cerebral palsy: Somatosensory Cortical Processing in Hemiplegic CP. *Developmental Medicine & Child Neurology*, *54*(4), 361–367. https://doi.org/10.1111/j.1469-8749.2011.04165.x

Niedermeyer, E. (1998). Sleep and EEG. In Niedermeyer, E. & Lopes da Silva, F. (Eds.), *Electroencephalography: Basic principles, Clinical applications, and Related issues.* (3rd ed., pp. 174–184). *Williams & Wilkins.*

Nurmi, T., Jaatela, J., Vallinoja, J., Mäenpää, H., & Piitulainen, H. (2021). Stronger proprioceptive BOLD-responses in the somatosensory cortices reflect worse sensorimotor function in adolescents with and without cerebral palsy. *NeuroImage: Clinical*, *32*, 102795. https://doi.org/10.1016/j.nicl.2021.102795

Ohara, S. (2000). Movement-related change of electrocorticographic activity in human supplementary motor area proper. *Brain*, *123*(6), 1203–1215. https://doi.org/10.1093/brain/123.6.1203

Oskoui, M., Coutinho, F., Dykeman, J., Jetté, N., & Pringsheim, T. (2013). An update on the prevalence of cerebral palsy: A systematic review and meta-analysis. *Developmental Medicine & Child Neurology*, *55*(6), 509–519. https://doi.org/10.1111/dmcn.12080

Palisano, R., Rosenbaum, P., Walter, S., Russell, D., Wood, E., & Galuppi, B. (1997). Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine and Child Neurology*, *39*(4), 214–223. https://doi.org/10.1111/j.1469-8749.1997.tb07414.x

Palisano, R., Rosenbaum, P., Walter, S., Russell, D., Wood, E., & Galuppi, B. (2008). Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine & Child Neurology*, *39*(4), 214–223. https://doi.org/10.1111/j.1469-8749.1997.tb07414.x

Palva, S., & Palva, J. M. (2007). New vistas for alpha-frequency band oscillations. *Trends in Neurosciences*, *30*(4), 150–158. https://doi.org/S0166-2236(07)00026-4

Parkes, L. M., Bastiaansen, M. C., & Norris, D. G. (2006). Combining EEG and fMRI to investigate the post-movement beta rebound. *NeuroImage*, *29*(3), 685–696. https://doi.org/S1053-8119(05)00607-5

Parkkonen, E., Laaksonen, K., Parkkonen, L., & Forss, N. (2018). Recovery of the 20 Hz Rebound to Tactile and Proprioceptive Stimulation after Stroke. *Neural Plasticity*, *2018*, 7395798. https://doi.org/10.1155/2018/7395798

Parkkonen, E., Laaksonen, K., Piitulainen, H., Parkkonen, L., & Forss, N. (2015). Modulation of the reverse similar 20-Hz motor-cortex rhythm to passive movement and tactile stimulation. *Brain and Behavior*, *5*(5), e00328. https://doi.org/10.1002/brb3.328

Parkkonen, E., Laaksonen, K., Piitulainen, H., Pekkola, J., Parkkonen, L., Tatlisumak, T., & Forss, N. (2017). Strength of 20-Hz Rebound and Motor Recovery After Stroke. *Neurorehabilitation and Neural Repair*, *31*(5), 475–486. https://doi.org/10.1177/1545968316688795

Pfurtscheller, G., Jr, A. S., & Edlinger, G. (1997). On the existence of different types of central beta rhythms below 30 Hz. *Electroencephalography and Clinical Neurophysiology*, *102*(4), 316–325. https://doi.org/S0013469496966122

Pfurtscheller, G., & Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *110*(11), 1842–1857. https://doi.org/S1388245799001418

Pfurtscheller, G., Neuper, C., Brunner, C., & Silva, F. L. da. (2005). Beta rebound after different types of motor imagery in man. *Neuroscience Letters*, *378*(3), 156–159. https://doi.org/S0304-3940(04)01549-6

Pfurtscheller, G., Pichler-Zalaudek, K., & Neuper, C. (1999). ERD and ERS in voluntary movement of different limbs. In *Handbook of Electroencephalogr and Clinical Neurophysiology. Event-Related Desynchronization. G. Pfurtscheller, F.H. Lopes da Silva (Eds.)* (Revised Edition, 6, pp. 254–268). Elsvier, Amsterdam.

Pfurtscheller, G., Zalaudek, K., & Neuper, C. (1998). Event-related beta synchronization after wrist, finger and thumb movement. *Electroencephalography and Clinical Neurophysiology*, *109*(2), 154–160.

Picard, N. (2003). Activation of the Supplementary Motor Area (SMA) during Performance of Visually Guided Movements. *Cerebral Cortex*, *13*(9), 977–986. https://doi.org/10.1093/cercor/13.9.977

Pihko, E., Nevalainen, P., Vaalto, S., Laaksonen, K., Mäenpää, H., Valanne, L., & Lauronen, L. (2014). Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: A magnetoencephalographic study. *Human Brain Mapping*, *35*(8), 4105–4117. https://doi.org/10.1002/hbm.22462

Piitulainen, H., Bourguignon, M., Hari, R., & Jousmäki, V. (2015a). MEG-compatible pneumatic stimulator to elicit passive finger and toe movements. *NeuroImage*, *112*, 310–317. https://doi.org/S1053-8119(15)00181-0

Piitulainen, H., Bourguignon, M., Smeds, E., Tiege, X. D., Jousmäki, V., & Hari, R. (2015b). Phasic stabilization of motor output after auditory and visual distractors. *Human Brain Mapping*, *36*(12), 5168–5182. https://doi.org/10.1002/hbm.23001

Piitulainen, H., Kulmala, J. P., Mäenpää, H., & Rantalainen, T. (2021). The gait is less stable in children with cerebral palsy in normal and dual-task gait

compared to typically developed peers. *Journal of Biomechanics*, *117*, 110244. https://doi.org/S0021-9290(21)00024-5

Pinto, C. B., Velez, F. G. S., Lopes, F., de Toledo Piza, P. V., Dipietro, L., Wang, Q. M., Mazwi, N. L., Camargo, E. C., Black-Schaffer, R., & Fregni, F. (2017). SSRI and Motor Recovery in Stroke: Reestablishment of Inhibitory Neural Network Tonus. *Frontiers in Neuroscience*, *11*, 637. https://doi.org/10.3389/fnins.2017.00637

Poitras, I., Martinie, O., Robert, M. T., Campeau-Lecours, A., & Mercier, C. (2021). Impact of Sensory Deficits on Upper Limb Motor Performance in Individuals with Cerebral Palsy: A Systematic Review. *Brain Sciences*, *11*(6), 744. https://doi.org/10.3390/brainsci11060744

Reddihough, D. S., & Collins, K. J. (2003). The epidemiology and causes of cerebral palsy. *Australian Journal of Physiotherapy*, *49*(1), 7–12. https://doi.org/10.1016/S0004-9514(14)60183-5

Riggs, L., Moses, S. N., Bardouille, T., Herdman, A. T., Ross, B., & Ryan, J. D. (2009). A complementary analytic approach to examining medial temporal lobe sources using magnetoencephalography. *NeuroImage*, *45*(2), 627–642. https://doi.org/10.1016/j.neuroimage.2008.11.018

Rosenbaum, P., Paneth, N., Leviton, A., Goldstein, M., Bax, M., Damiano, D., Dan, B., & Jacobsson, B. (2007). A report: The definition and classification of cerebral palsy April 2006. *Developmental Medicine and Child Neurology. Supplement*, *109*, 8–14.

Rossiter, H. E., Davis, E. M., Clark, E. V., Boudrias, M. H., & Ward, N. S. (2014). Beta oscillations reflect changes in motor cortex inhibition in healthy ageing. *NeuroImage*, *91*, 360–365. https://doi.org/10.1016/j.neuroimage.2014.01.012

Sack, A. T. (2009). Parietal cortex and spatial cognition. *Behavioural Brain Research*, *202*(2), 153–161. https://doi.org/10.1016/j.bbr.2009.03.012

Salenius, S., Schnitzler, A., Salmelin, R., Jousmäki, V., & Hari, R. (1997). Modulation of Human Cortical Rolandic Rhythms during Natural Sensorimotor Tasks. *NeuroImage*, *5*(3), 221–228. https://doi.org/10.1006/nimg.1997.0261

Salmelin, R., Hämäläinen, M., Kajola, M., & Hari, R. (1995). Functional segregation of movement-related rhythmic activity in the human brain. *NeuroImage*, *2*(4), 237–243. https://doi.org/S1053811985710312

Salmelin, R., & Hari, R. (1994). Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience*, *60*(2), 537–550. https://doi.org/0306-4522(94)90263-1

Sanes, J. N., & Donoghue, J. P. (2000). Plasticity and primary motor cortex. *Annual Review of Neuroscience*, *23*, 393–415. https://doi.org/10.1146/annurev.neuro.23.1.393

Schnitzler, A., Salenius, S., Salmelin, R., Jousmäki, V., & Hari, R. (1997). Involvement of primary motor cortex in motor imagery: A neuromagnetic study. *NeuroImage*, *6*(3), 201–208. https://doi.org/S1053-8119(97)90286-X

Seedat, Z. A., Quinn, A. J., Vidaurre, D., Liuzzi, L., Gascoyne, L. E., Hunt, B. A. E., O'Neill, G. C., Pakenham, D. O., Mullinger, K. J., Morris, P. G., Woolrich, M. W., & Brookes, M. J. (2020). The role of transient spectral 'bursts' in functional connectivity: A magnetoencephalography study. *NeuroImage*, *209*, 116537. https://doi.org/10.1016/j.neuroimage.2020.116537

Serrien, D. J., Strens, L. H. A., Oliviero, A., & Brown, P. (2002). Repetitive transcranial magnetic stimulation of the supplementary motor area (SMA) degrades bimanual movement control in humans. *Neuroscience Letters*, *328*(2), 89–92. https://doi.org/10.1016/S0304-3940(02)00499-8

Sherman, M. A., Lee, S., Law, R., Haegens, S., Thorn, C. A., Hämäläinen, M. S., Moore, C. I., & Jones, S. R. (2016). Neural mechanisms of transient neocortical beta rhythms: Converging evidence from humans, computational modeling, monkeys, and mice. *Proceedings of the National Academy of Sciences*, *113*(33). https://doi.org/10.1073/pnas.1604135113

Silen, T., Forss, N., Jensen, O., & Hari, R. (2000). Abnormal reactivity of the approximately 20-Hz motor cortex rhythm in Unverricht Lundborg type progressive myoclonus epilepsy. *NeuroImage*, *12*(6), 707–712. https://doi.org/10.1006/nimg.2000.0660

Simões, C., & Hari, R. (1999). Relationship between Responses to Contra- and Ipsilateral Stimuli in the Human Second Somatosensory Cortex SII. *NeuroImage*, *10*(4), 408–416. https://doi.org/10.1006/nimg.1999.0476

Sochůrková, D., Rektor, I., Jurák, P., & Stančák, A. (2006). Intracerebral recording of cortical activity related to self-paced voluntary movements: A Bereitschaftspotential and event-related desynchronization/synchronization. SEEG study. *Experimental Brain Research*, *173*(4), 637–649. https://doi.org/10.1007/s00221-006-0407-9

Stančák, A., Feige, B., Lücking, C. H., & Kristeva-Feige, R. (2000). Oscillatory cortical activity and movement-related potentials in proximal and distal movements. *Clinical Neurophysiology*, *111*(4), 636–650. https://doi.org/10.1016/S1388-2457(99)00310-7

Stančák, A., Riml, A., & Pfurtscheller, G. (1997). The effects of external load on movement-related changes of the sensorimotor EEG rhythms. *Electroencephalography and Clinical Neurophysiology*, *102*(6), 495–504. https://doi.org/10.1016/S0013-4694(96)96623-0

Stančák, A., Svoboda, J., Rachmanova, R., Vrana, J., Kralik, J., & Tintera, J. (2003). Desynchronization of cortical rhythms following cutaneous stimulation: Effects of stimulus repetition and intensity, and of the size of corpus callosum. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *114*(10), 1936–1947. https://doi.org/S1388245703002013

Staudt, M. (2002). Two types of ipsilateral reorganization in congenital hemiparesis: A TMS and fMRI study. *Brain*, *125*(10), 2222–2237. https://doi.org/10.1093/brain/awf227

Staudt, M. (2010). Reorganization after pre- and perinatal brain lesions: Pre- and perinatal brain lesions. *Journal of Anatomy*, *217*(4), 469–474. https://doi.org/10.1111/j.1469-7580.2010.01262.x

Steriade, M., Gloor, P., Llinás, R. R., Lopes da Silva, F. H., & Mesulam, M.-M. (1990). Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and Clinical Neurophysiology*, *76*(6), 481–508. https://doi.org/10.1016/0013-4694(90)90001-Z

Szurhaj, W., Derambure, P., Labyt, E., Cassim, F., Bourriez, J. L., Isnard, J., Guieu, J. D., & Mauguiere, F. (2003). Basic mechanisms of central rhythms reactivity to preparation and execution of a voluntary movement: A stereoelectroencephalographic study. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *114*(1), 107–119. https://doi.org/S1388245702003334

Tallon-Baudry, C., Bertrand, O., Wienbruch, C., Ross, B., & Pantev, C. (1997). Combined EEG and MEG recordings of visual 40 Hz responses to illusory triangles in human. *Neuroreport*, *8*(5), 1103–1107.

Tang, C. W., Hsiao, F. J., Lee, P. L., Tsai, Y. A., Hsu, Y. F., Chen, W. T., Lin, Y. Y., Stagg, C. J., & Lee, I. H. (2020). β-Oscillations Reflect Recovery of the Paretic Upper Limb in Subacute Stroke. *Neurorehabilitation and Neural Repair*, *34*(5), 450–462. https://doi.org/10.1177/1545968320913502

Tatti, E., Ricci, S., Mehraram, R., Lin, N., George, S., Nelson, A. B., & Ghilardi, M. F. (2019). Beta Modulation Depth Is Not Linked to Movement Features. *Frontiers in Behavioral Neuroscience*, *13*, 49. https://doi.org/10.3389/fnbeh.2019.00049

Tatti, E., Ricci, S., Nelson, A. B., Mathew, D., Chen, H., Quartarone, A., Cirelli, C., Tononi, G., & Ghilardi, M. F. (2020). Prior Practice Affects Movement-Related Beta Modulation and Quiet Wake Restores It to Baseline. *Frontiers in Systems Neuroscience*, *14*, 61. https://doi.org/10.3389/fnsys.2020.00061

Taulu, S., & Simola, J. (2006). Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Physics in Medicine and Biology*, *51*(7), 1759–1768. https://doi.org/S0031-9155(06)09790-9

Tiihonen, J., Hari, R., Kajola, M., Karhu, J., Ahlfors, S., & Tissari, S. (1991). Magnetoencephalographic 10-Hz rhythm from the human auditory cortex. *Neuroscience Letters*, *129*(2), 303–305. https://doi.org/10.1016/0304-3940(91)90486-D

Toledo, D. R., Manzano, G. M., Barela, J. A., & Kohn, A. F. (2016). Cortical correlates of response time slowing in older adults: ERP and ERD/ERS analyses during passive ankle movement. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *127*(1), 655–663. https://doi.org/S1388-2457(15)00319-3

Toma, K., Mima, T., Matsuoka, T., Gerloff, C., Ohnishi, T., Koshy, B., Andres, F., & Hallett, M. (2002). Movement Rate Effect on Activation and Functional Coupling of Motor Cortical Areas. *Journal of Neurophysiology*, *88*(6), 3377–3385. https://doi.org/10.1152/jn.00281.2002

Tonmukayakul, U., Shih, S. T. F., Bourke-Taylor, H., Imms, C., Reddihough, D., Cox, L., & Carter, R. (2018). Systematic review of the economic impact of cerebral palsy. *Research in Developmental Disabilities*, *80*, 93–101. https://doi.org/10.1016/j.ridd.2018.06.012

Toth, M., Kiss, A., Kosztolanyi, P., & Kondakor, I. (2007). Diurnal alterations of brain electrical activity in healthy adults: A LORETA study. *Brain Topography*, *20*(2), 63–76. https://doi.org/10.1007/s10548-007-0032-3

Trevarrow, M. P., Kleinsmith, J., Taylor, B. K., Wilson, T. W., & Kurz, M. J. (2021). The somatosensory cortical activity in individuals with cerebral palsy displays an aberrant developmental trajectory. *The Journal of Physiology*, *599*(4), 1281–1289. https://doi.org/10.1113/JP280400

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nature Reviews.Neuroscience*, *11*(2), 100–113. https://doi.org/10.1038/nrn2774

Uusitalo, M. A., & Ilmoniemi, R. J. (1997). Signal-space projection method for separating MEG or EEG into components. *Medical & Biological Engineering & Computing*, *35*(2), 135–140. https://doi.org/10.1007/bf02534144

Vinding, M. C., Tsitsi, P., Piitulainen, H., Waldthaler, J., Jousmäki, V., Ingvar, M., Svenningsson, P., & Lundqvist, D. (2019). Attenuated beta rebound to proprioceptive afferent feedback in Parkinson's disease. *Scientific Reports*, *9*(1), 2604–3. https://doi.org/10.1038/s41598-019-39204-3

Vogels, T. P., Sprekeler, H., Zenke, F., Clopath, C., & Gerstner, W. (2011). Inhibitory Plasticity Balances Excitation and Inhibition in Sensory Pathways and Memory Networks. *Science*, *334*(6062), 1569–1573. https://doi.org/10.1126/science.1211095

Vogt, S., & Thomaschke, R. (2007). From visuo-motor interactions to imitation learning: Behavioural and brain imaging studies. *Journal of Sports Sciences*, *25*(5), 497–517. https://doi.org/10.1080/02640410600946779

Vry, J., Linder-Lucht, M., Berweck, S., Bonati, U., Hodapp, M., Uhl, M., Faist, M., & Mall, V. (2008). Altered cortical inhibitory function in children with spastic diplegia: A TMS study. *Experimental Brain Research*, *186*(4), 611–618. https://doi.org/10.1007/s00221-007-1267-7

Wahl, M., Lauterbach-Soon, B., Hattingen, E., Jung, P., Singer, O., Volz, S., Klein, J. C., Steinmetz, H., & Ziemann, U. (2007). Human Motor Corpus Callosum: Topography, Somatotopy, and Link between Microstructure and Function. *Journal of Neuroscience*, *27*(45), 12132–12138. https://doi.org/10.1523/JNEUROSCI.2320-07.2007

Walker, S., Monto, S., Piirainen, J. M., Avela, J., Tarkka, I. M., Parviainen, T. M., & Piitulainen, H. (2020). Older Age Increases the Amplitude of Muscle Stretch-Induced Cortical Beta-Band Suppression But Does not Affect Rebound Strength. *Frontiers in Aging Neuroscience*, *12*, 117. https://doi.org/10.3389/fnagi.2020.00117

Ward, N. S. (2017). Restoring brain function after stroke—Bridging the gap between animals and humans. *Nature Reviews.Neurology*, *13*(4), 244–255. https://doi.org/10.1038/nrneurol.2017.34

Westner, B. U., Dalal, S. S., Gramfort, A., Litvak, V., Mosher, J. C., Oostenveld, R., & Schoffelen, J.-M. (2022). A unified view on beamformers for M/EEG source reconstruction. *NeuroImage*, *246*, 118789. https://doi.org/10.1016/j.neuroimage.2021.118789

Wijk, B. C. van, Beek, P. J., & Daffertshofer, A. (2012). Neural synchrony within the motor system: What have we learned so far? *Frontiers in Human Neuroscience*, *6*, 252. https://doi.org/10.3389/fnhum.2012.00252

Wilson, T. W., Heinrichs-Graham, E., & Becker, K. M. (2014). Circadian modulation of motor-related beta oscillatory responses. *NeuroImage*, *102 Pt 2*, 531–539. https://doi.org/10.1016/j.neuroimage.2014.08.013

Wingert, J. R., Burton, H., Sinclair, R. J., Brunstrom, J. E., & Damiano, D. L. (2008). Tactile sensory abilities in cerebral palsy: Deficits in roughness and object discrimination. *Developmental Medicine & Child Neurology*, *50*(11), 832–838. https://doi.org/10.1111/j.1469-8749.2008.03105.x

Wingert, J. R., Burton, H., Sinclair, R. J., Brunstrom, J. E., & Damiano, D. L. (2009). Joint-Position Sense and Kinesthesia in Cerebral Palsy. *Archives of Physical Medicine and Rehabilitation*, *90*(3), 447–453. https://doi.org/10.1016/j.apmr.2008.08.217

Wolters, C. H., Anwander, A., Tricoche, X., Weinstein, D., Koch, M. A., & MacLeod, R. S. (2006). Influence of tissue conductivity anisotropy on EEG/MEG field and return current computation in a realistic head model: A simulation and visualization study using high-resolution finite element modeling. *NeuroImage*, *30*(3), 813–826. https://doi.org/10.1016/j.neuroimage.2005.10.014

Xifra-Porxas, A., Niso, G., Larivière, S., Kassinopoulos, M., Baillet, S., Mitsis, G. D., & Boudrias, M. H. (2019). Older adults exhibit a more pronounced modulation of beta oscillations when performing sustained and dynamic handgrips. *NeuroImage*, *201*, 116037. https://doi.org/S1053-8119(19)30618-4

Xue, T., Yan, Z., Meng, J., Wang, W., Chen, S., Wu, X., Gu, F., Tao, X., Wu, W., Chen, Z., Bai, Y., Wang, Z., & Zhang, J. (2022). Efficacy of Neurostimulations for Upper Extremity Function Recovery after Stroke: A Systematic Review and Network Meta-Analysis. *Journal of Clinical Medicine*, *11*(20), 6162. https://doi.org/10.3390/jcm11206162

Yamawaki, N., Stanford, I. M., Hall, S. D., & Woodhall, G. L. (2008). Pharmacologically induced and stimulus evoked rhythmic neuronal oscillatory activity in the primary motor cortex in vitro. *Neuroscience*, *151*(2), 386–395. https://doi.org/S0306-4522(07)01335-8

Yeo, S. H., Lim, Z. I., Mao, J., & Yau, W. P. (2017). Effects of Central Nervous System Drugs on Recovery After Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Drug Investigation*, *37*(10), 901–928. https://doi.org/10.1007/s40261-017-0558-4

Zhang, X., Li, H., Xie, T., Liu, Y., Chen, J., & Long, J. (2020). Movement speed effects on beta-band oscillations in sensorimotor cortex during voluntary activity. *Journal of Neurophysiology*, *124*(2), 352–359. https://doi.org/10.1152/jn.00238.2020

ORIGINAL PUBLICATIONS

I

COMPARING MEG AND EEG IN DETECTING THE ~20-HZ RHYTHM MODULATION TO TACTILE AND PROPRIOCEPTIVE STIMULATION

by

Illman, M., Laaksonen, K., Liljeström, M., Jousmäki, V.,
Piitulainen, H., & Forss, N. 2020

NeuroImage, 215, 116804

https://doi.org/10.1016/j.neuroimage.2020.116804

NeuroImage 215 (2020) 116804

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Comparing MEG and EEG in detecting the ~20-Hz rhythm modulation to tactile and proprioceptive stimulation

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ARTICLE INFO

Keywords:
Beta rebound
Beta rhythm
Beta suppression
Passive movement
Sensorimotor cortex
Tactile stimulation

ABSTRACT

Modulation of the ~20-Hz brain rhythm has been used to evaluate the functional state of the sensorimotor cortex both in healthy subjects and patients, such as stroke patients. The ~20-Hz brain rhythm can be detected by both magnetoencephalography (MEG) and electroencephalography (EEG), but the comparability of these methods has not been evaluated. Here, we compare these two methods in the evaluating of ~20-Hz activity modulation to somatosensory stimuli.

Rhythmic ~20-Hz activity during separate tactile and proprioceptive stimulation of the right and left index finger was recorded simultaneously with MEG and EEG in twenty-four healthy participants.

Both tactile and proprioceptive stimulus produced a clear suppression at 300–350 ms followed by a subsequent rebound at 700–900 ms after stimulus onset, detected at similar latencies both with MEG and EEG. The relative amplitudes of suppression and rebound correlated strongly between MEG and EEG recordings. However, the relative strength of suppression and rebound in the contralateral hemisphere (with respect to the stimulated hand) was significantly stronger in MEG than in EEG recordings.

Our results indicate that MEG recordings produced signals with higher signal-to-noise ratio than EEG, favoring MEG as an optimal tool for studies evaluating sensorimotor cortical functions. However, the strong correlation between MEG and EEG results encourages the use of EEG when translating studies to clinical practice. The clear advantage of EEG is the availability of the method in hospitals and bed-side measurements at the acute phase.

1. Introduction

The ~20-Hz beta rhythm, detected over the Rolandic area, is modulated by somatosensory stimuli and motor activity, i.e. tactile stimulation (Cheyne et al., 2003; Gaetz and Cheyne, 2006; Houdayer et al., 2006; Pfurtscheller et al., 2001; Salmelin and Hari, 1994), voluntary movement (Cassim et al., 2001; Feige et al., 1996), passive movement (Alegre et al., 2002; Cassim et al., 2001; Parkkonen et al., 2015), action observation (Hari et al., 1998), motor imagining (Neuper et al., 2005; Schnitzler et al., 1997) or even to distracting auditory and visual stimuli (Piitulainen et al., 2015b). The amplitude of the rhythm is typically reduced soon after stimulus onset (suppression; event-related desynchronization (ERD), or movement related beta desynchronization (MRBD)), followed by an increase in the strength of the rhythm (rebound; event-related synchronization (ERS), or post movement beta rebound (PMBR)). The 'suppression' is thought to reflect activation (Chen et al., 1998; Pfurtscheller and Lopes da Silva, 1999) and the' rebound' active inhibition or reduced excitability of the sensorimotor cortex (Cassim et al., 2001; Chen et al., 1998; Gaetz et al., 2011).

The ~20-Hz rebound has been used to assess the functional state of the sensorimotor cortex, and since it reflects changes in inhibitory mechanisms, it has been considered to be a suitable marker of neural

Abbreviations: EEG, electroencephalography; MEG, magnetoencephalography; MSR, magnetically shielded room; PCA, principal component analysis; PSD, power-spectra density; SMI, primary sensorimotor cortex; TFR, time-frequency representations; TSE, temporal spectral evolution.

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https://doi.org/10.1016/j.neuroimage.2020.116804
Received 16 December 2019; Received in revised form 6 March 2020; Accepted 31 March 2020
Available online 7 April 2020

plasticity in the brain (Gaetz et al., 2010; Mary et al., 2015). Indeed, the ~20-Hz rebound has been successfully used as a neurophysiological biomarker to evaluate motor recovery after stroke (Laaksonen et al., 2012; Parkkonen et al., 2017), and to characterize neurophysiological changes in Parkinson's disease (Degardin et al., 2009; Hall et al., 2014), schizophrenia (Brookes et al., 2015; Liddle et al., 2016; Robson et al., 2015) and Unverricht-Lundborg type epilepsy (Silen et al., 2000).

Although the modulation of the ~20-Hz rhythm has been studied both with MEG and EEG, there are no studies examining this phenomenon simultaneously using both methods. Both MEG and EEG measure electrical activity generated by tens of thousands of simultaneously active cortical pyramidal cells from outside the head, with the difference that EEG measures electrical potentials and MEG magnetic fields generated by neuronal currents. Both methods have their advantages. In MEG, the magnetic fields propagate through the head almost unchanged and provide thus a less spatially distorted signal, which allows more accurate source localization (Hari, 2011). MEG is also less sensitive to disturbances caused by movements and muscle (Claus et al., 2012; Hämäläinen et al., 1993; Hari and Puce, 2017; Whitham et al., 2007). On the other hand, MEG devices are available only in a few centers, and MEG needs to be recorded in a magnetically shielded room (MSR), that attenuates external electrical interference, thus providing a very low interference environment also for measuring EEG. EEG is cheaper, widely available, and can be brought directly to the patient. The better availability and lower operating costs make EEG an attractive method to be used especially in clinical settings.

We have successfully used the ~20-Hz rebound as a motor recovery-related neurophysiological biomarker in acute stroke patients using MEG (Laaksonen et al., 2012; Parkkonen et al., 2017). In the present study, we aimed to clarify if the ~20-Hz rebound is equally well identified in EEG recordings allowing its use in future clinical studies. The use of EEG would allow to explore larger patient groups, and to include more severely affected stroke patients not suitable for measurements outside the ward.

2. Materials and methods

2.1. Subjects and data availability

Twenty-four healthy participants (11 females, age 19—35, mean 23 ± 4yrs) volunteered in the experiment. Twenty-two subjects were right-handed, one left-handed and one ambidextrous, according to the Edinburgh Handedness Inventory (Oldfield, 1971).

The local ethics committee of Aalto University approved the experiment in accordance with the Declaration of Helsinki. All subjects gave written informed consent prior to participation.

2.2. Experimental design

In order to modulate the ~20-Hz sensorimotor cortex rhythm, two different stimuli, tactile and proprioceptive stimulation, were applied in separate sessions. The order of the sessions was randomized. The participants were instructed to remain relaxed, not to pay attention to the stimuli, and to fixate on a 12 × 15 cm picture at a distance of 2.2 m in front of them. The subjects wore earplugs throughout the measurement to attenuate possible weak noise artefacts, caused by the stimulators.

Tactile stimulation. Tactile stimuli were delivered alternately to both index fingertips by pneumatic diaphragms driven by compressed air (stimulus duration 180 ms, peaking at 40 ms) with an interstimulus interval of 3 s (6 s each finger) controlled by the acquisition computer. During the stimulation, the participants held their hands relaxed on a pillow.

Proprioceptive stimulation. Proprioceptive stimulation was elicited by a pneumatic -artificial muscle embedded in a mechanical movement actuator (Piitulainen et al., 2015a) causing a fast flexion-extension movement of the index finger. The stimulus was delivered in separate sessions to the right and left index finger with an ISI of 5 s. The duration (130 ms) and onset (35 ms mechanical delay from the trigger pulse onset to actual movement onset) of the movement were detected with a 3-axis accelerometer (ADXL335 iMEMS Accelometer, Analog Devices Inc., Norwood, MA, USA), attached to the nail of the index finger. The range of the movement was ~5 mm with the used compressed air pressure of 4 bar. The stimulated hand was supported with pillows to the level of the movement actuator and the tip of the index finger was lightly taped on the artificial muscle. A piece of surgical tape was applied around the fingertip to minimize possible tactile sensation caused by the movement. A visual barrier was used to prevent motion-induced visual contamination.

Resting state recordings. After the stimulation protocols, resting state data with eyes open 3 min was recorded.

2.3. Data acquisition

Rhythmic brain activity was recorded with a 306-channel (204 planar gradiometers, 102 magnetometers) whole-scalp MEG system (Elekta Neuromag, Elekta Oy, Helsinki, Finland) at the MEG Core, Aalto NeuroImaging, Aalto University. EEG was recorded simultaneously with a MEG-compatible EEG cap (ANT Neuro waveguard™original), containing 60 Ag–AgCl surface electrodes mounted according to the international 10–20 system. The measurements were performed in a magnetically shielded room (MSR; Imedco AG, Hägendorf, Switzerland), where the participant was comfortably seated with the head in the helmet-shaped MEG sensor array. Five indicator coils were attached onto the EEG-cap (three to the forehead and one above each ear) to define the subject's head position with respect to the MEG sensors. The location of the indicator coils together with three anatomical landmarks (left and right preauricular points and nasion) and 100–200 additional points from the scalp surface, were determined with a 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA), prior to the measurements. The head position with respect to the sensor array was measured at the beginning of each measurement session (and its stability was monitored across measurement periods). In addition, the head position was tracked with continuous head position monitoring throughout the MEG measurement. Two vertical electro-oculogram electrodes (EOG) were used to detect artefacts caused by eye blinks.

MEG and EEG signals were acquired at a sampling frequency of 1000 Hz, and the signal was band-pass filtered to 0.1–330 Hz. The impedance of the EEG electrodes was kept below 10 kΩ in fifteen subjects and below 5 kΩ in nine subjects (impedance meter changed). The adequacy and quality of the data was evaluated during the measurement based on the raw signals and on-line averaged evoked responses.

2.4. Data processing and analysis

Preprocessing. For each participant, the MEG signals of the different stimulation sessions were transformed to the same head-coordinate system within participant, which in our case was the mean position between tactile and proprioceptive recordings, using a custom made Matlab script. These averaged head coordinates were used as reference head position in the Maxfilter software (v2.2; Elekta Oy, Helsinki, Finland) for coordinate matching and head movement compensation. This procedure enables better comparability between the MEG recordings. To compute grand average topographic maps, the head coordinates of the different stimulation sessions of all participants were transformed to the same standard position with respect to the MEG sensors. Since a larger head-coordinate transformation can increase noise in the MEG data, this transformation was only used to compute the topographic maps. Along with coordinate transfers, the MEG raw signals were preprocessed off-line with the MaxFilter software, using the signal-space separation method with temporal extension (tSSS), including head movement compensation with a threshold of 25 mm (Taulu, 2005; Taulu and Simola, 2006). For tSSS, the length of the data buffer was 16 s, the subspace correlation limit 0.98,

and the inside expansion order 8, and outside expansion 3.

All further analyses were done using custom-written routines in MNE-Python (Gramfort et al., 2013). The individual EEG signals were referenced with respect to the average over all EEG electrodes (excluding bad channels). Since the reference used in EEG analyses may have an effect on the results, we tested a few additional EEG-reference alternatives: (1) a surface Laplacian (SL), using a next-nearest-neighbor derivation, was computed to reduce head volume conduction effects and to obtain a reference-free EEG (Hjorth, 1975; McFarland et al., 1997), and (2) bipolar montage, according to clinical recommendation in somatosensory evoked potential measurements (Cruccu et al., 2008). However, the results of these two alternative references are not presented in this context, as the average reference produced the strongest signals of ~20-Hz modulation and was thus chosen to be used in the final analysis.

Stimulus related evoked responses were removed from the raw data by subtracting the averaged evoked responses from each epoch to better reveal the modulation of the ~20-Hz activity (i.e. induced response). The evoked component can distract the baseline determination of ~20-Hz activity in further analysis (David et al., 2006). Eye movement artefacts were removed using a principal component analysis (PCA) (Uusitalo and Ilmoniemi, 1997), removing two magnetometer, two gradiometer and two EEG components related to eye blinks from the signals.

Spontaneous ~20-Hz activity. To determine the frequencies and amplitudes of spontaneous resting state beta activity, power-spectral densities (PSD) were calculated from the eyes-open resting state data using the Welch method, with a sliding 2048-point fast Fourier transform (FFT) with no overlap and a Hann window function. From the PSD, the peak frequencies in the beta frequency bands (β_1 ~13–19 and β_2 ~19–27) were extracted using automated peak detection for each subject individually for both the right and the left hemispheres. To visually ensure the strongest frequency range of beta rhythm modulation, time-frequency representations (TFRs) were calculated for all conditions in the frequency range of 3–36 Hz for a time window from −700 to 3200 ms with respect to stimulus onset, for each subject. The Morlet wavelet transformation was used in TFR calculation (Tallon-Baudry et al., 1997a, 1997b). The spectral and temporal resolution of the TFRs was balanced by scaling the number of cycles by frequency (number of cycles was set to $f/2$).

Modulation of ~20-Hz rhythm. The modulation of the ~20-Hz sensorimotor cortex rhythm was quantified using the temporal spectral evolution (TSE) method (Salmelin and Hari, 1994), where the continuous data was first band-pass filtered, then rectified and averaged time-locked to the stimulus onset. The pre-stimulus time (-500–-100 ms) was set to zero level, to obtain both negative and positive values. TSE curves were computed for three frequency bands (13–23 Hz, 15–25 Hz and 17–27 Hz) for each subject separately, and the individual frequency band with strongest modulation was visually selected for further analysis. This band was used for both MEG and EEG analysis as the strongest modulation occurred at the same band in both methods. The analysis period for both conditions was from −700 to 3200 ms with respect to stimulus onset. In order to quantify the peak amplitudes and latencies of suppression and rebound, the most responsive MEG and EEG channel was selected from the left and right hemisphere separately. If peak suppression and rebound were strongest in different channels, separate channels were selected for further analyses. The peak values were converted into relative values by calculating the percentage of decrease/increase of the rhythm with respect to the pre-stimulus baseline (time period from −500 to −100 ms).

2.5. Statistical analysis

Kolmogorov–Smirnov and Shapiro–Wilkin tests (IBM SPSS Statistics 24) were used to test the normal distribution of the relative values of suppression and rebound. Due to non-normal distribution, correlations between MEG and EEG strengths were calculated with the nonparametric Spearman's correlation coefficient. For the same reason, the nonparametric Wilcoxon signed-rank test was used to analyze significant differences between MEG and EEG results. A p-value < 0.05 was considered as statistically significant.

3. Results

The quality of the data of MEG/EEG recordings for all twenty-four subjects was good, despite of two MEG and 1–3 bad EEG channels throughout the measurements, which were not located in the sensorimotor cortex area. The number of applied stimuli used in the TSE analysis was 105 ± 11 (mean ± SD) for tactile and 108 ± 11 for proprioceptive stimuli. Fig. 1 shows the TSE curve in one representative participant for both tactile and proprioceptive stimuli.

3.1. Spontaneous ~20-Hz activity

In the eyes-open resting state condition, the strongest frequency points of β_1 (~13–19 Hz) and β_2 (~19–27 Hz) were detected both in MEG and EEG over the left and right sensorimotor regions. No differences in the frequencies nor strengths of the ~20-Hz peaks at rest were observed between the hemispheres nor between MEG and EEG measurements (Table 1).

3.2. Modulation of the ~20-Hz rhythm

Frequency band. The modulation of the beta rhythm to tactile and proprioceptive stimulation was observed at a frequency range of 13–27 Hz, from which the 10 Hz bandwidth of strongest modulation was individually selected for each subject. The strongest modulation occurred interindividually in slightly different frequency bands, and therefore, the accurate 10 Hz bandwidth was individually selected for further analysis.

Latencies. Both MEG and EEG showed clear modulation of the ~20-Hz rhythm to both tactile and proprioceptive stimulation, as Fig. 2 illustrates. Both stimuli induced an initial suppression at 300–400 ms duration, strongest at around 330 ms, followed by a subsequent rebound of 2000–2500 ms duration, strongest at around 820 ms. The latencies of suppression and rebound were very similar between MEG and EEG recordings (Table 2).

Spatial distribution of the ~20-Hz modulation. Fig. 3 shows the grand averaged (n = 24) topographic distribution of the ~20-Hz suppression (at 350 ms after stimulus onset) and rebound (at 800 ms after stimulus onset) for MEG magnetometers and EEG electrodes. Suppression and rebound of the ~20-Hz rhythm was seen bilaterally over the sensorimotor cortices for unilateral stimulations both for MEG and EEG. As demonstrated by earlier (Salenius et al., 1997; Salmelin and Hari, 1994), the modulation of the rhythm was always strongest in the contralateral hemisphere to the stimulated hand. This was more pronounced in MEG than EEG recordings.

Suppression and rebound amplitudes to tactile and proprioceptive stimulation. Fig. 4 illustrates the relative (%) peak amplitudes of suppression and rebound to tactile and proprioceptive stimulation. To tactile stimulation, the suppression was significantly stronger in MEG than in EEG recordings in the contralateral hemisphere to both left and right finger stimulation (−28 ± 2% vs. −22 ± 2%, $p < 0.01$ for left and −25 ± 2% vs. −20 ± 2%, $p < 0.01$ for right finger stimulation). Also the rebound amplitudes were stronger in MEG than in EEG recordings (63 ± 9% vs. 48 ± 6%, $p < 0.05$ for left and 53 ± 8% vs. 41 ± 5%, $p < 0.07$ for right finger stimulation), albeit the difference for right finger stimulation did not reach significance. Table 2 shows relative peak amplitudes for suppression and rebound.

To proprioceptive stimulation, the suppression was significantly stronger in MEG than in EEG in the contralateral hemisphere to left finger stimulation (−27 ± 2% vs. −21 ± 2%, $p < 0.01$, respectively), and right finger stimulation (−25 ± 2% vs. −21 ± 2, $p < 0.05$). The rebound amplitudes in the contralateral hemisphere to both left and right finger stimulation were significantly stronger in MEG than in EEG recordings (53 ± 9% vs. 39 ± 5%, $p < 0.05$ for left and 53 ± 9% vs. 39 ± 5%, $p <$

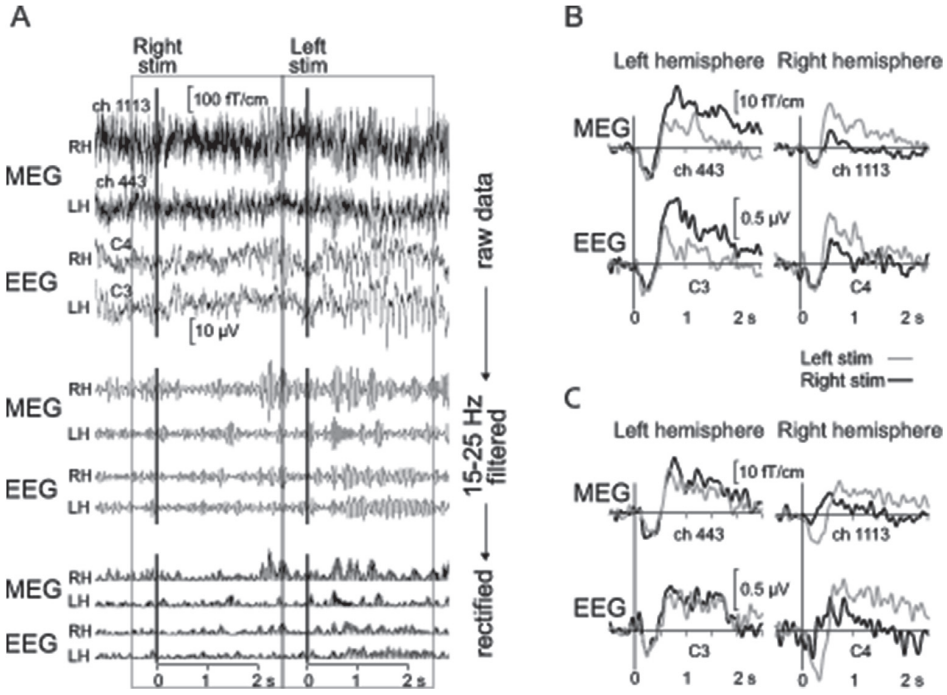

Fig. 1. Modulation of the ~20-Hz rhythm in one participant. (A) In TSE analysis, MEG and EEG raw data was filtered to the beta band (15–25 Hz), then rectified and averaged with respect to the (B) tactile and (C) proprioceptive stimulation. The most representative channels over the SMI region from the right (RH) and left hemispheres (LH) are shown. Stimulus onset is indicated by a vertical line at 0 s.

Table 1
Frequencies and amplitudes (n = 24) of the strongest point (mean ± SEM) of the spectral β_1 (~13–19 Hz) and β_2 (~19–27 Hz) frequencies in the eyes-open condition.

	β_1		β_2	
	RH	LH	RH	LH
Peak frequency (Hz)				
MEG	16.3 ± 0.3	16.2 ± 0.3	21.3 ± 0.3	21.1 ± 0.3
EEG	16.1 ± 0.4	16.2 ± 0.4	21.8 ± 0.5	21.7 ± 0.5
Peak amplitude				
MEG $(fT/cm)^2$	12.7 ± 2.8	12.3 ± 2.6	14.0 ± 2.8	11.9 ± 2.2
EEG $(\mu V)^2$	1.2 ± 0.2	1.4 ± 0.3	1.0 ± 0.1	1.4 ± 0.3

LH, left hemisphere.
RH, right hemisphere.

0.05 for right finger stimulation).

The amplitudes of suppression and rebound in the ipsilateral hemisphere to the stimulated hand did not differ between MEG and EEG measurements neither to tactile nor to proprioceptive stimuli. More detailed values are shown in Table 2.

3.3. Correlation between MEG and EEG measurements

The suppression and rebound strengths correlated strongly between MEG and EEG measurements both to tactile and proprioceptive stimulation. Fig. 5A illustrates the correlations of suppression in the hemisphere contralateral to the stimulated hand between MEG and EEG recordings. To tactile stimulation, the correlation was r = 0.70 ($p < 0.01$) for left and r = 0.70 ($p < 0.01$) for right finger stimulation, and to proprioceptive stimulation r = 0.64 ($p < 0.01$) for left and r = 0.70 ($p < 0.01$) for right finger stimulation (Table 3).

Correlations of the rebound strengths in the hemisphere contralateral to the stimulated hand between MEG and EEG measurements are shown in Fig. 5B. The correlation to tactile stimulation was r = 0.62 ($p < 0.01$) for left and r = 0.80 ($p < 0.01$) for right finger, and to proprioceptive stimulation r = 0.84 ($p < 0.01$) for left and r = 0.81 ($p < 0.01$) for right finger stimulation. Table 3 shows more information about correlation.

4. Discussion

To our knowledge, this is the first study that compares the modulation of the ~20-Hz rhythm in simultaneously measured MEG and EEG. This comparison is of clinical significance, as the ~20-Hz modulation could be used as an indicator of recovery potential after stroke if the measurements were easily available. Our results demonstrate that the modulation of the ~20-Hz rhythm is well detectable both using MEG and EEG; the suppression and rebound of the rhythm to both tactile and proprioceptive stimulation peaked at similar latencies and locations in both MEG and EEG recordings. However, the modulation of the rhythm was stronger in MEG than in EEG recordings.

4.1. ~20-Hz modulation in MEG vs. EEG

In the present study, the ~20-Hz rhythm modulation to sensory stimulation detected with MEG and EEG was in good agreement with previous studies using MEG and EEG (Alegre et al., 2002; Houdayer et al., 2006; Laaksonen et al., 2012; Neuper and Pfurtscheller, 2001; Parkkonen et al., 2015; Pfurtscheller and Neuper, 1994; Pfurtscheller et al., 1996a, 1996b; Salmelin and Hari, 1994). The rebound amplitudes in the contralateral hemisphere to the stimulated hand were stronger in MEG than in EEG recordings. Magnetic fields propagate through the head almost unchanged and provide thus a less spatially distorted signal, whereas in EEG the membranes, skull, scalp and spinal fluid greatly modify the electrical current measured from the surface of the head (Antonakakis et al., 2019). For this reason, MEG typically has better spatial resolution than EEG, and thus it can separate simultaneously active sources more precisely. This was evident also in the current topographical maps. As MEG is biased towards tangential currents, it is a particularly suitable method to detect activity arising from the fissural

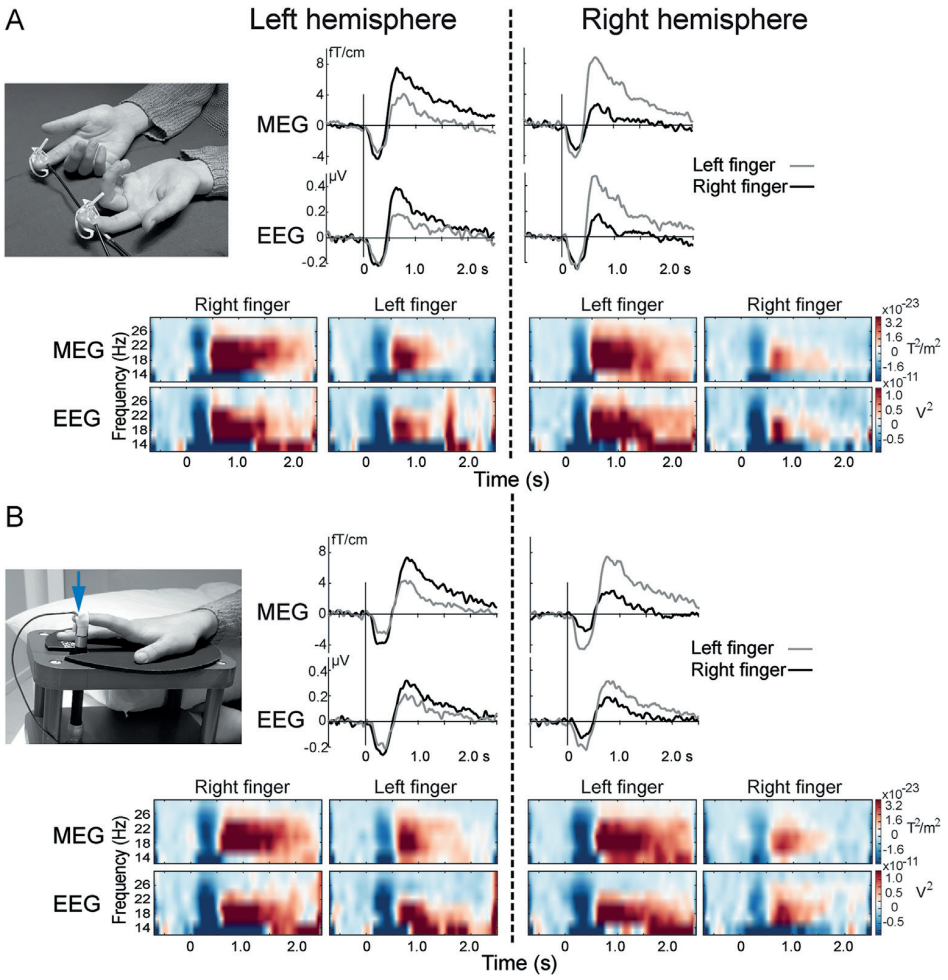

Fig. 2. ~20-Hz rhythm modulation to (A) tactile and (B) proprioceptive stimulation. Grand averaged (N = 24) TSE curves from one most representative channel over the left and right sensorimotor areas are shown on the right side of stimulus setup images, and corresponding time frequency representations (TFR) are presented below them. The vertical line at 0 s indicates the onset of the stimulus.

Table 2
The relative amplitudes and latencies (mean ± SEM) of the ~20-Hz suppression and rebound (n = 24) with respect to the baseline level elicited by tactile and proprioceptive stimulation.

Tactile stim	Left finger				Right finger			
	MEG IH	EEG IH	MEG CH	EEG CH	MEG CH	EEG CH	MEG IH	EEG IH
Suppression								
Relative amplitude (%)	−20 ± 2	−18 ± 2	−28 ± 2	−22 ± 2	−25 ± 2	−20 ± 2	−20 ± 2	−21 ± 2
Peak latency (ms)	319 ± 19	297 ± 19	303 ± 15	313 ± 20	314 ± 14	300 ± 21	321 ± 17	330 ± 21
Rebound								
Relative amplitude (%)	28 ± 5	23 ± 3	63 ± 9	48 ± 6	53 ± 8	41 ± 5	22 ± 4	21 ± 2
Peak latency (ms)	837 ± 43	792 ± 54	725 ± 37	741 ± 42	788 ± 40	739 ± 44	827 ± 48	768 ± 42
Proprioceptive stim	Left finger				Right finger			
	MEG IH	EEG IH	MEG CH	EEG CH	MEG CH	EEG CH	MEG IH	EEG IH
Suppression								
Relative amplitude (%)	−18 ± 2	−19 ± 2	−27 ± 2	−21 ± 2	−25 ± 2	−21 ± 2	−15 ± 2	−17 ± 1
Peak latency (ms)	357 ± 22	339 ± 21	332 ± 17	315 ± 16	360 ± 18	316 ± 14	362 ± 21	349 ± 17
Rebound								
Relative amplitude (%)	36 ± 7	29 ± 4	53 ± 9	39 ± 5	53 ± 9	39 ± 5	25 ± 4	23 ± 3
Peak latency (ms)	831 ± 46	874 ± 38	853 ± 33	856 ± 34	869 ± 36	879 ± 55	821 ± 44	817 ± 42

IH, ipsilateral hemisphere with respect to stimulus.
CH, contralateral hemisphere with respect to stimulus.

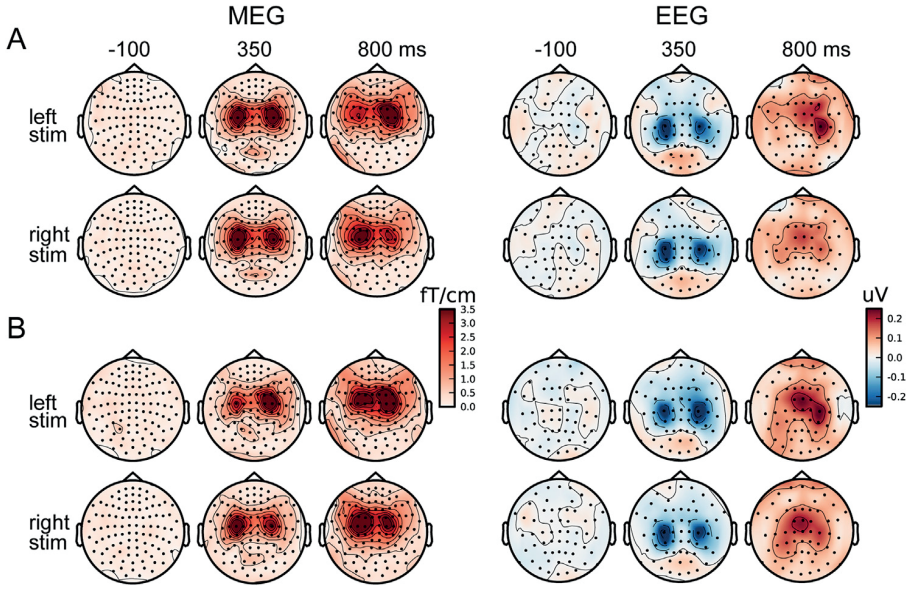

Fig. 3. Topographic maps showing group averaged (n = 24) field strengths of the ~20-Hz rhythm modulation to (A) tactile and (B) proprioceptive stimulation both in MEG and EEG (magnetic field vs. electric scalp potential). Note that MEG topoplots shows vector sums of gradiometers (positive value) in each location.

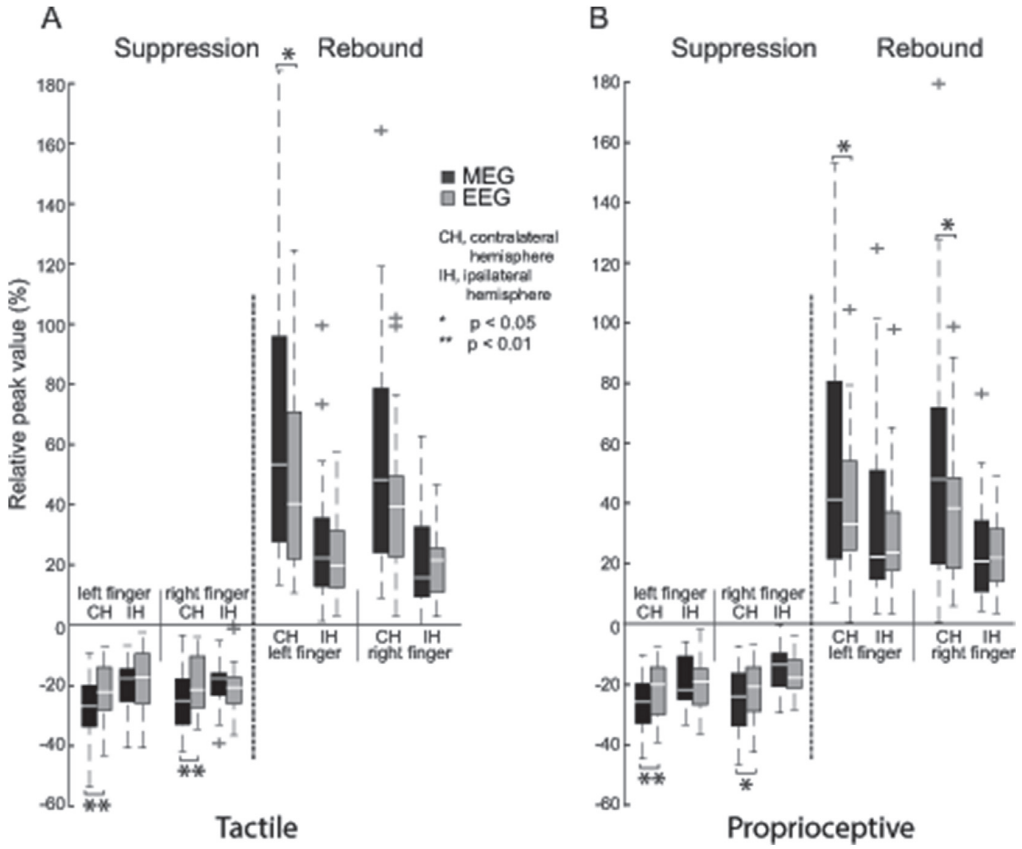

Fig. 4. Peak amplitudes of ~20-Hz rhythm suppression and rebound to (A) tactile and (B) proprioceptive stimulation. Note that values are relative amplitudes with respect to baseline. The boxes include 50% of the data points and horizontal lines inside boxes indicates median values. The whiskers show data range without outliers, which are shown by the crosses. The outliers were defined as a value more than 1.5 times the interquartile range away from the top or bottom of the box. Statistical significances, based on Wilcoxon signed-rank test, are denoted as * $P < 0.05$ and **$P < 0.01$.

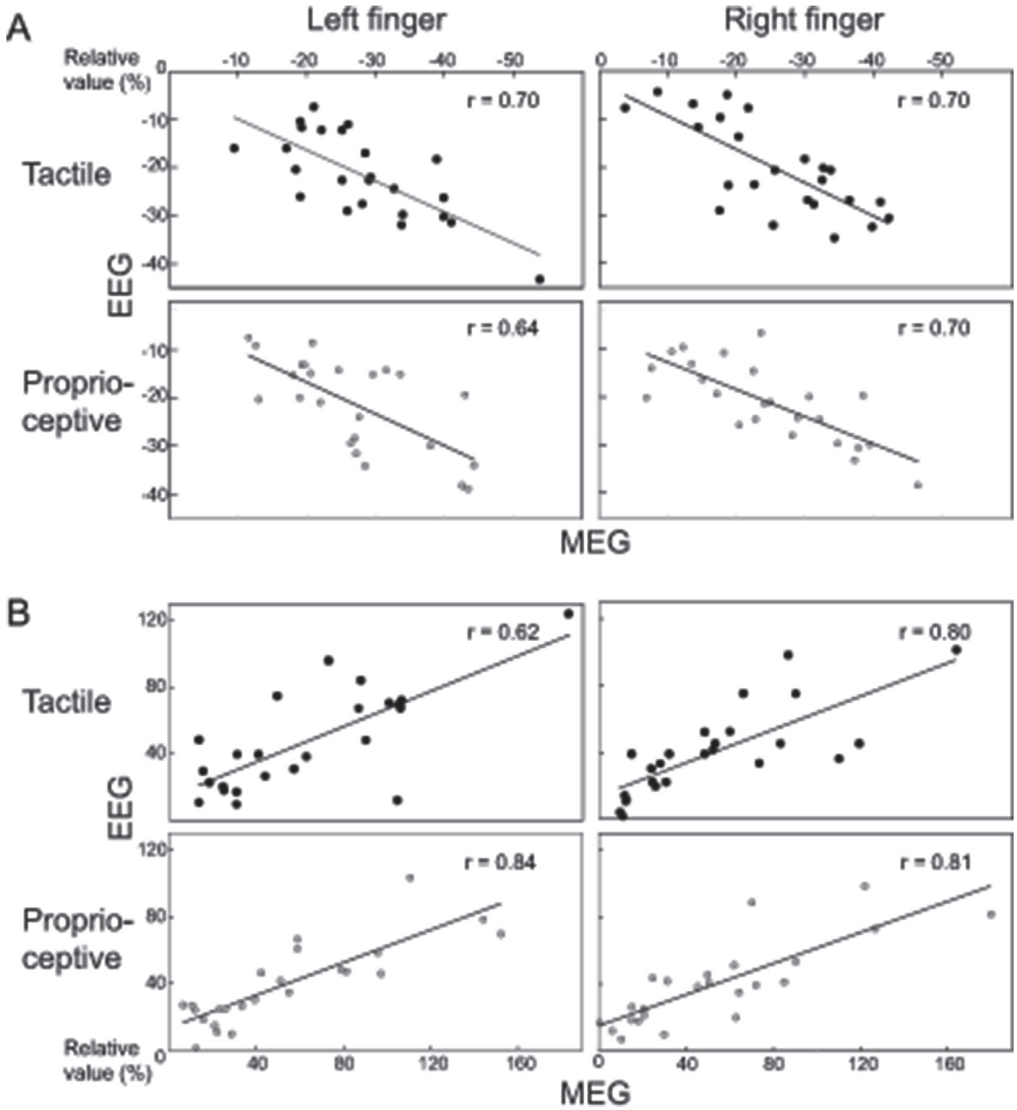

Fig. 5. Correlation of the relative amplitude values (%) of the ~20-Hz rhythm to (A) suppression and (B) rebound between MEG and EEG recordings. Correlations are shown only for the contralateral responses with respect to the stimulated finger. Please note that the correlation is positive for both the suppression and rebound responses.

Table 3
Spearman's correlation coefficients (r) of the ~20-Hz rhythm suppression and rebound amplitudes with respect to baseline level between MEG and EEG results.

Tactile stim	Left finger		Right finger	
	LH	RH	LH	RH
Suppression	0.72**	0.70**	0.70**	0.36
Rebound	0.81**	0.62**	0.80**	0.81**
Proprioceptive stim	Left finger		Right finger	
	LH	RH	LH	RH
Suppression	0.66**	0.64**	0.70**	0.33
Rebound	0.73**	.84**	0.81**	0.88**

LH, left hemisphere.
RH, right hemisphere.
**P < 0.01.

cortex, such as large parts of the primary sensorimotor (SMI) cortex, but at the same time the sensitivity to deeper sources is weaker (Hari and Puce, 2017; Hillebrand and Barnes, 2002). The depth and orientation of the source significantly affect its measurability with MEG and EEG; MEG detects better tangential sources, while EEG detects better radial as well as deeper sources (Hunold et al., 2016). Since the ~20-Hz rhythm is mainly generated in the pre-and postcentral walls of the central fissure, MEG provides an excellent tool to detect this rhythm, which was also observed in our results of the stronger ~20-Hz suppression and rebound in MEG than EEG. Combining MEG and EEG could also provide valuable additional information on source localization of the ~20-Hz suppression and rebound (Antonakakis et al., 2019), as well as improve overall SNR (Goldenholz et al., 2009).

Our main objective was to compare the strength of ~20-Hz modulation between MEG and EEG recordings. In line with our hypothesis, we observed stronger modulation in MEG compared to EEG in some of the examined variables, most likely due to better overall signal-to-noise ratio in MEG signals. However, we did not correct for multiple comparisons because use of e.g. Bonferroni correction carries the risk of a Type II error, and some clear differences are possibly removed (Perneger, 1998).

In EEG studies, the reference location affects the analysis results, in contrast to the reference-free MEG, making MEG analyses more

straightforward. As the purpose of this study was to compare EEG with MEG results, it was important to ascertain whether the references methods commonly used in the ~20-Hz rhythm modulation studies has an effect on the EEG results (Pfurtscheller and Lopes da Silva, 1999). The average reference was decided to be used in the final comparison between MEG and EEG, as the suppression and rebound came out more strongly and the overall noise decreased, compared to the original reference (AFz) in the on-line measurement. The surface Laplacian derivatives were tested as well, but as it reduced the peak amplitude strength of suppression and rebound, the results are not presented here. Likewise, analyses were also performed according to the clinical recommendations used in somatosensory evoked potential (SEP) measurements (Cruccu et al., 2008), but also here the modulations were weaker and are hence not discussed further in this context.

Although the measurements were made in a highly undisturbed environment in a MSR, both MEG and EEG data contain unavoidable noise from the human physiology and devices in use. The overall noise level can be even higher in a hospital than in the MSR environment, affecting the results of EEG in clinical settings. In principle, more averaged responses would improve the signal-to-noise ratio, but the problem with long measurement sessions and extensive repetitions of stimuli is the attenuation of brain responses, due to short-term habituation and changes in vigilance.

4.2. ~20-Hz modulation to tactile vs. proprioceptive stimulation

Passive movement, e.g., proprioceptive stimulus has rarely been used to modulate the beta rhythm, and there are only a few comparative studies between different somatosensory stimuli. The results have been variable; passive movement has been shown to produce a similar strong rebounds as tactile stimulation (Alegre et al., 2002; Muller et al., 2003), whereas, other studies have reported stronger rebounds to both passive and active self-paced movement than tactile stimulation (Houdayer et al., 2006; Parkkonen et al., 2015). ~20-Hz rhythm modulation to self-paced movement has been explored more extensively, and based on these studies, it can be concluded that the ~20-Hz rebound is quite sensitive to variations in kinematics of the movement. Faster movement, as well as a wider movement range or a larger group of active muscles have been shown to produce stronger (Cassim et al., 2000; Fry et al., 2016; Pfurtscheller et al., 1998). These factors underlie the importance to use well-known or standardized stimuli in forthcoming patient studies. In our study, the tactile and proprioceptive stimuli of the index finger generated clear and relatively well comparable rebounds and suppressions, although the range of the passive movement was rather small. In the present study, the passive movement was carried out by the computer-controlled mechanical device that was easy to control and features (e.g., like timing, duration, and intensity) are constant and adjustable. Based on the results, both stimulus modalities used in the present study are useful and easy to implement in future clinical studies, as patients may not be capable to perform a volitional or complex task. In addition, it is recommended to keep the stimulus as simple as possible as complexity of the movement is shown to reduce the rhythmic activity of the brain (Manganotti et al., 1998). Tactile stimulation can be recommended to be used to modulate the ~20-Hz rhythm, especially in clinical studies. It is easy to implement pneumatically or by simple electrical stimulation of the fingertip (Stancak et al., 2003). However, the electrical stimulation may activate also the pain receptors and potentially cause electromagnetic artefacts.

4.3. Frequency band of ~20-Hz modulation

The frequency band of strongest ~20-Hz modulation differed slightly between participants and stimuli, in line with earlier studies (Houdayer et al., 2006; Laaksonen et al., 2012; Pihko et al., 2014), but was consistent for MEG and EEG data at individual level. The resting state power spectra with eyes open showed mainly two ~20-Hz rhythm components (~13–19 Hz and ~19–27 Hz) over the sensorimotor region, varying in shape and intensity between individuals, as found in previous study (Leppäaho et al., 2019). Our study did not show hemispheric differences in the amplitudes of the β_1 (~13–19 Hz) and β_2 (~19–27 Hz) peaks, similarly to previous studies (Laaksonen et al., 2012; Parkkonen et al., 2015). The selection of the strongest frequency band was not unambiguous for each participant from their power spectra and TFRs. For this reason, we calculated TSE in three different frequency bands and selected the frequency band with the strongest modulation. In most participants, the modulation of ~20-Hz rhythm peaked in 13–23 Hz band for both tactile and proprioceptive stimulation, but 15–25 Hz band was also very common. Earlier studies have shown that there are at least two distinct beta rhythms with different frequencies and functional roles. For example, rebound peaks at a lower frequency band than suppression (Cassim et al., 2000; Feige et al., 1996; Hall et al., 2011; Jurkiewicz et al., 2006; Laaksonen et al., 2012; Pfurtscheller et al., 1997; Szurhaj et al., 2003). This was also evident in or study; the rebound strength increases when the lower (13–23 Hz) frequency band was selected, but it has no effect on the suppression strength.

In addition to possible functional differences, several studies have also shown that the ~20-Hz suppression and rebound have different generator areas in SMI cortex (Bardouille and Bailey, 2019; Jurkiewicz et al., 2006; Pfurtscheller et al., 1997; Salmelin and Hari, 1994; Salmelin et al., 1995). Both suppression and rebound are primarily generated in the SMI cortex, but the peak rebound has been detected more anterior, mainly in the precentral gyrus, than the suppression, that is peaking more posteriorly in the postcentral gyrus (Bardouille and Bailey, 2019; Feige et al., 1996; Fry et al., 2016; Jurkiewicz et al., 2006; Salmelin et al., 1995). In our study, the maximum amplitude of suppression and rebound were often detected in different MEG sensors or EEG electrodes in the respective TSE curves. This was evident especially for MEG. However, the variation was not spatially systematic across the participants.

5. Conclusions

Our results suggest that both MEG and EEG are feasible methods for objective detection of the SMI cortex ~20-Hz modulation. However, the strength of suppression and rebound in the contralateral hemisphere to the stimulated hand was stronger in MEG than in EEG. Based on these results, MEG is recommended to be used in studies evaluating alterations in sensorimotor rhythm, whenever MEG is readily available. Due to its strongest signal-to-noise ratio, MEG may also be more sensitive in detecting changes of ~20-Hz rhythm in longitudinal studies. In addition, patient measurements are often more sensitive to various interfering factors, resulting in higher noise levels in the registration, which further advocates the use of MEG. However, as the correlation between MEG and EEG results were strong, the use of EEG is supported in clinical studies due to its better availability and possibility to bedside measurements of EEG.

This study presented two easy-to-implement stimuli for modulating the ~20-Hz rhythm using either MEG or EEG. Particularly, in patient studies, there is a need to use well-standardized stimulation methods to make the different studies easily comparable.

CRediT statements

Mia Illman: Conceptualization, Investigation, Data curation, Writing- Original draft, Visualization, Methodology, Validation. **Kristina Laaksonen**: Conceptualization, Supervision, Writing - Review & Editing, Methodology. **Mia Liljeström**: Software, Writing - Review & Editing. **Veikko Jousmäki**: Resources, Writing - Review & Editing. **Harri Piitulainen**: Writing - Review & Editing, Conceptualization, Methodology, Funding acquisition, Supervision, Project administration. **Nina Forss:** Funding acquisition, Writing - Review & Editing.

Acknowledgements

Funding: This work was supported by the SalWe Research Program for Mind and Body, Tekes – the Finnish Funding Agency for Technology and Innovation [grant number 1104/10]; Academy of Finland [grant numbers 296240, 307250, 326988, 327288]; Aalto NeuroImaging, Aalto Brain Centre and Jane and Aatos Erkko Foundation.

References

Alegre, M., Labarga, A., Gurtubay, I.G., Iriarte, J., Malanda, A., Artieda, J., 2002. Beta electroencephalograph changes during passive movements: sensory afferences contribute to beta event-related desynchronization in humans. Neurosci. Lett. 331, 29–32.

Antonakakis, M., Schrader, S., Wollbrink, A., Oostenveld, R., Rampp, S., Haueisen, J., Wolters, C.H., 2019. The effect of stimulation type, head modeling, and combined EEG and MEG on the source reconstruction of the somatosensory P20/N20 component. Hum. Brain Mapp. 40, 5011–5028.

Bardouille, T., Bailey, L., CamCAN Group, 2019. Evidence for age-related changes in sensorimotor neuromagnetic responses during cued button pressing in a large open-access dataset. Neuroimage 193, 25–34.

Brookes, M.J., Hall, E.L., Robson, S.E., Price, D., Palaniyappan, L., Liddle, E.B., Liddle, P.F., Robinson, S.E., Morris, P.G., 2015. Complexity measures in magnetoencephalography: measuring "disorder" in schizophrenia. PloS One 10, e0120991.

Cassim, F., Monaca, C., Szurhaj, W., Bourriez, J.L., Defebvre, L., Derambure, P., Guieu, J.D., 2001. Does post-movement beta synchronization reflect an idling motor cortex? Neuroreport 12, 3859–3863.

Cassim, F., Szurhaj, W., Sediri, H., Devos, D., Bourriez, J., Poirot, I., Derambure, P., Defebvre, L., Guieu, J., 2000. Brief and sustained movements: differences in event-related (de)synchronization (ERD/ERS) patterns. Clin. Neurophysiol. 111, 2032–2039.

Chen, R., Yaseen, Z., Cohen, L.G., Hallett, M., 1998. Time course of corticospinal excitability in reaction time and self-paced movements. Ann. Neurol. 44, 317–325.

Cheyne, D., Gaetz, W., Garnero, L., Lachaux, J.P., Ducorps, A., Schwartz, D., Varela, F.J., 2003. Neuromagnetic imaging of cortical oscillations accompanying tactile stimulation. Brain Res. Cogn. Brain Res. 17, 599–611.

Claus, S., Velis, D., Lopes da Silva, F.H., Viergever, M.A., Kalitzin, S., 2012. High frequency spectral components after secobarbital: the contribution of muscular origin–a study with MEG/EEG. Epilepsy Res. 100, 132–141.

Cruccu, G., Aminoff, M.J., Curio, G., Guerit, J.M., Kakigi, R., Mauguiere, F., Rossini, P.M., Treede, R.D., Garcia-Larrea, L., 2008. Recommendations for the clinical use of somatosensory-evoked potentials. Clin. Neurophysiol. 119, 1705–1719.

David, O., Kilner, J.M., Friston, K.J., 2006. Mechanisms of evoked and induced responses in MEG/EEG. Neuroimage 31, 1580–1591.

Degardin, A., Houdayer, E., Bourriez, J.L., Destee, A., Defebvre, L., Derambure, P., Devos, D., 2009. Deficient "sensory" beta synchronization in Parkinson's disease. Clin. Neurophysiol. 120, 636–642.

Feige, B., Kristeva-Feige, R., Rossi, S., Pizzella, V., Rossini, P.M., 1996. Neuromagnetic study of movement-related changes in rhythmic brain activity. Brain Res. 734, 252–260.

Fry, A., Mullinger, K.J., O'Neill, G.C., Barratt, E.L., Morris, P.G., Bauer, M., Folland, J.P., Brookes, M.J., 2016. Modulation of post-movement beta rebound by contraction force and rate of force development. Hum. Brain Mapp. 37, 2493–2511.

Gaetz, W., Cheyne, D., 2006. Localization of sensorimotor cortical rhythms induced by tactile stimulation using spatially filtered MEG. Neuroimage 30, 899–908.

Gaetz, W., Macdonald, M., Cheyne, D., Snead, O.C., 2010. Neuromagnetic imaging of movement-related cortical oscillations in children and adults: age predicts post-movement beta rebound. Neuroimage 51, 792–807.

Gaetz, W., Edgar, J.C., Wang, D.J., Roberts, T.P., 2011. Relating MEG measured motor cortical oscillations to resting gamma-aminobutyric acid (GABA) concentration. Neuroimage 55, 616–621.

Goldenholz, D.M., Ahlfors, S.P., Hämäläinen, M.S., Sharon, D., Ishitobi, M., Vaina, L.M., Stufflebeam, S.M., 2009. Mapping the signal-to-noise-ratios of cortical sources in magnetoencephalography and electroencephalography. Hum. Brain Mapp. 30, 1077–1086.

Gramfort, A., Luessi, M., Larson, E., Engemann, D.A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., Hämäläinen, M., 2013. MEG and EEG data analysis with MNE-python. Front. Neurosci. 7, 267.

Hall, S.D., Stanford, I.M., Yamawaki, N., McAllister, C.J., Ronnqvist, K.C., Woodhall, G.L., Furlong, P.L., 2011. The role of GABAergic modulation in motor function related neuronal network activity. Neuroimage 56, 1506–1510.

Hall, S.D., Prokic, E.J., McAllister, C.J., Ronnqvist, K.C., Williams, A.C., Yamawaki, N., Witton, C., Woodhall, G.L., Stanford, I.M., 2014. GABA-mediated changes in inter-hemispheric beta frequency activity in early-stage Parkinson's disease. Neuroscience 281, 68–76.

Hämäläinen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev. Mod. Phys. 65, 34.

Hari, R., Puce, A., 2017. MEG-EEG Primer. Oxford University Press.

Hari, R., 2011. Magnetoencephalography: methods and applications. In: Schomer, D.L., Lopes da Silva, F.H. (Eds.), Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications and Related Fields, sixth ed. ed. Lippincott Williams & Wilkins, Philadelphia, pp. 865–900.

Hari, R., Forss, N., Avikainen, S., Kirveskari, E., Salenius, S., Rizzolatti, G., 1998. Activation of human primary motor cortex during action observation: a neuromagnetic study. Proc. Natl. Acad. Sci. U.S.A. 95, 15061–15065.

Hillebrand, A., Barnes, G.R., 2002. A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. Neuroimage 16, 638–650.

Hjorth, B., 1975. An on-line transformation of EEG scalp potentials into orthogonal source derivations. Electroencephalogr. Clin. Neurophysiol. 39, 526–530.

Houdayer, E., Labyt, E., Cassim, F., Bourriez, J.L., Derambure, P., 2006. Relationship between event-related beta synchronization and afferent inputs: analysis of finger movement and peripheral nerve stimulations. Clin. Neurophysiol. 117, 628–636.

Hunold, A., Funke, M.E., Eichardt, R., Stenroos, M., Haueisen, J., 2016. EEG and MEG: sensitivity to epileptic spike activity as function of source orientation and depth. Physiol. Meas. 37, 1146–1162.

Jurkiewicz, M.T., Gaetz, W.C., Bostan, A.C., Cheyne, D., 2006. Post-movement beta rebound is generated in motor cortex: evidence from neuromagnetic recordings. Neuroimage 32, 1281–1289.

Laaksonen, K., Kirveskari, E., Mäkelä, J.P., Kaste, M., Mustanoja, S., Nummenmaa, L., Tatlisumak, T., Forss, N., 2012. Effect of afferent input on motor cortex excitability during stroke recovery. Clin. Neurophysiol. 123, 2429–2436.

Leppäaho, E., Renvall, H., Salmela, E., Kere, J., Salmelin, R., Kaski, S., 2019. Discovering heritable modes of MEG spectral power. Hum. Brain Mapp. 40, 1391–1402.

Liddle, E.B., Price, D., Palaniyappan, L., Brookes, M.J., Robson, S.E., Hall, E.L., Morris, P.G., Liddle, P.F., 2016. Abnormal salience signaling in schizophrenia: the role of integrative beta oscillations. Hum. Brain Mapp. 37, 1361–1374.

Manganotti, P., Gerloff, C., Toro, C., Katsuta, H., Sadato, N., Zhuang, P., Leocani, L., Hallett, M., 1998. Task-related coherence and task-related spectral power changes during sequential finger movements. Electroencephalogr. Clin. Neurophysiol. 109, 50–62.

Mary, A., Bourguignon, M., Wens, V., Op de Beeck, M., Leproult, R., De Tiege, X., Peigneux, P., 2015. Aging reduces experience-induced sensorimotor plasticity. A magnetoencephalographic study. Neuroimage 104, 59–68.

McFarland, D.J., McCane, L.M., David, S.V., Wolpaw, J.R., 1997. Spatial filter selection for EEG-based communication. Electroencephalogr. Clin. Neurophysiol. 103, 386–394.

Muller, G.R., Neuper, C., Rupp, R., Keinrath, C., Gerner, H.J., Pfurtscheller, G., 2003. Event-related beta EEG changes during wrist movements induced by functional electrical stimulation of forearm muscles in man. Neurosci. Lett. 340, 143–147.

Neuper, C., Pfurtscheller, G., 2001. Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. Int. J. Psychophysiol. 43, 41–58.

Neuper, C., Scherer, R., Reiner, M., Pfurtscheller, G., 2005. Imagery of motor actions: differential effects of kinesthetic and visual-motor mode of imagery in single-trial EEG. Brain Res. Cogn. Brain Res. 25, 668–677.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Parkkonen, E., Laaksonen, K., Piitulainen, H., Parkkonen, L., Forss, N., 2015. Modulation of the reverse similar20-hz motor-cortex rhythm to passive movement and tactile stimulation. Brain Behav 5, e00328.

Parkkonen, E., Laaksonen, K., Piitulainen, H., Pekkola, J., Parkkonen, L., Tatlisumak, T., Forss, N., 2017. Strength of ~20-hz rebound and motor recovery after stroke. Neurorehabilitation Neural Repair 31, 475–486.

Perneger, T.V., 1998. What's wrong with bonferroni adjustments. BMJ 316, 1236–1238.

Pfurtscheller, G., Neuper, C., 1994. Event-related synchronization of mu rhythm in the EEG over the cortical hand area in man. Neurosci. Lett. 174, 93–96.

Pfurtscheller, G., Lopes da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin. Neurophysiol. 110, 1842–1857.

Pfurtscheller, G., Stancak Jr., A., Neuper, C., 1996a. Post-movement beta synchronization. A correlate of an idling motor area? Electroencephalogr. Clin. Neurophysiol. 98, 281–293.

Pfurtscheller, G., Stancak Jr., A., Neuper, C., 1996b. Event-related synchronization (ERS) in the alpha band–an electrophysiological correlate of cortical idling: a review. Int. J. Psychophysiol. 24, 39–46.

Pfurtscheller, G., Stancak Jr., A., Edlinger, G., 1997. On the existence of different types of central beta rhythms below 30 hz. Electroencephalogr. Clin. Neurophysiol. 102, 316–325.

Pfurtscheller, G., Zalaudek, K., Neuper, C., 1998. Event-related beta synchronization after wrist, finger and thumb movement. Electroencephalogr. Clin. Neurophysiol. 109, 154–160.

Pfurtscheller, G., Krausz, G., Neuper, C., 2001. Mechanical stimulation of the fingertip can induce bursts of beta oscillations in sensorimotor areas. J. Clin. Neurophysiol. 18, 559–564.

Pihko, E., Nevalainen, P., Vaalto, S., Laaksonen, K., Mäenpää, H., Valanne, L., Lauronen, L., 2014. Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: a magnetoencephalographic study. Hum. Brain Mapp. 35, 4105–4117.

Piitulainen, H., Bourguignon, M., Hari, R., Jousmäki, V., 2015a. MEG-compatible pneumatic stimulator to elicit passive finger and toe movements. Neuroimage 112, 310–317.

Piitulainen, H., Bourguignon, M., Smeds, E., De Tiege, X., Jousmäki, V., Hari, R., 2015b. Phasic stabilization of motor output after auditory and visual distractors. Hum. Brain Mapp. 36, 5168–5182.

Robson, S.E., Brookes, M.J., Hall, E.L., Palaniyappan, L., Kumar, J., Skelton, M., Christodoulou, N.G., Qureshi, A., Jan, F., Katshu, M.Z., Liddle, E.B., Liddle, P.F.,

Morris, P.G., 2015. Abnormal visuomotor processing in schizophrenia. Neuroimage Clin 12, 869–878.
Salenius, S., Schnitzler, A., Salmelin, R., Jousmäki, V., Hari, R., 1997. Modulation of human cortical rolandic rhythms during natural sensorimotor tasks. Neuroimage 5, 221–228.
Salmelin, R., Hari, R., 1994. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 60, 537–550.
Salmelin, R., Hämäläinen, M., Kajola, M., Hari, R., 1995. Functional segregation of movement-related rhythmic activity in the human brain. Neuroimage 2, 237–243.
Schnitzler, A., Salenius, S., Salmelin, R., Jousmäki, V., Hari, R., 1997. Involvement of primary motor cortex in motor imagery: a neuromagnetic study. Neuroimage 6, 201–208.
Silen, T., Forss, N., Jensen, O., Hari, R., 2000. Abnormal reactivity of the approximately 20-hz motor cortex rhythm in unverricht lundborg type progressive myoclonus epilepsy. Neuroimage 12, 707–712.
Stancak, A., Svoboda, J., Rachmanova, R., Vrana, J., Kralik, J., Tintera, J., 2003. Desynchronization of cortical rhythms following cutaneous stimulation: effects of stimulus repetition and intensity, and of the size of corpus callosum. Clin. Neurophysiol. 114, 1936–1947.
Szurhaj, W., Derambure, P., Labyt, E., Cassim, F., Bourriez, J.L., Isnard, J., Guieu, J.D., Mauguiere, F., 2003. Basic mechanisms of central rhythms reactivity to preparation and execution of a voluntary movement: a stereoelectroencephalographic study. Clin. Neurophysiol. 114, 107–119.
Tallon-Baudry, C., Bertrand, O., Delpuech, C., Permier, J., 1997a. Oscillatory gamma-band (30-70 hz) activity induced by a visual search task in humans. J. Neurosci. 17, 722–734.
Tallon-Baudry, C., Bertrand, O., Wienbruch, C., Ross, B., Pantev, C., 1997b. Combined EEG and MEG recordings of visual 40 hz responses to illusory triangles in human. Neuroreport 8, 1103–1107.
Taulu, S., M, K., 2005. Presentation of electromagnetic multichannel data: the signal space separation method. J. Appl. Phys. 97 article 124905.
Taulu, S., Simola, J., 2006. Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. Phys. Med. Biol. 51, 1759–1768.
Uusitalo, M.A., Ilmoniemi, R.J., 1997. Signal-space projection method for separating MEG or EEG into components. Med. Biol. Eng. Comput. 35, 135–140.
Whitham, E.M., Pope, K.J., Fitzgibbon, S.P., Lewis, T., Clark, C.R., Loveless, S., Broberg, M., Wallace, A., DeLosAngeles, D., Lillie, P., Hardy, A., Fronsko, R., Pulbrook, A., Willoughby, J.O., 2007. Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 hz are contaminated by EMG. Clin. Neurophysiol. 118, 1877–1888.

II

THE EFFECT OF ALERTNESS AND ATTENTION ON THE MODULATION OF THE BETA RHYTHM TO TACTILE STIMULATION

by

Illman, M., Laaksonen, K., Liljeström, M., Piitulainen, H.,
& Forss N 2021

Physiological Reports, 9(12), e14818

https://doi.org/10.14814/phy2.14818

Received: 3 March 2021 | Accepted: 5 March 2021

DOI: 10.14814/phy2.14818

ORIGINAL ARTICLE

Physiological Reports

The effect of alertness and attention on the modulation of the beta rhythm to tactile stimulation

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Funding information
This work was supported by the SalWe Research Program for Mind and Body, Tekes – the Finnish Funding Agency for Technology and Innovation [grant number 1104/10]; Academy of Finland [grant numbers 296240, 307250, 326988, 327288]; Aalto NeuroImaging, Aalto Brain Centre and Jane and Aatos Erkko Foundation.

Abstract

Beta rhythm modulation has been used as a biomarker to reflect the functional state of the sensorimotor cortex in both healthy subjects and patients. Here, the effect of reduced alertness and active attention to the stimulus on beta rhythm modulation was investigated. Beta rhythm modulation to tactile stimulation of the index finger was recorded simultaneously with MEG and EEG in 23 healthy subjects (mean 23, range 19—35 years). The temporal spectral evolution method was used to obtain the peak amplitudes of beta suppression and rebound in three different conditions (neutral, snooze, and attention). Neither snooze nor attention to the stimulus affected significantly the strength of beta suppression nor rebound, although a decrease in suppression and rebound strength was observed in some subjects with a more pronounced decrease of alertness. The reduction of alertness correlated with the decrease of suppression strength both in MEG (left hemisphere r = 0.49; right hemisphere r = 0.49, $*p < 0.05$) and EEG (left hemisphere r = 0.43; right hemisphere r = 0.72, $**p < 0.01$). The results indicate that primary sensorimotor cortex beta suppression and rebound are not sensitive to slightly reduced alertness nor active attention to the stimulus at a group level. Hence, tactile stimulus-induced beta modulation is a suitable tool for assessing the sensorimotor cortex function at a group level. However, subjects' alertness should be maintained high during recordings to minimize individual variability.

KEYWORDS

beta oscillation, event-related desynchronization, event-related synchronization, vigilance

1 | INTRODUCTION

The sensorimotor beta rhythm is mainly generated in the primary sensorimotor (SMI) cortex (Bardouille et al., 2019; Cheyne et al., 2003; Gaetz & Cheyne, 2006; Jurkiewicz et al., 2006), and it is known to be modulated by tactile (Cheyne et al., 2003; Gaetz & Cheyne, 2006; Illman et al., 2020; Parkkonen et al., 2015), electrical (Houdayer et al., 2006; Salenius et al., 1997; Salmelin & Hari, 1994), and proprioceptive stimulation (i.e., passive movement; Alegre et al., 2002; Illman et al., 2020; Parkkonen et al., 2015), as well as active movement (Cassim et al., 2000; Feige et al., 1996; Fry et al., 2016), action observation (Hari et al., 1998), or imagining motor action (Hari et al., 1998; Pfurtscheller et al., 2006; Schnitzler et al., 1997), and even by brief auditory or visual stimuli (Piitulainen et al., 2015). These stimuli and

tasks, induce a rapid reduction (suppression or event-related desynchronization, ERD) which is followed by a more delayed increase (rebound or event-related synchronization, ERS) in the strength of rhythmic oscillations with respect to the baseline level (Pfurtscheller, 2001). It has been suggested that the suppression reflects cortical activation of the SMI cortex related to sensory afference and/or, movement preparation or initiation (Neuper et al., 2006; Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999; Pfurtscheller et al., 1996). The rebound is thought to be associated with reduced excitability or active inhibition of the SMI cortex (Cassim et al., 2001; Chen et al., 1998; Engel & Fries, 2010; Gaetz et al., 2011; Pfurtscheller et al., 1996; Salmelin et al., 1995).

The beta rebound has been proposed to reflect the functional state of the SMI cortex in various neurological diseases such as stroke (Laaksonen et al., 2012; Parkkonen et al., 2017; Tang et al., 2020), schizophrenia (Brookes et al., 2015; Liddle et al., 2016), Parkinson's disease (Degardin et al., 2009; Hall et al., 2014; Vinding et al., 2019), and cerebral palsy (Demas et al., 2019; Pihko et al., 2014). However, patients are prone to changes in their alertness during MEG/EEG recordings, which may alter the oscillatory activity, and thus potentially affect the estimated cortical level of excitability. Alertness may easily decrease during MEG/EEG recordings in healthy individuals, and even more so in patients, for example, in acute stroke patients and patients suffering from cognitive disorders. In this study, we simulated clinical MEG and EEG measurement protocols to quantify the effect of alertness and active attention to the stimuli on the level of SMI beta rhythm modulation in healthy subjects. This new information is important for all future clinical and basic research studies that attempt to utilize the beta rhythm modulation to assess the SMI cortex function.

2 | METHODS

2.1 | Subjects

Twenty-three healthy subjects (12 females, age 19–35, mean 23 ± 4 yrs) participated in the experiment. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971).

The study was approved by the local ethics committee of Aalto University in accordance with the Declaration of Helsinki. Prior to the study, all participants signed written informed consent.

2.2 | Stimuli and experimental design

Cerebral signals were recorded during three conditions to examine how the level of vigilance affects SMI cortex beta rhythm modulation. The conditions were selected from a practical point of view, as some patients may not be able to follow instructions during the MEG or EEG recordings. In the *neutral* condition, participants were fixating on a picture in front of them (size 12 × 15 cm, a distance of 2.2 m). The participants were instructed not to pay attention to the stimuli, and to think whatever comes into their mind. In the *attention* condition, the participants were fixating at the same picture as in the neutral condition, counting quietly in their mind the total number of the received tactile stimuli. The number of received stimuli was asked immediately after the attention task to ensure the subjects' focus on the stimuli. During the *snooze* condition, the participants kept their eyes closed, without paying attention to the stimuli, and were allowed to fall asleep. The duration of all conditions was about nine to ten minutes and the conditions were measured in randomized order.

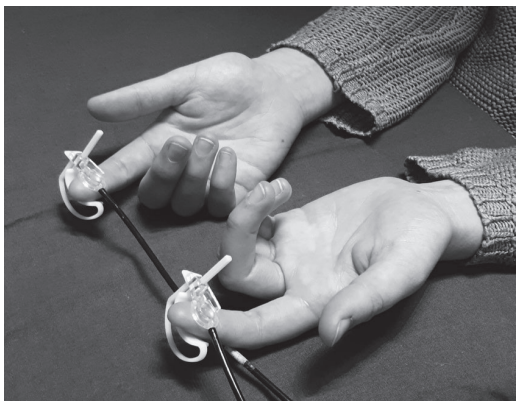

FIGURE 1 Tactile stimulus setup for beta rhythm modulation

Modulation of beta rhythm was induced by tactile stimuli that were delivered alternately to both index fingertips with an interstimulus interval (ISI) of 6 s for a given finger (3 s between right and left side stimulation). The stimuli were mechanically induced by pneumatic diaphragms driven by compressed air. The duration of the stimulus was 180 ms, peaking at 40 ms. During the stimulation periods, the participants held their hands relaxed on a pillow (Figure 1). Earplugs were used throughout the measurements to prevent possible stimulus-induced noise artifacts.

2.3 | Data acquisition

The simultaneous MEG and EEG measurements were carried out in a magnetically shielded room (Imedco AG, Hägendorf, Switzerland), with a 306-channel (204 planar gradiometers, 102 magnetometers) whole-head MEG system (Vectorview, Elekta Oy, Helsinki, Finland) at the MEG Core, Aalto NeuroImaging, Aalto University. Scalp EEG was recorded simultaneously with a MEG-compatible

60-channel EEG-cap (ANT Neuro waveguard™original), where the Ag-AgCl surface electrodes were placed according to the international 10–20 system. During the measurements, the participants were seated comfortably with their heads in the helmet-shaped MEG sensor array. Prior to the measurement, five indicator coils were attached to the EEG-cap (three to the forehead and two above the ears) to define the subject's head position with respect to the MEG sensors. The location of the indicator coils, anatomical landmarks (left and right preauricular points and nasion), and 100–200 additional points from the scalp surface, were determined with a 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA). At the beginning of each measurement session, the head position inside the MEG helmet was measured with respect to the sensor array, and continuous head position tracking was monitored throughout the whole measurement. Eye movements were recorded with two vertical electrooculogram electrodes (EOG).

All data were recorded at a sampling frequency of 1000 Hz, and the MEG and EEG signals were band-pass filtered to 0.1–330 Hz. The impedance of the EEG electrodes was verified to be below 5 kΩ prior to the recordings.

2.4 | MEG and EEG signal processing

2.4.1 | Preprocessing

To improve the comparability of the different measurement conditions, MEG raw signals were transformed to the same average head-coordinate system within each subject. The data was preprocessed off-line using the temporal signal-space-separation method (tSSS) with head movement compensation (Taulu & Kajola, 2005; Taulu & Simola, 2006) implemented in the MaxFilter software (v2.2; Elekta Oy, Helsinki, Finland).

Further analyses of MEG and EEG data were done using MNE python 0.17 (Gramfort et al., 2013). The original EEG data (unipolar referential AFz) was re-referenced with a common average reference overall electrodes (excluding bad channels). The average reference was chosen because our previous study indicated that this approach produced the highest signal-to-noise ratio and thus the strongest beta rhythm modulation (Illman et al., 2020). Artifacts related to eye blinks (two magnetometer and two gradiometer components) were removed with principal component analysis (PCA; Uusitalo & Ilmoniemi, 1997).

2.4.2 | Spectral analysis

Power spectral density (PSD) was calculated to observe changes in rhythmic brain oscillations at theta (4–7 Hz), alpha (8–12 Hz), and beta (13–25 Hz) frequencies during the different conditions. However, these PSDs do not represent spontaneous rhythmic brain oscillations, as they are affected by tactile stimulation. PSDs were computed for the neutral, attention, and snooze conditions by using the Welch method, with a sliding 2048-point fast Fourier transform (FFT) with a non-overlapping Hanning window. The peak power of theta, alpha, and beta frequencies was determined from the PSDs over the right and left SMI cortex and occipital area.

2.4.3 | Beta rhythm modulation

Time-frequency representations (TFRs) were calculated to visualize changes in rhythmic activity in the three different conditions. TFRs for each subject were computed using a Morlet wavelet transformation in the frequency range of 2–40 Hz for a time window from –700 to 3200 ms with respect to stimulus onset (Tallon-Baudry et al., 1997). Using wavelets, spectral and temporal resolution at different frequencies can be balanced by scaling the number of cycles by frequency. For this purpose, we set the number of cycles to f/2.

The strength of SMI cortex beta rhythm modulation was determined by computing the temporal spectral evolution (TSE) with respect to the onset of the tactile stimulus (Engemann & Gramfort, 2015; Hari & Salmelin, 1997). First, the pre-processed raw data was bandpass filtered to 13–25 Hz. This 12-Hz wide frequency band was chosen as our previous study (Illman et al., 2020) showed that individually selected 10 Hz frequency bands between 13 and 25 Hz (13–23 or 15–25 Hz) capture the strongest beta rhythm modulation. However, comparing individually selected frequency bands with common 13–25 Hz frequency band (capturing both the lower (β1) and higher (β2) beta bands) resulted in similar beta modulation curves. Therefore, we used in the present study the 13–25 Hz beta band for all the subjects, as standardized parameters particularly important in future clinical use. After filtering, interfering somatosensory evoked responses were subtracted from the raw data (David et al., 2006). A Hilbert transform was applied to the data to obtain the envelope signal, and the data were averaged with respect to stimulus onset. TSE curves were calculated from –500 to 3000 ms with respect to stimulus onset. The peak latencies and amplitudes of beta suppression and rebound were determined from the most representative MEG and EEG channels over the left and right SMI cortices. One or two channels with the strongest modulation were selected from both hemispheres (two channels were selected if the strongest suppression and rebound were seen over the different channels). Relative peak values (in %) of suppression (negative peak) and rebound (positive peak) were calculated with respect to the pre-stimulus baseline (–500 to –100 ms).

2.5 | Evaluation of alertness

2.5.1 | Questionnaire

The participants were asked to complete a questionnaire right after the MEG-EEG measurement, to determine their overall alertness throughout the study. In the questionnaire, the participants evaluated their alertness subjectively during the three different conditions on a seven-step Likert scale; 0 = Fell asleep, 1 = Fully tired, 2 = Moderately tired, 3 = Slightly tired, 4 = Slightly alert, 5 = Moderately alert, 6 = Fully alert.

2.5.2 | Sleep stage scoring

As the main purpose of the study was to clarify the effect of alertness on the modulation of the beta rhythm, the stage of alertness during the snooze condition was explored further. Sleep stages in the snooze condition were scored according to the AASM manual (American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events; Berry et al., 2012). The sleep stage was estimated from channels of the central, occipital and frontal regions, throughout the snooze condition in 30 s epochs. EOG channels were included in the sleep stage evaluation. Only Stage W, Stage N1, and Stage N2 were observed due to the short recording time. Stage W represents alert wakefulness to drowsiness (>50% of alpha rhythm and visible eye blinks), Stage N1 indicates sleep onset (vertex sharp waves, >50% of low voltage mixed frequency (LVMF) and slow eye movements), and Stage N2 light sleep (LVMF and K-complexes or sleep spindles). Results are expressed in percentage with respect to the total snooze condition.

2.6 | Statistical analysis

The non-parametric Wilcoxon test was used to test differences in subjects' self-assessment of alertness between the neutral, attention, and snooze conditions. Normal distribution of relative peak values of beta suppression and rebound, and spectral peak amplitudes and frequencies, were tested with the Shapiro–Wilk test (IBM SPSS Statistics 26), resulting in a non-normal distribution of the data. Statistical differences of suppression and rebound between the three different conditions were tested with the nonparametric Wilcoxon signed-rank test. Spectral amplitudes of alpha, beta, and theta amplitudes were strongly skewed, and therefore the amplitudes were transformed logarithmically before the t-test. In contrast, the nonparametric Wilcoxon signed-rank test was used to test the frequencies, since the logarithmic correction had a minor effect on the normality of the data.

Correlation between the state of alertness (%) and the change in beta suppression/rebound strength in the neutral versus snooze conditions was tested with Spearman's correlation coefficient. The percentage decrease in alertness in the snooze condition was determined by summing the sleep stages N1 and N2 (weighting N2 by two).

A p-value <0.05 was considered statistically significant in all tests. Bonferroni correction was used to correct the effect of multiple tests.

3 | RESULTS

The measurements were performed successfully for all subjects and the quality of the obtained MEG and EEG data was good, despite a few poorly functioning MEG (2 channels) and EEG (1–3 channels) channels. In the attention condition, the subjects were highly focused on the stimuli, and all of them responded correctly to the number of stimuli at the end of the attention task. Most subjects (21 out of 23) had previous experience in participating in a MEG study, hence it was easy for them to relax in the snooze condition. For the TSE analysis, 95 ± 2 (mean ± SEM) averaged events were obtained in the neutral, 94 ± 1 in the attention, and 95 ± 1 in the snooze condition.

3.1 | Level of alertness

Questionnaire. According to the questionnaire, the participants felt clearly more tired (mean ± SD) in the snooze condition (1.6 ± 0.4) compared with the neutral (3.7 ± 0.3, $p < 0.01$), and attention condition (3.8 ± 0.4, $p < 0.01$); see Figure 2a.

Sleep stage scores. Figure 2b presents the subjects' sleeping stages during the snooze condition. Due to the short measurement session, only three different stages of sleep were observed: Stage W, Stage N1, and Stage N2. On average, the subjects were in the a*wake stage* 70 ± 7%, *sleep stage N1* 26 ± 6%, and *sleep stage N2* 4 ± 2% of the total time of the snooze condition.

3.2 | Peak power of theta, alpha, and beta frequencies during the different conditions

Figure 2c illustrates grand averaged (n = 23) power spectra over left and right SMI and occipital areas in the three conditions both in MEG and EEG. The peak power differed between the conditions in the theta and alpha frequencies, but not in the beta frequency band. The peak power over

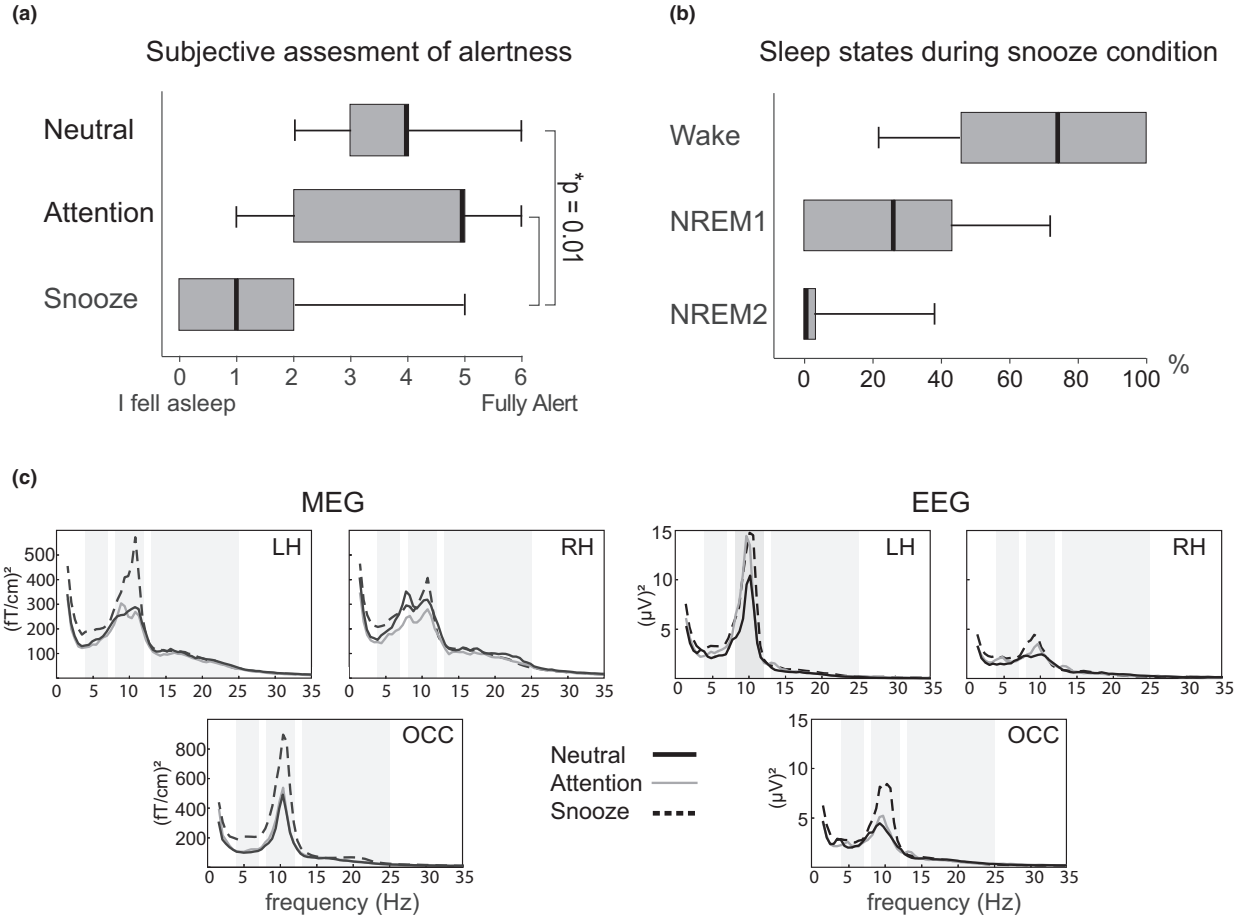

FIGURE 2 Assessment of participants' alertness during the different conditions. (a) Participants' subjective assessment of the alertness in the Neutral, Attention and Snooze conditions based on a questionnaire (Likert scale: 0 = I fell asleep, 1 = Fully tired, 2 = Moderately tired, 3 = Slightly tired, 4 = Slightly Alert, 5 = Moderately alert, 6 = Fully alert). (b) Sleep stage scores (in %) during the snooze condition according to the AASM manual (American Academy of Sleep Medicine Manual for Scoring of Sleep and Associated Events) based on the EEG recordings. (c) Grand averaged (n = 23) power spectra over left (LH) and right (RH) sensorimotor and occipital (OCC) areas during the Neutral, Attention, and Snooze conditions. The spectra have been calculated over the entire condition, including the changes of rhythmic activity caused by tactile stimulation

the occipital area was significantly stronger in the snooze vs. neutral conditions both in *the alpha* (MEG 1572 ± 266 vs. 659 ± 134 $(fT/cm)^2$, $^{**}p < 0.01$; EEG 32.6 ± 0.6 vs. 15.1 ± 3.4 $(\mu V)^2$, $^{*}p < 0.05$), and *theta frequency* band (MEG 238 ± 24 vs. 121 ± 16 $(fT/cm)^2$, $^{***}p < 0.001$, EEG 3.9 ± 0.6 vs. 2.7 ± 0.6 $(\mu V)^2$, $^{**}p < 0.01$). The frequency of the peak power within the theta, alpha, and beta bands did not differ significantly between the conditions. Table 1 represents the peak power and frequency for each band and condition.

3.3 | Modulation of the beta rhythm

The modulation of the beta rhythm followed a similar pattern in all conditions both in MEG and EEG. An initial suppression of the beta rhythm peaked at around 300 ms after tactile stimulation, followed by a rebound at around 700–800 ms (Figure 3b). Beta rhythm suppression and rebound to tactile finger stimulation were observed bilaterally in sensors over the SMI cortices both in MEG and EEG. Suppression and rebound latencies did not differ significantly between the conditions (Table 2). As expected, the responses were clearly stronger in the contralateral hemisphere with respect to the stimulated hand, and therefore, the following results are provided only for the contralateral responses.

3.3.1 | Time-frequency representation

Figure 3a illustrates the grand average (n = 23) strength and temporal behavior of the beta rhythm with respect to

TABLE 1 Peak power and its frequency (mean ±SEM) for theta (4–7 Hz), alpha (8–12 Hz), and beta (14–25 Hz) bands during neutral, attention, and snooze conditions. The alpha frequency was determined for left and right sensorimotor (SMI) and occipital (OCC) areas, beta for left and right SMI areas, and theta for OCC area

	Theta		Alpha		Beta	
	OCC	Left SMI	Right SMI	OCC	Left SMI	Right SMI
MEG						
Peak frequency (Hz)						
Neutral condition	5.3 ± 0.1	10.3 ± 0.3	9.9 ± 0.3	10.2 ± 0.1	18.5 ± 0.6	18.0 ± 0.6
Attention condition	5.1 ± 0.2	10.3 ± 0.3	9.8 ± 0.3	10.0 ± 0.2	18.5 ± 0.7	18.1 ± 0.6
Snooze condition	5.4 ± 0.1	9.9 ± 0.3	9.7 ± 0.3	10.2 ± 0.2	17.9 ± 0.6	17.3 ± 0.5
Power $(fT/cm)^2$						
Neutral condition	121 ± 16	496 ± 93	393 ± 60	659 ± 134	148 ± 31	138 ± 35
Attention condition	140 ± 20	397 ± 71	368 ± 66	828 ± 197	130 ± 30	119 ± 24
Snooze condition	238 ± 24	531 ± 71	531 ± 78	1572 ± 266	141 ± 30	128 ± 20
EEG						
Peak frequency (Hz)						
Neutral condition	5.2 ± 0.2	9.8 ± 0.3	9.8 ± 0.3	10.1 ± 0.2	17.2 ± 0.4	17.7 ± 0.5
Attention condition	5.2 ± 0.2	10.0 ± 0.3	9.9 ± 0.3	9.9 ± 0.2	17.5 ± 0.5	16.8 ± 0.5
Snooze condition	5.1 ± 0.2	10.0 ± 0.3	9.6 ± 0.2	10.0 ± 0.2	17.8 ± 0.6	17.5 ± 0.6
Power $(\mu V)^2$						
Neutral condition	2.7 ± 0.6	6.0 ± 1.3	6.1 ± 1.4	15.1 ± 3.4	1.0 ± 0.2	1.1 ± 0.2
Attention condition	2.9 ± 0.6	6.5 ± 1.8	6.7 ± 1.9	22.6 ± 5.5	0.9 ± 0.2	1.1 ± 0.2
Snooze condition	3.9 ± 0.6	8.1 ± 1.8	8.6 ± 1.8	32.6 ± 6.0	1.1 ± 0.3	1.3 ± 0.3

stimulus onset in all three different conditions. Both in MEG and EEG, the temporal behavior of the beta suppression and rebound was similar in all three conditions. However, the strengths of suppression and rebound appear slightly diminished in the snooze compared to the attention and neutral conditions, especially in MEG. In the attention condition, the rebound appeared somewhat prolonged compared to the neutral and snooze conditions, especially in the left hemisphere.

3.3.2 | Beta rhythm modulation

Figure 3b illustrates the grand average (n = 23) TSE curves over the contralateral SMI cortex with respect to the stimulated hand during the neutral, attention, and snooze conditions. Figure 3c shows that the contralateral relative peak strengths of beta suppression and rebound did not differ significantly between the conditions. In MEG, the rebound appeared to be lower in the snooze condition compared to the neutral condition (34 ± 5 vs. 44 ± 7 in the left and 50 ± 7 vs. 59 ± 8 right hemisphere), although the difference was not significant. Table 2 shows the mean strengths of the beta rhythm modulation.

Figure 4 shows the individual relative peak strengths of suppression and rebound for all subjects. The subjects were divided into two groups "Alertness unchanged" and "Alertness decreased", indicating a pronounced reduction of the suppression and rebound in the snooze condition in the subjects with decreased alertness (n = 8) compared to subjects whose alertness did not change remarkably. However, the individual variation between different situations is worthy to note. Furthermore, Figure 5 illustrates the correlations between the level of alertness during the snooze condition and the change in suppression and rebound strength between the neutral and snooze conditions. Reduced alertness correlated significantly with the reduction of suppression strength in the right hemisphere in all subjects both in MEG r = 0.49, $*p < 0.05$ and EEG right hemisphere r = 0.72, $**p < 0.01$, hence, the larger the change in alertness the stronger the reduction in suppression strength. In contrast, no correlations between changes in alertness and changes in rebound strengths were observed.

3.3.3 | Baseline beta power

Table 3 shows mean (± SEM) baseline beta power values from –500 to –100 ms during the neutral, attention, and snooze

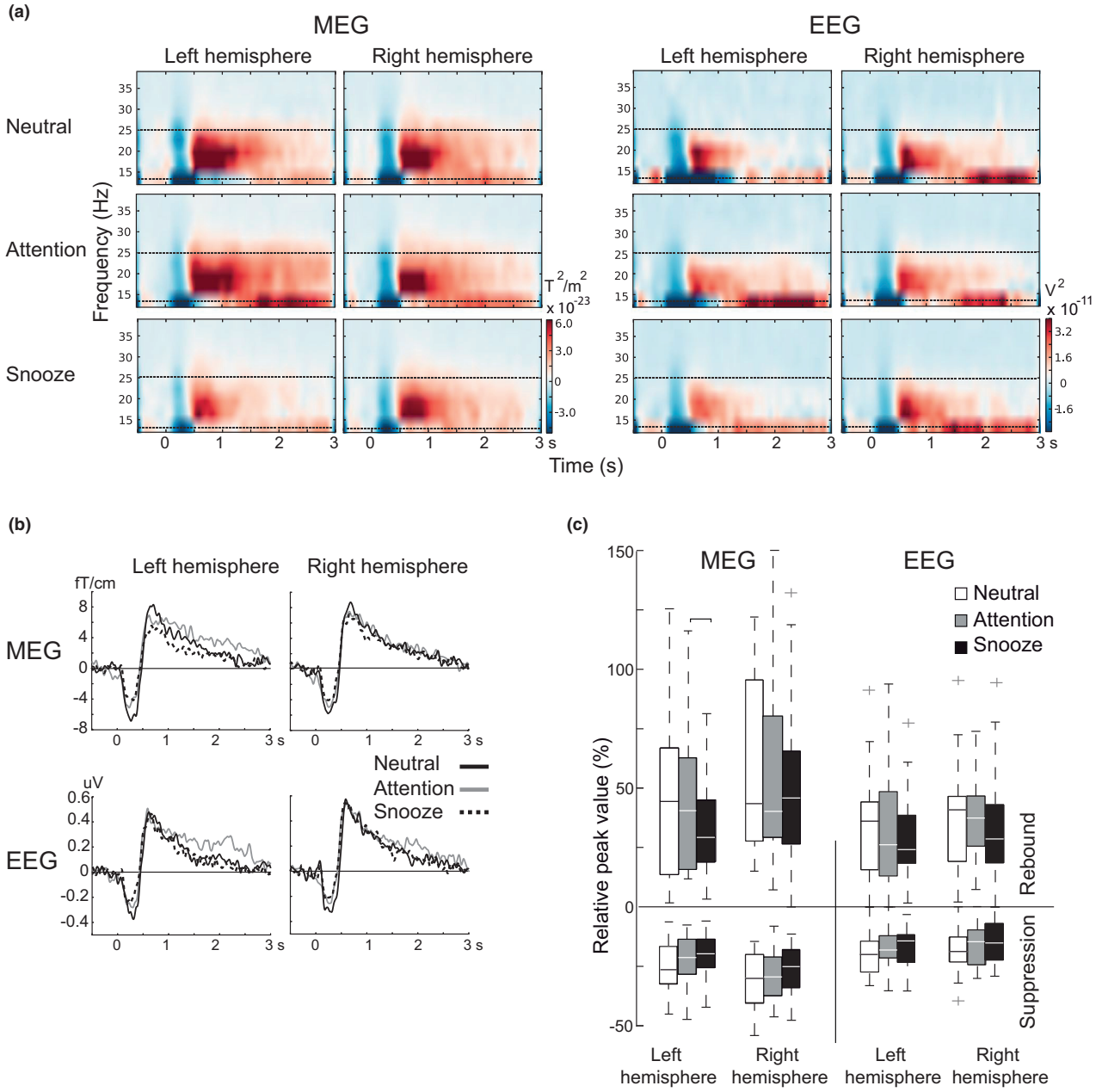

FIGURE 3 Modulation of beta rhythm during the Neutral, Attention, and Snooze conditions. (a) Grand averaged (n = 23) TFR images, and (b) TSE curves of the contralateral responses with respect to tactile stimulation in MEG and EEG. Zero point indicates the start of the stimulus. (c) Relative peak amplitudes (%) of beta suppression and rebound to tactile stimulation in the Neutral, Attention, and Snooze condition. The figure illustrates the responses of the contralateral hemisphere to the stimulated hand. 50% of the data points are inside the grey boxes and the white horizontal lines inside the boxes indicate the median values of beta suppression and rebound. Outliers of the data are shown by crosses

conditions. The baseline beta power remains stable between different conditions, with exception of the left hemisphere in MEG, which showed a significant difference between the neutral and attention conditions ($p = 0.02$). Figure 6 illustrates all subjects' individual baseline changes in different conditions. The subjects are further divided into the "Alertness unchanged" and "Alertness decreased" groups, showing that baseline changes are larger in the "Alertness decreased" group in MEG.

As the baseline values showed some differences between the conditions, the beta suppression and rebound strengths were analyzed from absolute values (Table 2). In line with the results obtained from the analysis of relative peak strengths, the absolute suppression and rebound strengths did not show significant differences between the conditions.

In summary, at the group level, the strength of suppression and rebound did not differ between the three conditions.

TABLE 2 Beta rhythm modulation strengths (relative to baseline) and latencies (mean ±SEM) in three different conditions for contra (CH) and ipsilateral (IH) hemispheres.

	Right stimulation				Left stimulation			
	MEG CH	EEG CH	MEG IH	EEG IH	MEG IH	EEG IH	MEG CH	EEG CH
Rebound								
Neutral								
Relative amplitude (%)	44 ± 7	35 ± 4	24 ± 4	16 ± 3	27 ± 4	23 ± 3	59 ± 8	37 ± 5
Peak latency (ms)	740 ± 33	759 ± 47	790 ± 38	773 ± 46	793 ± 37	728 ± 36	714 ± 30	667 ± 38
Absolute amplitude[a]	16.3 ± 4	0.89 ± 0.1					15.8 ± 3	0.91 ± 0.1
Attention								
Relative amplitude (%)	45 ± 7	33 ± 6	23 ± 4	16 ± 3	20 ± 4	18 ± 3	57 ± 8	39 ± 4
Peak latency (ms)	829 ± 48	761 ± 44	812 ± 46	808 ± 48	793 ± 47	737 ± 43	702 ± 32	682 ± 32
Absolute amplitude[a]	15.1 ± 3	0.79 ± 0.1					15.2 ± 3	0.90 ± 0.1
Snooze								
Relative amplitude (%)	34 ± 5	30 ± 4	24 ± 4	19 ± 3	22 ± 3	22 ± 3	50 ± 7	35 ± 4
Peak latency (ms)	773 ± 41	711 ± 41	729 ± 33	729 ± 38	801 ± 44	700 ± 28	703 ± 32	656 ± 26
Absolute amplitude[a]	10.7 ± 2	0.72 ± 0.1					13.4 ± 2	0.86 ± 0.1
Suppression								
Neutral								
Relative amplitude (%)	–25 ± 2	–20 ± 2	–25 ± 2	–19 ± 2	–19 ± 2	–16 ± 2	–31 ± 2	–18 ± 2
Peak latency (ms)	298 ± 15	326 ± 20	320 ± 13	327 ± 21	343 ± 26	321 ± 17	293 ± 20	288 ± 19
Absolute amplitude[a]	–10.4 ± 2	–0.58 ± 0.1					–9.6 ± 2	–0.51 ± 0.1
Attention								
Relative amplitude (%)	–22 ± 2	–17 ± 2	–23 ± 2	–17 ± 1	–20 ± 2	–16 ± 2	–29 ± 2	–17 ± 2
Peak latency (ms)	269 ± 20	266 ± 19	314 ± 20	302 ± 20	318 ± 19	275 ± 26	255 ± 22	272 ± 19
Absolute amplitude[a]	–7.9 ± 1	–0.47 ± 0.1					–8.7 ± 2	–0.46 ± 0.1
Snooze								
Relative amplitude (%)	–20 ± 2	–17 ± 2	–21 ± 2	–13 ± 2	–15 ± 2	–12 ± 1	–26 ± 2	–15 ± 2
Peak latency (ms)	235 ± 17	270 ± 21	275 ± 17	313 ± 24	300 ± 22	329 ± 20	250 ± 18	275 ± 218
Absolute amplitude[a]	–6.3 ± 1	–0.43 ± 0.1					–7.5 ± 1	–0.38 ± 0.1

[a]MEG, fT/cm; EEG, uV.

However, there was a weak correlation between reductions in alertness and beta suppression strength.

4 | DISCUSSION

To our knowledge, this is the first study investigating the effect of change in alertness on beta rhythm modulation. At the group level, reduced alertness or active attention to the received tactile somatosensory stimulus did not significantly affect the SMI beta rhythm modulation. However, in some subjects with a pronounced reduction in alertness, a remarkable decrease of suppression and rebound strength was observed. Moreover, reduced alertness correlated with changes in suppression strength, indicating that at the individual level changes in alertness may affect the strength of rhythmic modulation. This is an important topic especially as the beta modulation has been proposed to serve as a biomarker of the functional state of the SMI cortex in several neurological conditions, where the alertness may often be reduced.

4.1 | Power spectra

Spontaneous rhythmic brain activity changes remarkably between stages of alertness and from a sleep stage to another. Spontaneous alpha and beta rhythms are predominant during wakefulness. When a person enters into a light sleep, the alpha rhythm is reduced, while slower rhythmic activity (theta 4–7 Hz and delta 1–4 Hz) enhances (Broughton & Hasan, 1995), predominantly in the frontal cortex (Marzano

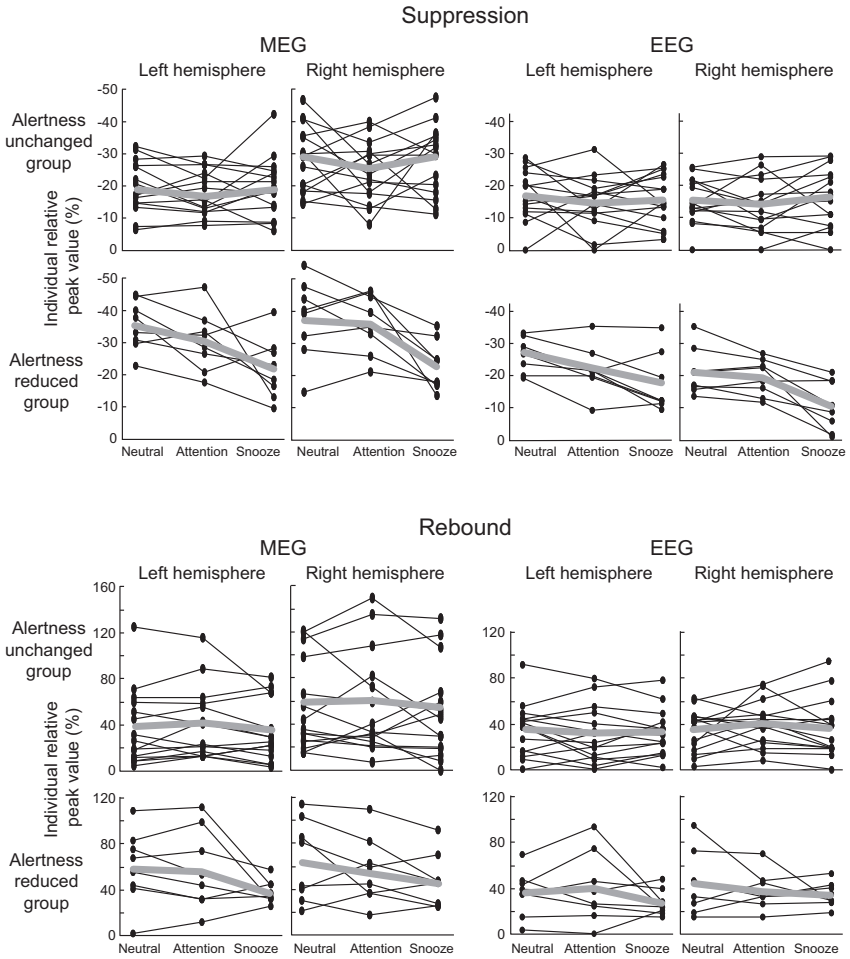

FIGURE 4 Individual relative peak strengths of the beta suppressions and rebounds for all subjects in the Neutral, Attention, and Snooze conditions. Subjects are divided into two categories; "Alertness reduced" (n = 8) and "Alertness unchanged" group (n = 15), based on sleep state scores and alertness self-assessment in the snooze condition. Subjects with more than 35% of sleep stages N1 and N2 and who also reported falling asleep during the snooze condition according to self-assessment, were included in the "Alertness reduced" group

et al., 2013). Our observed increase in theta rhythm strength in the snooze condition confirms that our results are reflecting well the effect of reduced alertness on rhythmic brain activity. In contrast, the increased alpha rhythm during the snooze condition is most likely due to the well-known effect of eyes closure at the beginning of the snooze condition before falling asleep. MEG measurements in a quiet environment of the magnetically shielded room may cause the experience of boredom, sustained attention, or even mental fatigue, which can affect a variety of brain rhythms (Lal & Craig, 2001; Langner & Eickhoff, 2013; Shigihara et al., 2013; Tanaka et al., 2012, 2014). Low vigilance has been described to reduce the power of spontaneous beta oscillations in the SMI cortex (Belyavin & Wright, 1987), but such changes in the beta rhythm were not observed in the current study. However, in the present study, the actual spontaneous data were not recorded as the data was contaminated with the tactile stimuli.

Natural inter-individual variation of beta rhythm peak frequency and strength is expansive, and heritability regulated (Salmelin & Hari, 1994; Smit et al., 2005). The circadian regulation has an effect on the spontaneous beta power, which has been described to be weakest in the morning and increasing towards the afternoon (Cacot et al., 1995; Toth et al., 2007). Such circadian changes have also been described to have an effect on the modulation of the beta power, primarily on the beta suppression (Wilson et al., 2014). To control for circadian changes in rhythmic activity, in the present study, the measurements were recorded between 11 am and 5 pm, a time span, where the rhythm is supposed to be strongest.

4.2 | Effects of alertness on the modulation of the SMI beta rhythm

At the group level, reduced alertness did not significantly affect the strength of SMI beta rhythm modulation. Although reductions in suppression and rebound strengths were observed in some subjects with markedly reduced alertness, changes in the opposite directions were also observed, and thus the changes were not consistent across the examined subjects. Inter-individual variation in the level of alertness may have had an effect on the large variability of the results. Furthermore, the eyes closure in the snooze condition may have affected the results. However, an earlier study indicated that eye closure alone does not alter the strength of beta rhythm modulation (Rimbert

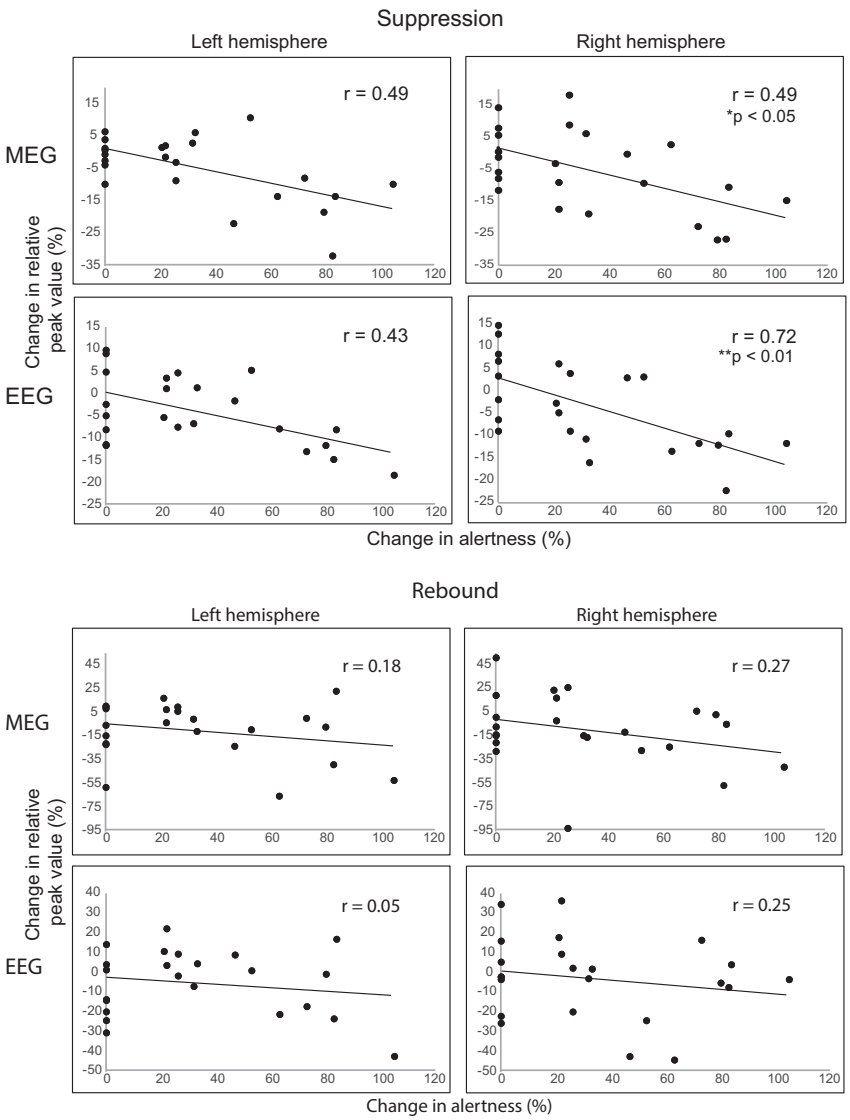

FIGURE 5 Correlations between the level of alertness in the snooze condition and changes in the strength of beta suppression and rebound between the neutral and snooze condition. The change in alertness is described by the percentage of summed sleep stages N1 and N2 (N2 weighted by two)

MEG (fT/cm)	LH	RH	EEG (μV)	LH	RH
Neutral	37.7 ± 3	29.2 ± 3	Neutral	2.6 ± 0.3	2.4 ± 0.3
Attention	33.8 ± 3*	28.9 ± 3	Attention	2.5 ± 0.3	2.4 ± 0.3
Snooze	31.9 ± 3	28.0 ± 2	Snooze	2.4 ± 0.2	2.4 ± 0.2

*$p < 0.05$.

TABLE 3 Baseline (–500 to −100 ms) beta power values (mean ±SEM) from TSE curves over left (LH) and right (RH) sensorimotor cortex during the neutral, attention, and snooze conditions in MEG and EEG

et al., 2018). The correlation analysis between changes in alertness and changes in beta modulation indicated that decreased alertness affected mainly the strength of beta suppression but not rebound. This is an interesting finding as, in contrast, the beta rebound has previously shown to be more sensitive to changes in stimulus modality (such as tactile vs. electrical stimulus or speed and range of movement Cassim et al., 2000; Fry et al., 2016; Houdayer et al., 2006; Parkkonen et al., 2015; Pfurtscheller et al., 1998; Salenius et al., 1997; Salmelin & Hari, 1994) than the suppression. The suppression and rebound are thought to arise from separate neuronal populations, and to have distinct functional roles (Cassim et al., 2000; Chen et al., 1998; Hall et al., 2011; Jurkiewicz et al., 2006; Salmelin et al., 1995). The current study is in line with these earlier findings as the suppression and rebound appeared to respond to changes in alertness in distinct ways.

Based on the results, decreased alertness does not significantly affect the strength of beta modulation, especially the beta rebound, at the group level. These findings support the reliability of group-level findings of changes in beta suppression/

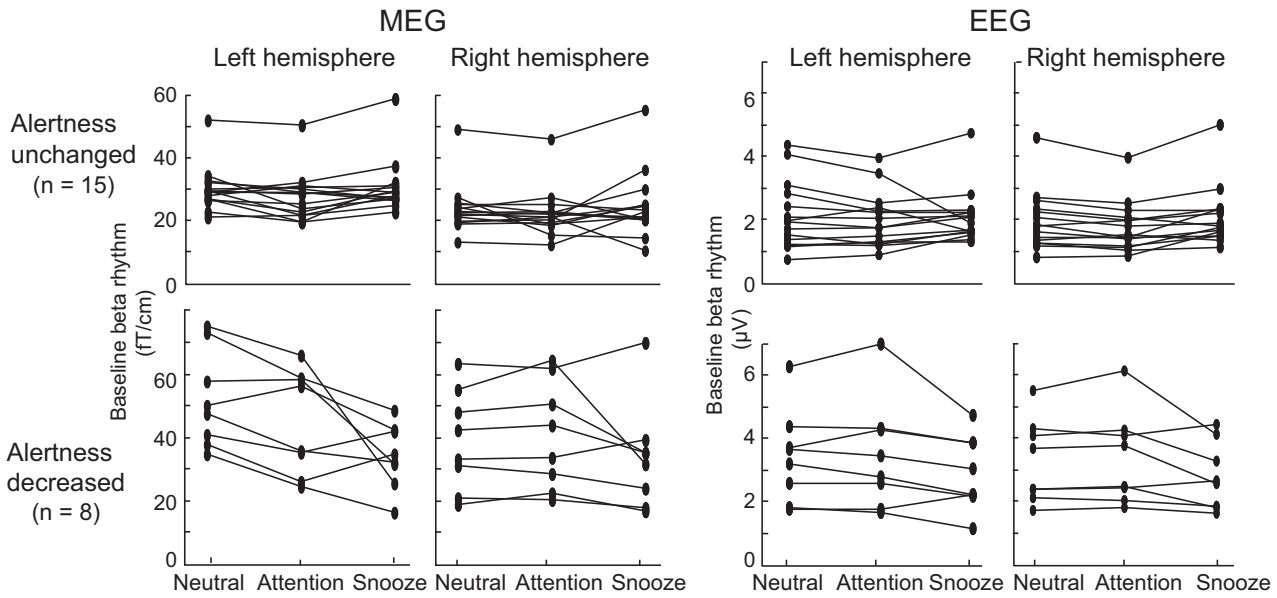

FIGURE 6 Baseline beta power in TSE for all subjects during the Neutral, Attention, and Snooze conditions. Subjects in the "Alertness reduced" group had over 35% of sleep stages N1 and N2 and they also reported to fall asleep according to self-assessment during the snooze condition

rebound, that is, in different clinical conditions. Especially the minimal effect of reduced alertness on the strength of beta rebound is important, as the beta rebound has been suggested as a biomarker of the functional state of the SMI cortex after stroke (Laaksonen et al., 2012; Parkkonen et al., 2017, 2018; Tang et al., 2020). However, at the individual level, alterations in alertness may affect beta rhythm modulation, especially beta suppression, which should be taken into account in longitudinal experiments to avoid misinterpretations.

In the present study, the level of alertness was assessed in three different ways, which all confirmed a decrease in alertness in the snooze condition. Although drowsiness of healthy subjects is not equivalent to reduced alertness of an acutely ill patient, the results clearly indicate that beta modulation is suitable as a biomarker also in acute patients. In our experience, only some acute stroke patients had challenges in maintaining alertness during measurement. Taken together, the possible effect of decreased alertness on beta modulation is not significant at the group level. However, it is advisable to monitor changes in the level of alertness during measurements and to encourage the study subjects to be eyes open and keep their vigilance as good as possible. Moreover, it is recommended that measurements are taken at the time of day when subjects are most alert.

4.3 | Effects of active attention to the stimulus on the modulation of the SMI rhythms

In general, attention to a sensory stimulus has been shown to alter rhythmic brain activity. Visual alpha is most extensively studied, and it has been shown to reduce brain regions primarily engaged in visual tasks and enhance in regions that are less involved (Van Diepen et al., 2019; Foxe & Snyder, 2011; Klimesch, 2012; Palva & Palva, 2007). These spatial modulations in alpha power are thought to reflect a general mechanism of attentional gating in the cortical processing involved and inhibition in various other brain regions. Much less is known about the effects of attention on the beta rhythm of the Rolandic sensorimotor cortex. Beta band power has shown to be negatively correlated with the dorsal attention network including the sensorimotor area (Sadaghiani et al., 2010). Beta rhythm decreases during the attention task associated with multisensory stimuli (Friese et al., 2016; Misselhorn et al., 2019), and to increase in relation to faster reaction time (i.e., increased alertness) to visual stimuli (Kaminski et al., 2012), as well as during enhanced attention to tactile stimuli (Bardouille et al., 2010). More focused attention to a tactile stimulus either increased (Bardouille et al., 2010; Dockstader et al., 2010) or decreased (Bauer et al., 2006) the strength of beta suppression and rebound. The expectation of an upcoming tactile stimulus has been shown to produce the suppression prior to the stimulus (van Ede et al., 2010), however, the attention-related beta suppression was not seen prior to the stimulus onset in our study. These varying results indicate that active attention affects the sensorimotor cortex beta rhythm, but the large variety of stimuli and tasks used in the studies may have different impacts on the beta rhythm. The simple attention task used in the present study additionally showed a prolonged beta rebound in the left hemisphere, which may reflect that vigilance is more regulated in the left

hemisphere, as has also been shown in a previous study (Kim et al., 2017). However, the current study indicates that the unwanted attention to the regularly repetitive tactile stimulation has only inconsistent minor changes on the beta rhythm modulation, and thus the unfavorable behavior of subjects does not distort the results.

4.4 | Baseline beta power

In line with some earlier studies (Anderson & Ding, 2011; van Ede et al., 2010, 2011; Jones et al., 2010), a slightly decreased pre-stimulus baseline was observed in the attention condition compared to the other conditions, which may have an effect on the relative suppression and rebound strengths. However, the difference was significant only in the left hemisphere. As any baseline differences between different conditions may affect the results, the suppression and rebound strengths were revised from the absolute strengths (as done, e.g., in Muthukumaraswamy et al., 2013). The absolute modulation strengths did not differ between the conditions in line with the results obtained from the relative values. Therefore, the effect of the baseline power appeared to be negligible, and the baseline normalized relative values are appropriate also for clinical use.

5 | CONCLUSION

The present study simulated the measurement protocol of acute stroke patients to study the effect of alertness and attention to the stimulus on SMI beta modulation. Neither reduced alertness nor active attention to the stimulus had a significant effect on the strength of suppression or rebound of the beta rhythm at the group level. This important observation shows that minor changes in alertness do not significantly affect the results of beta modulation studies. However, the effect of alertness on beta modulation was individual and may be stronger in some subjects and patients. Thus, individual results should be evaluated with caution. It is also important to minimize the effects of changes in alertness in longitudinal patient studies, where the risk of changes in alertness can be substantial between measurements.

ACKNOWLEDGMENTS

The authors thank all the subjects who participated in this study.

CONFLICT OF INTEREST

No conflicts of interest, financial or otherwise, are declared by authors. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

MI, KL, HP conceptualized and designed the study. MI performed the experiments and analyze data. MI drafted the manuscript. All authors edited and revised the manuscript, and approved the final version of the manuscript.

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REFERENCES

Alegre, M., Labarga, A., Gurtubay, I. G., Iriarte, J., Malanda, A., & Artieda, J. (2002). Beta electroencephalograph changes during passive movements: sensory afferences contribute to beta event-related desynchronization in humans. *Neuroscience Letters*, *331*(1), 29–32. https://doi.org/10.1016/S0304-3940(02)00825-X

Anderson, K. L., & Ding, M. (2011). Attentional modulation of the somatosensory mu rhythm. *Neuroscience*, *180*, 165–180. https://doi.org/10.1016/j.neuroscience.2011.02.004

Bardouille, T., & Bailey, L., Camcan Group. (2019). Evidence for age-related changes in sensorimotor neuromagnetic responses during cued button pressing in a large open-access dataset. *NeuroImage*, *193*, 25–34. https://doi.org/10.1016/j.neuroimage.2019.02.065

Bardouille, T., Picton, T. W., & Ross, B. (2010). Attention modulates beta oscillations during prolonged tactile stimulation. *The European Journal of Neuroscience*, *31*(4), 761–769. https://doi.org/10.1111/j.1460-9568.2010.07094.x

Bauer, M., Oostenveld, R., Peeters, M., & Fries, P. (2006). Tactile spatial attention enhances gamma-band activity in somatosensory cortex and reduces low-frequency activity in parieto-occipital areas. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *26*(2), 490–501. https://doi.org/10.1523/JNEUROSCI.5228-04.2006

Belyavin, A., & Wright, N. A. (1987). Changes in electrical activity of the brain with vigilance. *Electroencephalography and Clinical Neurophysiology*, *66*(2), 137–144. https://doi.org/10.1016/0013-4694(87)90183-0

Berry, R. B., Brooks, R., Gamaldo, C. E., Harding, S. M., Lloyd, R. M., Marcus, C. L., & Vaughn, B. V. (2012). The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications version 2.2. *American Academy of Sleep Medicine*. http://www.aasmnet.org/resources/pdf/scoring-manual-preface.pdf.

Brookes, M. J., Hall, E. L., Robson, S. E., Price, D., Palaniyappan, L., Liddle, E. B., Liddle, P. F., Robinson, S. E., & Morris, P. G. (2015). Complexity measures in magnetoencephalography: measuring "disorder" in schizophrenia. *PLoS One*, *10*(4), e0120991. https://doi.org/10.1371/journal.pone.0120991

Broughton, R., & Hasan, J. (1995). Quantitative topographic electroencephalographic mapping during drowsiness and sleep onset. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*, *12*(4), 372–386. https://doi.org/10.1097/00004691-199512040-00007

Cacot, P., Tesolin, B., & Sebban, C. (1995). Diurnal variations of EEG power in healthy adults. *Electroencephalography and Clinical Neurophysiology*, *94*(5), 305–312. https://doi.org/10.1016/0013-4694(94)00298-Y

Cassim, F., Monaca, C., Szurhaj, W., Bourriez, J. L., Defebvre, L., Derambure, P., & Guieu, J. D. (2001). Does post-movement beta synchronization reflect an idling motor cortex? *NeuroReport*, *12*(17), 3859–3863. https://doi.org/10.1097/00001756-200112040-00051

Cassim, F., Szurhaj, W., Sediri, H., Devos, D., Bourriez, J., Poirot, I., Derambure, P., Defebvre, L., & Guieu, J. (2000). Brief and sustained movements: differences in event-related (de)synchronization (ERD/ERS) patterns. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *111*(11), 2032–2039. https://doi.org/10.1016/S1388-2457(00)00455-7

Chen, R., Yaseen, Z., Cohen, L. G., & Hallett, M. (1998). Time course of corticospinal excitability in reaction time and self-paced movements. *Annals of Neurology*, *44*(3), 317–325. https://doi.org/10.1002/ana.410440306

Cheyne, D., Gaetz, W., Garnero, L., Lachaux, J. P., Ducorps, A., Schwartz, D., & Varela, F. J. (2003). Neuromagnetic imaging of cortical oscillations accompanying tactile stimulation. *Cognitive Brain Research*, *17*(3), 599–611. https://doi.org/10.1016/S0926-6410(03)00173-3

David, O., Kilner, J. M., & Friston, K. J. (2006). Mechanisms of evoked and induced responses in MEG/EEG. *NeuroImage*, *31*(4), 1580–1591. https://doi.org/10.1016/j.neuroimage.2006.02.034

Degardin, A., Houdayer, E., Bourriez, J. L., Destee, A., Defebvre, L., Derambure, P., & Devos, D. (2009). Deficient "sensory" beta synchronization in Parkinson's disease. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *120*(3), 636–642. https://doi.org/10.1016/j.clinph.2009.01.001

Démas, J., Bourguignon, M., Périvier, M., De Tiège, X., Dinomais, M., & Van Bogaert, P. (2020). Mu rhythm: State of the art with special focus on cerebral palsy. *Annals of Physical and Rehabilitation Medicine*, *63*(5), 439–446. https://doi.org/10.1016/j.rehab.2019.06.007

Dockstader, C., Cheyne, D., & Tannock, R. (2010). Cortical dynamics of selective attention to somatosensory events. *NeuroImage*, *49*(2), 1777–1785. https://doi.org/10.1016/j.neuroimage.2009.09.035

Engel, A. K., & Fries, P. (2010). Beta-band oscillations–signalling the status quo? *Current Opinion in Neurobiology*, *20*(2), 156–165. https://doi.org/10.1016/j.conb.2010.02.015

Engemann, D. A., & Gramfort, A. (2015). Automated model selection in covariance estimation and spatial whitening of MEG and EEG signals. *NeuroImage*, *108*, 328–342. https://doi.org/10.1016/j.neuroimage.2014.12.040

Feige, B., Kristeva-Feige, R., Rossi, S., Pizzella, V., & Rossini, P. M. (1996). Neuromagnetic study of movement-related changes in rhythmic brain activity. *Brain Research*, *734*(1–2), 252–260. https://doi.org/10.1016/0006-8993(96)00648-8

Foxe, J. J., & Snyder, A. C. (2011). The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Frontiers in Psychology*, *2*, 154. https://doi.org/10.3389/fpsyg.2011.00154

Friese, U., Daume, J., Göschl, F., König, P., Wang, P., & Engel, A. K. (2016). Oscillatory brain activity during multisensory attention reflects activation, disinhibition, and cognitive control. *Scientific Reports*, *6*, 32775. https://doi.org/10.1038/srep32775

Fry, A., Mullinger, K. J., O'Neill, G. C., Barratt, E. L., Morris, P. G., Bauer, M., Folland, J. P., & Brookes, M. J. (2016). Modulation of post-movement beta rebound by contraction force and rate of force development. *Human Brain Mapping*, *37*(7), 2493–2511. https://doi.org/10.1002/hbm.23189

Gaetz, W., & Cheyne, D. (2006). Localization of sensorimotor cortical rhythms induced by tactile stimulation using spatially filtered MEG. *NeuroImage*, *30*(3), 899–908. https://doi.org/10.1016/j.neuroimage.2005.10.009

Gaetz, W., Edgar, J. C., Wang, D. J., & Roberts, T. P. (2011). Relating MEG measured motor cortical oscillations to resting gamma-aminobutyric acid (GABA) concentration. *NeuroImage*, *55*(2), 616–621.

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., & Hämäläinen, M. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience*, *7*, 267.

Hall, S. D., Prokic, E. J., McAllister, C. J., Ronnqvist, K. C., Williams, A. C., Yamawaki, N., Witton, C., Woodhall, G. L., & Stanford, I. M. (2014). GABA-mediated changes in inter-hemispheric beta frequency activity in early-stage Parkinson's disease. *Neuroscience*, *281*, 68–76. https://doi.org/10.1016/j.neuroscience.2014.09.037

Hall, S. D., Stanford, I. M., Yamawaki, N., McAllister, C. J., Ronnqvist, K. C., Woodhall, G. L., & Furlong, P. L. (2011). The role of GABAergic modulation in motor function related neuronal network activity. *NeuroImage*, *56*(3), 1506–1510. https://doi.org/10.1016/j.neuroimage.2011.02.025

Hari, R., Forss, N., Avikainen, S., Kirveskari, E., Salenius, S., & Rizzolatti, G. (1998). Activation of human primary motor cortex during action observation: a neuromagnetic study. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(25), 15061–15065. https://doi.org/10.1073/pnas.95.25.15061

Hari, R., & Salmelin, R. (1997). Human cortical oscillations: a neuromagnetic view through the skull. *Trends in Neurosciences*, *20*(1), 44–49. https://doi.org/10.1016/S0166-2236(96)10065-5

Houdayer, E., Labyt, E., Cassim, F., Bourriez, J. L., & Derambure, P. (2006). Relationship between event-related beta synchronization and afferent inputs: analysis of finger movement and peripheral nerve stimulations. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *117*(3), 628–636. https://doi.org/10.1016/j.clinph.2005.12.001

Illman, M., Laaksonen, K., Liljeström, M., Jousmäki, V., Piitulainen, H., & Forss, N. (2020). Comparing MEG and EEG in detecting the ~20-Hz rhythm modulation to tactile and proprioceptive stimulation. *NeuroImage*, *215*, 116804. https://doi.org/10.1016/j.neuroimage.2020.116804

Jones, S. R., Kerr, C. E., Wan, Q., Pritchett, D. L., Hämäläinen, M., & Moore, C. I. (2010). Cued spatial attention drives functionally relevant modulation of the mu rhythm in primary somatosensory cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(41), 13760–13765. https://doi.org/10.1523/JNEUROSCI.2969-10.2010

Jurkiewicz, M. T., Gaetz, W. C., Bostan, A. C., & Cheyne, D. (2006). Post-movement beta rebound is generated in motor cortex: Evidence from neuromagnetic recordings. *NeuroImage*, *32*(3), 1281–1289. https://doi.org/10.1016/j.neuroimage.2006.06.005

Kaminski, J., Brzezicka, A., Gola, M., & Wrobel, A. (2012). Beta band oscillations engagement in human alertness process. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *85*(1), 125–128. https://doi.org/10.1016/j.ijpsycho.2011.11.006

Kim, J. H., Kim, D. W., & Im, C. H. (2017). Brain areas responsible for vigilance: An EEG Source Imaging Study. *Brain Topography*, *30*(3), 343–351. https://doi.org/10.1007/s10548-016-0540-0

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

Laaksonen, K., Kirveskari, E., Mäkelä, J. P., Kaste, M., Mustanoja, S., Nummenmaa, L., Tatlisumak, T., & Forss, N. (2012). Effect of afferent input on motor cortex excitability during stroke recovery. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *123*(12), 2429–2436. https://doi.org/10.1016/j.clinph.2012.05.017

Lal, S. K., & Craig, A. (2001). A critical review of the psychophysiology of driver fatigue. *Biological Psychology*, *55*(3), 173–194. https://doi.org/10.1016/S0301-0511(00)00085-5

Langner, R., & Eickhoff, S. B. (2013). Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin*, *139*(4), 870–900. https://doi.org/10.1037/a0030694

Liddle, E. B., Price, D., Palaniyappan, L., Brookes, M. J., Robson, S. E., Hall, E. L., Morris, P. G., & Liddle, P. F. (2016). Abnormal salience signaling in schizophrenia: The role of integrative beta oscillations. *Human Brain Mapping*, *37*(4), 1361–1374. https://doi.org/10.1002/hbm.23107

Marzano, C., Moroni, F., Gorgoni, M., Nobili, L., Ferrara, M., & de Gennaro, L. (2013). How we fall asleep: Regional and temporal differences in electroencephalographic synchronization at sleep onset. *Sleep Medicine*, *14*(11), 1112–1122. https://doi.org/10.1016/j.sleep.2013.05.021

Misselhorn, J., Friese, U., & Engel, A. K. (2019). Frontal and parietal alpha oscillations reflect attentional modulation of cross-modal matching. *Scientific Reports*, *9*(1), 5030-w. https://doi.org/10.1038/s41598-019-41636-w

Muthukumaraswamy, S. D., Myers, J. F., Wilson, S. J., Nutt, D. J., Lingford-Hughes, A., Singh, K. D., & Hamandi, K. (2013). The effects of elevated endogenous GABA levels on movement-related network oscillations. *NeuroImage*, *66*, 36–41. https://doi.org/10.1016/j.neuroimage.2012.10.054

Neuper, C., Wortz, M., & Pfurtscheller, G. (2006). ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Progress in Brain Research*, *159*, 211–222.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Palva, S., & Palva, J. M. (2007). New vistas for alpha-frequency band oscillations. *Trends in Neurosciences*, *30*(4), 150–158.

Parkkonen, E., Laaksonen, K., Parkkonen, L., & Forss, N. (2018). Recovery of the 20 Hz rebound to tactile and proprioceptive stimulation after stroke. *Neural Plasticity*, *2018*, 7395798.

Parkkonen, E., Laaksonen, K., Piitulainen, H., Parkkonen, L., & Forss, N. (2015). Modulation of the reverse similar20-Hz motor-cortex rhythm to passive movement and tactile stimulation. *Brain and Behavior*, *5*(5), e00328.

Parkkonen, E., Laaksonen, K., Piitulainen, H., Pekkola, J., Parkkonen, L., Tatlisumak, T., & Forss, N. (2017). Strength of ~20-Hz rebound and motor recovery after stroke. *Neurorehabilitation and Neural Repair*, *31*(5), 475–486. https://doi.org/10.1177/1545968316688795

Pfurtscheller, G. (2001). Functional brain imaging based on ERD/ERS. *Vision Research*, *41*(10–11), 1257–1260. https://doi.org/10.1016/S0042-6989(00)00235-2

Pfurtscheller, G., Brunner, C., Schlögl, A., & Lopes da Silva, F. H. (2006). Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. *NeuroImage*, *31*(1), 153–159. https://doi.org/10.1016/j.neuroimage.2005.12.003

Pfurtscheller, G., & Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *110*(11), 1842–1857. https://doi.org/10.1016/S1388-2457(99)00141-8

Pfurtscheller, G., Stancak, A. Jr, & Neuper, C. (1996). Post-movement beta synchronization. A correlate of an idling motor area? *Electroencephalography and Clinical Neurophysiology*, *98*(4), 281–293. https://doi.org/10.1016/0013-4694(95)00258-8

Pfurtscheller, G., Zalaudek, K., & Neuper, C. (1998). Event-related beta synchronization after wrist, finger and thumb movement. *Electroencephalography and Clinical Neurophysiology*, *109*(2), 154–160. https://doi.org/10.1016/S0924-980X(97)00070-2

Pihko, E., Nevalainen, P., Vaalto, S., Laaksonen, K., Mäenpää, H., Valanne, L., & Lauronen, L. (2014). Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: A magnetoencephalographic study. *Human Brain Mapping*, *35*(8), 4105–4117. https://doi.org/10.1002/hbm.22462

Piitulainen, H., Bourguignon, M., Smeds, E., de Tiege, X., Jousmäki, V., & Hari, R. (2015). Phasic stabilization of motor output after auditory and visual distractors. *Human Brain Mapping*, *36*(12), 5168–5182. https://doi.org/10.1002/hbm.23001

Rimbert, S., Al-Chwa, R., Zaepffel, M., & Bougrain, L. (2018). Electroencephalographic modulations during an open- or closed-eyes motor task. *PeerJ*, *6*, e4492. https://doi.org/10.7717/peerj.4492

Sadaghiani, S., Scheeringa, R., Lehongre, K., Morillon, B., Giraud, A. L., & Kleinschmidt, A. (2010). Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalography/functional magnetic resonance imaging study. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *30*(30), 10243–10250. https://doi.org/10.1523/JNEUROSCI.1004-10.2010

Salenius, S., Schnitzler, A., Salmelin, R., Jousmäki, V., & Hari, R. (1997). Modulation of human cortical rolandic rhythms during natural sensorimotor tasks. *NeuroImage*, *5*(3), 221–228. https://doi.org/10.1006/nimg.1997.0261

Salmelin, R., Hämäläinen, M., Kajola, M., & Hari, R. (1995). Functional segregation of movement-related rhythmic activity in the human brain. *NeuroImage*, *2*(4), 237–243. https://doi.org/10.1006/nimg.1995.1031

Salmelin, R., & Hari, R. (1994). Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience*, *60*(2), 537–550. https://doi.org/10.1016/0306-4522(94)90263-1

Schnitzler, A., Salenius, S., Salmelin, R., Jousmäki, V., & Hari, R. (1997). Involvement of primary motor cortex in motor imagery: a neuromagnetic study. *NeuroImage*, *6*(3), 201–208. https://doi.org/10.1006/nimg.1997.0286

Shigihara, Y., Tanaka, M., Ishii, A., Kanai, E., Funakura, M., & Watanabe, Y. (2013). Two types of mental fatigue affect spontaneous oscillatory brain activities in different ways. *Behavioral and Brain Functions: BBF*, *9*, 2. https://doi.org/10.1186/1744-9081-9-2

Smit, D. J., Posthuma, D., Boomsma, D. I., & Geus, E. J. (2005). Heritability of background EEG across the power

spectrum. *Psychophysiology*, *42*(6), 691–697. https://doi.org/10.1111/j.1469-8986.2005.00352.x

Tallon-Baudry, C., Bertrand, O., Wienbruch, C., Ross, B., & Pantev, C. (1997). Combined EEG and MEG recordings of visual 40 Hz responses to illusory triangles in human. *NeuroReport*, *8*(5), 1103–1107. https://doi.org/10.1097/00001756-199703240-00008

Tanaka, M., Ishii, A., & Watanabe, Y. (2014). Neural effects of mental fatigue caused by continuous attention load: a magnetoencephalography study. *Brain Research*, *1561*, 60–66. https://doi.org/10.1016/j.brainres.2014.03.009

Tanaka, M., Shigihara, Y., Ishii, A., Funakura, M., Kanai, E., & Watanabe, Y. (2012). Effect of mental fatigue on the central nervous system: an electroencephalography study. *Behavioral and Brain Functions: BBF*, *8*, 48. https://doi.org/10.1186/1744-9081-8-48

Tang, C. W., Hsiao, F. J., Lee, P. L., Tsai, Y. A., Hsu, Y. F., Chen, W. T., Lin, Y. Y., Stagg, C. J., & Lee, I. H. (2020). beta-Oscillations Reflect Recovery of the Paretic Upper Limb in Subacute Stroke. *Neurorehabilitation and Neural Repair*, *34*(5), 450–462.

Taulu, S., & Kajola, M. (2005). Presentation of electromagnetic multichannel data: The signal space separation method. *Journal of Applied Physics*, *97*(12), 124905. https://doi.org/10.1063/1.1935742

Taulu, S., & Simola, J. (2006). Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Physics in Medicine and Biology*, *51*(7), 1759–1768. https://doi.org/10.1088/0031-9155/51/7/008

Toth, M., Kiss, A., Kosztolanyi, P., & Kondakor, I. (2007). Diurnal alterations of brain electrical activity in healthy adults: A LORETA study. *Brain Topography*, *20*(2), 63–76. https://doi.org/10.1007/s10548-007-0032-3

Uusitalo, M. A., & Ilmoniemi, R. J. (1997). Signal-space projection method for separating MEG or EEG into components. *Medical & Biological Engineering & Computing*, *35*(2), 135–140. https://doi.org/10.1007/BF02534144

van Diepen, R. M., Foxe, J. J., & Mazaheri, A. (2019). The functional role of alpha-band activity in attentional processing: the current zeitgeist and future outlook. *Current Opinion in Psychology*, *29*, 229–238. https://doi.org/10.1016/j.copsyc.2019.03.015

van Ede, F., de Lange, F., Jensen, O., & Maris, E. (2011). Orienting attention to an upcoming tactile event involves a spatially and temporally specific modulation of sensorimotor alpha- and beta-band oscillations. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *31*(6), 2016–2024. https://doi.org/10.1523/JNEUROSCI.5630-10.2011

van Ede, F., Jensen, O., & Maris, E. (2010). Tactile expectation modulates pre-stimulus beta-band oscillations in human sensorimotor cortex. *NeuroImage*, *51*(2), 867–876.

Vinding, M. C., Tsitsi, P., Piitulainen, H., Waldthaler, J., Jousmäki, V., Ingvar, M., Svenningsson, P., & Lundqvist, D. (2019). Attenuated beta rebound to proprioceptive afferent feedback in Parkinson's disease. *Scientific Reports*, *9*(1), 2604–2613. https://doi.org/10.1038/s41598-019-39204-3

Wilson, T. W., Heinrichs-Graham, E., & Becker, K. M. (2014). Circadian modulation of motor-related beta oscillatory responses. *NeuroImage*, *102*(Pt 2), 531–539. https://doi.org/10.1016/j.neuroimage.2014.08.013

How to cite this article: Illman M, Laaksonen K, Liljeström M, Piitulainen H, Forss N. The effect of alertness and attention on the modulation of the beta rhythm to tactile stimulation. *Physiol Rep*. 2021;9:e14818. https://doi.org/10.14814/phy2.14818

III

REPRODUCIBILITY OF ROLANDIC BETA RHYTHM MODULATION IN MEG AND EEG

by

Illman, M., Laaksonen, K., Jousmäki, V., Forss, N., & Piitulainen, H. 2022

Journal of Neurophysiology, 127, 559–570

https://doi.org/10.1152/jn.00267.2021

american physiological society

JNP JOURNAL OF NEUROPHYSIOLOGY

J Neurophysiol 127: 559–570, 2022.
First published January 19, 2022; doi:10.1152/jn.00267.2021

RESEARCH ARTICLE

Sensory Processing

Reproducibility of Rolandic beta rhythm modulation in MEG and EEG

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Abstract

The Rolandic beta rhythm, at ~20 Hz, is generated in the somatosensory and motor cortices and is modulated by motor activity and sensory stimuli, causing a short lasting suppression that is followed by a rebound of the beta rhythm. The rebound reflects inhibitory changes in the primary sensorimotor (SMI) cortex, and thus it has been used as a biomarker to follow the recovery of patients with acute stroke. The longitudinal stability of beta rhythm modulation is a prerequisite for its use in long-term follow-ups. We quantified the reproducibility of beta rhythm modulation in healthy subjects in a 1-year-longitudinal study both for MEG and EEG at T_0, 1 month ($T_{1\text{-month}}$, n = 8) and 1 year ($T_{1\text{-year}}$, n = 19). The beta rhythm (13–25 Hz) was modulated by fixed tactile and proprioceptive stimulations of the index fingers. The relative peak strengths of beta suppression and rebound did not differ significantly between the sessions, and intersession reproducibility was good or excellent according to intraclass correlation-coefficient values (0.70–0.96) both in MEG and EEG. Our results indicate that the beta rhythm modulation to tactile and proprioceptive stimulation is well reproducible within 1 year. These results support the use of beta modulation as a biomarker in long-term follow-up studies, e.g., to quantify the functional state of the SMI cortex during rehabilitation and drug interventions in various neurological impairments.

NEW & NOTEWORTHY The present study demonstrates that beta rhythm modulation is highly reproducible in a group of healthy subjects within a year. Hence, it can be reliably used as a biomarker in longitudinal follow-up studies in different neurological patient groups to reflect changes in the functional state of the sensorimotor cortex.

cortical oscillation; cutaneous stimulus; event-related desynchronization; event-related synchronization; passive movement

INTRODUCTION

Oscillatory activity in the sensorimotor cortex at rest is dominated by the ~20-Hz beta rhythm, which attenuates as a result of the person's voluntary movement (1), evoked passive movement, or imagined movement (2–6). In addition, the ~20-Hz beta rhythm is modulated by somatosensory afferent stimuli, such as tactile or electrical stimulation (7–11). The beta rhythm is suppressed briefly after the onset of a stimulus or before self-paced movement. This so-called beta suppression (or event-related desynchronization; ERD) is thought to reflect the excitation of the sensorimotor cortex (12, 13). The suppression is followed by an increase of the beta rhythm above baseline level. This beta rebound (or event-related synchronization; ERS) is associated with neural deactivation or inhibition of the sensorimotor cortex (3, 14, 15). The generator area of the rebound is usually located more anterior than the suppression in the sensorimotor cortex (7, 16, 17). The rebound and suppression are regulated by distinct subunits of GABAergic interneurons (18–21).

Alterations in beta suppression and rebound have been reported in various neurological and psychiatric patient groups, such as stroke (22, 23), schizophrenia (24, 25), Parkinson's disease (26–28), and cerebral palsy (29–31). Longitudinal studies in patients with stroke have revealed that the strength of the sensorimotor cortex beta rebound correlates with recovery of motor function after acute stroke (11, 32, 33). Consequently, the beta rhythm modulation has been considered as a biomarker of the inhibitory state of the

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Submitted 14 June 2021 / Revised 22 December 2021 / Accepted 10 January 2022

sensorimotor cortex, and it may thus be useful in the evaluation of changes in cortical inhibition during development, aging, and various interventions and the recovery process after brain injury, such as stroke. Espenhahn et al. (34) found the beta rhythm modulation to be well reproducible within a few weeks, but no previous study has investigated the reproducibility of beta suppression and rebound in longer-term measurements, to prove its feasibility for follow-up studies.

The primary aim of the present study was to examine the reproducibility of beta rhythm modulation to tactile and proprioceptive stimulation over a period of 1 year in healthy individuals separately for magnetoencephalography (MEG) and electroencephalography (EEG). In addition, reproducibility of baseline beta power was assessed, as it may affect the estimation of the relative suppression and rebound strengths. Based on previous experiments, indicating a high or excellent reproducibility of MEG and EEG measures related to somatosensory stimuli (35, 36), we hypothesized that the beta rhythm modulation is a reproducible measure when using both MEG and EEG. Stability of the beta modulation over a long period is necessary for its reliable use in clinical follow-up studies.

MATERIALS AND METHODS

Subjects

Twenty-one healthy subjects in total were recruited for the study. Nineteen of them (10 females, age 19–35, means ± SD: 23 ± 5 year) were able to complete the 1-year follow-up (13 ± 1.3 month). Additional 1-month follow-up recordings (31 ± 2 days) were performed for 8 (4 females, age 19–31, means ± SD: 25 ± 4 year) of the 21 subjects. All the subjects were right-handed (85 ± 12 on the scale from −100 to 100) according to Edinburgh Handedness Inventory score (37), and had no medication affecting their central nervous system (CNS).

The Aalto University Research Ethics Committee approved the study in accordance with the Declaration of Helsinki. The subjects were asked to sign written informed consent before all follow-up measurements.

Experimental Design

Reproducibility of the sensorimotor cortex beta rhythm suppression and rebound was assessed between baseline T_0 and 1-year $T_{1\text{-year}}$ follow-up (n = 19) and between baseline T_0 and a 1-month $T_{1\text{-month}}$ (n = 8) measurement sessions.

During the combined MEG/EEG measurement, the subject was fixating at a picture in front of them (size 12 × 15 cm, distance of 2.2 m), while the index fingers were stimulated with tactile and proprioceptive stimuli (Fig. 1) in two separate recordings, respectively. The order of the recordings was randomized. Stimulus-related potential auditory and visual contamination were prevented by using earplugs and visual barrier, respectively. The subject was asked not to pay attention to the stimuli. The total duration of measurement in the magnetically shielded room (MSR) was ~45 min, and the tactile and proprioceptive stimulus periods lasted ~9 min each.

Tactile stimulation.

Tactile stimuli were given alternately to the left and right hand index fingers every 3 s. The stimuli were produced with Aalto NeuroImaging in-house built pneumatic stimulator utilizing pneumatic diaphragms (4-D NeuroImaging Inc., San Diego, CA) driven by compressed air (4 bar) with a stimulus duration of 180 ms, peaking at 40 ms. The subject held their hands relaxed on a pillow during the stimulation.

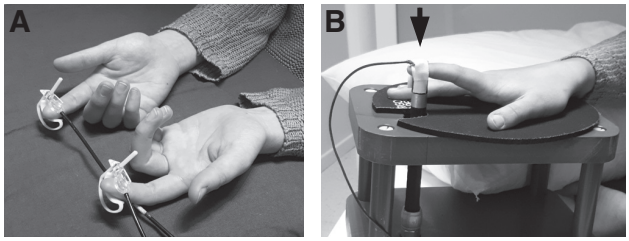

Figure 1. The experimental setup for magnetoencephalography (MEG) compatible tactile (*A*) and proprioceptive (*B*) stimulators.

Proprioceptive stimulation.

The proprioceptive stimuli were evoked to the left and right index finger in separate recordings. A mechanical movement actuator system (38), built at Aalto University, was used to evoke fast flexion-extension movement of the index finger every 5 s (duration 130 ms, mechanical delay from the trigger pulse 35 ms). The movement kinematics were recorded with an MEG-compatible three-axis accelerometer system, built at Aalto NeuroImaging based on an ADXL335 iMEMS Accelometer (Analog Devices Inc., Norwood, MA) attached on the index finger. Compressed air (4 bar) was applied to the actuator resulting in a movement range of ~5 mm. To minimize possible tactile sensation of the fingertip, the index finger was taped with surgical tape. To confirm the correct finger position during the measurement, the finger was lightly taped to the actuator and the stimulated hand was supported in a comfortable relaxed position with pillows.

Data Acquisition

The simultaneous MEG/EEG measurements were recorded at Aalto University (MEG Core, Aalto NeuroImaging), with a 306-channel (204 planar gradiometers, 102 magnetometers) whole scalp MEG system (Elekta Neuromag, Elekta Oy, Helsinki, Finland). A 60-channel MEG-compatible EEG cap (ANT Neuro waveguard original) with Ag-AgCl surface electrodes mounted according to the international 10-20 system, was used for EEG recordings. In addition, eye blink artifacts were detected with two vertical electro-oculogram electrodes (EOG). The MEG/EEG recordings were performed in a magnetically shielded room (MSR; Imedco AG, Hägendorf, Switzerland). Before the recordings, two indicator coils were attached above the ears and three onto the forehead of the EEG cap. The location of these five coils, three anatomical landmarks (left and right preauricular points and nasion) and additional 100–200 points from the surface of head, were determined with a three-dimensional (3-D) digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT). The head position was determined in the beginning of each measurement session and continuously during the measurement by sending a low current to the indicator coils and detecting the position of the coils with respect to the MEG sensor array.

A sampling frequency of 1000 Hz and bandpass filter 0.1–330 Hz was used in MEG, EEG, and accelerometer recordings. The impedances of the EEG electrodes were verified to be below 5–10 kΩ before the recording.

Data Processing and Analysis

Preprocessing.

A custom-made MATLAB script was used to transform the MEG raw signals from the different measurement sessions (T_0, $T_{1\text{-month}}$, $T_{1\text{-year}}$) to the same average head-coordinate system, separately to tactile and proprioceptive stimuli, for each subject. This improves the comparability of different measurement sessions when the obtained reference head positions are used for coordinate matching in the Maxfilter software (v2.2; Elekta Oy, Helsinki, Finland). MEG raw signals were filtered with the signal-space separation method with temporal extension (tSSS) and head movement compensation (threshold 25 mm) was obtained (39). The following parameters were used in the Maxfilter software: buffer length 16 s, subspace correlation limit 0.98, inside expansion order 8, and outside expansion 3.

Hereafter, the MEG and EEG data were analyzed with MNE Python (v. 0.17) (40). The EEG signals were re-referenced to the average reference over all good quality channels, individually for each subject. Eye blink artifacts (two magnetometer and two gradiometer components) were removed with principal component analysis (PCA; 41). Evoked responses related to stimulus onset, which can disturb the baseline detection of the beta modulation, were subtracted from each epoch from both MEG and EEG data (42).

Determination of beta rhythm modulation.

The temporal spectral evolution (TSE) method was used to quantify the strength of the stimulus-related beta rhythm modulation in the follow-up measurements (7). MEG and EEG data were first filtered to a 13- to 25-Hz frequency band (a symmetric linear-phase FIR filter with a transition band of 1 Hz at the low- and high cutoff frequency and Hamming window, filter length 3.3), which in a previous study has been found to show the strongest beta rhythm modulation for all subjects (43). The lower beta frequencies are needed specifically to detect the beta rebound (5, 29, 44). After bandpass filtering, a Hilbert transform was applied to obtain the envelope signal, after which the data were averaged from −500 to 3,000 ms with respect to the stimulus trial. Peak strengths and latencies of the beta rhythm suppression and rebound were determined from the individual TSE curves. MEG and EEG channels used for rebound/suppression determination were individually selected over the sensorimotor cortex areas and they remained the same (within one subject) in all sessions. Channels were selected based on the strongest response, noticing that in some subjects the suppression and rebound were more pronounced in different channels (one or two channels in one hemisphere). The baseline beta rhythm power was determined from these individually selected MEG and EEG channels from a time window of −500 to −100 ms, and the absolute suppression and rebound strengths were converted to relative values (in percentage) with respect to the prestimulus baseline from −500 to −100 ms to allow better comparability between different subjects and measurement sessions. The interstimulus intervals of the stimuli were chosen to allow a return of the beta rhythm to baseline level well before next stimulus onset, i.e., to keep the baseline stable during the measurement.

Beta rhythm modulation to tactile and proprioceptive stimuli was visualized with topographic TSE maps and time-frequency representations (TFRs; 45) averaged over all subjects in both MEG and EEG. TFRs, in the frequency range of 3–36 Hz and a time window of −700 to 3,200 ms with respect to stimulus onset, were calculated using Morlet wavelets by scaling the number of cycles by frequency (f/2).

Statistical Analysis

Statistical tests were performed with IBM SPSS Statistics (v. 27.0. Armonk, NY, IBM Corp). The Shapiro–Wilk test was used to test the normality of the data. The latencies and relative peak strengths of the beta rhythm suppression and rebound turned out to be not normally distributed, and therefore the nonparametric Wilcoxon test was used to test differences in the latency and strength of beta suppression and rebound between the follow-up measurements.

Correlations of beta suppression and rebound strengths between the follow-up measurements were determined with Spearman's correlation coefficient test. The reproducibility of suppression and rebound was in addition tested with the intraclass correlation coefficient (ICC) with two-way random effects and absolute agreement. In addition, coefficient of variation (CV) was defined to show interindividual variability of beta suppression and rebound at T_0, $T_{1\text{-month}}$, and $T_{1\text{-year}}$.

The effect of multiple tests was corrected with Bonferroni correction. A P value between 0.05 and 0.001 was used to assess significance.

RESULTS

A consistent number of trials (means ± SD) were collected for the TSE analysis between T_0 and $T_{1\text{-month}}$ follow-up measurements to tactile (105 ± 11 vs. 101 ± 6) and proprioceptive (108 ± 12 vs. 101 ± 10) stimulation. As can be seen from the results, the number of trials was higher at T_0 than at $T_{1\text{-year}}$ measurements to tactile (105 ± 11 vs. 92 ± 13, $P > 0.001$) and proprioceptive (108 ± 12 vs. 99 ± 7, $P > 0.001$) stimulation.

Spatiotemporal Characteristics of Beta Rhythm Modulation

Spatial distribution of beta suppression and rebound.

Figure 2*A* illustrates group averaged (n = 21) spatial distribution of beta rhythm suppression and rebound at T_0 both in MEG and EEG. Beta suppression and rebound were observed bilaterally over the sensorimotor cortex shortly after the onset of both tactile and proprioceptive stimuli, with stronger responses in the contralateral hemisphere (especially rebound) in relation to the stimulated hand. These contralateral responses were taken for further analysis.

Time-frequency representation.

Figure 2*B* shows contralateral beta rhythm modulations (group averaged over 21 subjects) to tactile and proprioceptive stimuli at T_0. The decrease of beta rhythm is most

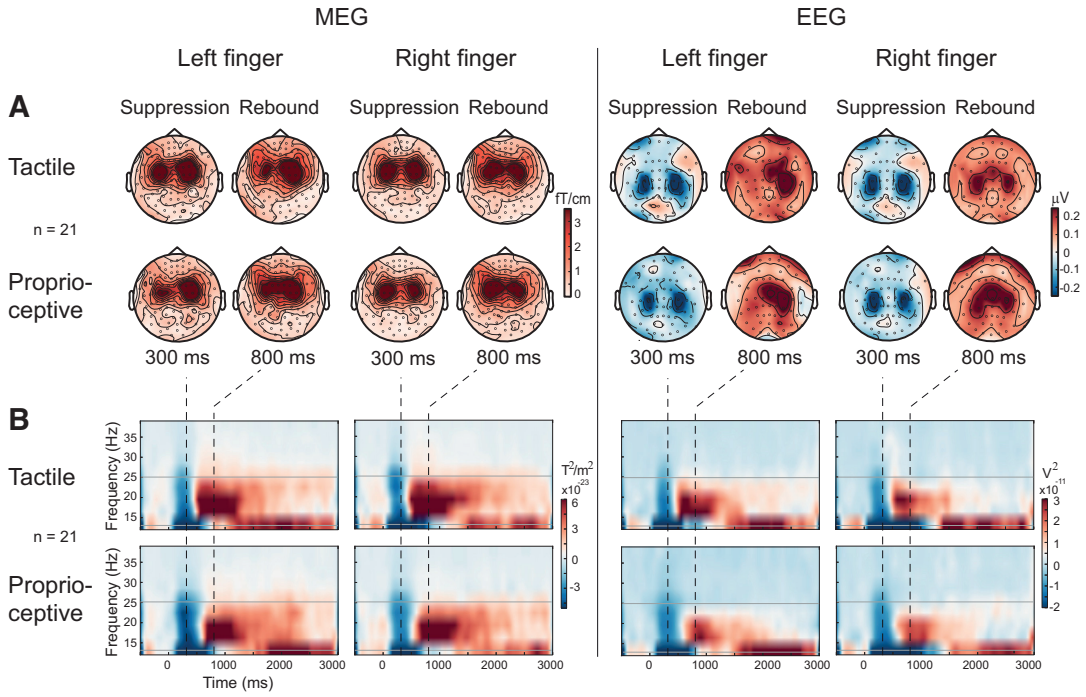

Figure 2. Grand averaged (n = 21 subjects) topographic distributions and time frequency representations (TFR) of the beta rhythm modulation to tactile and proprioceptive stimulation in the baseline T_0 measurement. *A*: topographic maps show magnetic field strengths (magnetoencephalography, MEG) and electrical scalp potentials (electroencephalography, EEG) of the beta suppression and rebound to left and right stimuli. Note that MEG topographies reflect the vector sum of the gradiometer pairs, and thus obtain only positive values. *B*: TFR images illustrates temporal evolution of the beta frequency power from one of the most representative gradiometer over the sensorimotor cortex contralateral to the stimulation with respect to trigger onset at 0 s. Black dashed lines indicate the time instants if the suppression and rebound illustrated in *A*. Gray lines indicate the beta frequency band used in temporal spectral evolution (TSE) analysis.

pronounced at 250–350 ms and subsequently increased at 700–850 ms after the onset of tactile and proprioceptive stimuli.

Reproducibility of Beta Suppression and Rebound

Reproducibility within 1 year.

Latencies. Mean latencies of beta suppression and rebound for both stimuli in MEG and EEG are shown in Table 1. No statistically significant differences ($P > 0.28$) in suppression or rebound latencies were observed between the different measurements (T_0, $T_{1\text{-month}}$, and $T_{1\text{-year}}$) and stimuli.

Strength of beta suppression and rebound. Figure 3*A* shows group averaged (n = 19) TSE curves to tactile and proprioceptive stimuli at T_0 and $T_{1\text{-year}}$. Beta rhythm suppression and rebound are well identifiable in all sessions both in MEG and EEG, and the suppression and rebound strengths appear similar between T_0 and $T_{1\text{-year}}$ sessions. Supplemental Fig. S1 (see https://doi.org/10.6084/m9.figshare.17032178.v1) shows the individual TSE curves for all subjects at three different measurement sessions.

Figure 4*A* illustrates the relative peak strengths (% to baseline) of beta suppression and rebound at T_0 and $T_{1\text{-year}}$ both in MEG and EEG to left and right finger stimulation. Beta suppression and rebound strengths did not differ significantly (MEG P = 1.0; EEG $P > 0.053$) between the 1-year follow-up measurements (T_0 vs. $T_{1\text{-year}}$, n = 19). Mean values and standard deviations of the relative peak strengths for beta suppression and rebound are shown in Table 1.

Intersession correlations. Figure 5*A* presents the relative peak strengths of beta suppression and rebound individually (n = 19) at T_0 and $T_{1\text{-year}}$. The suppression and rebound strengths are well reproducible both in MEG and EEG for most of the subjects. Intraclass correlation coefficient values indicated good to excellent intersession reproducibility for suppression 0.72–0.96 and rebound 0.70–0.95 strengths. However, the ICC values appeared to be stronger for the dominant compared with the nondominant hand. Figure 5*B* shows scatterplots respectively for suppression and rebound strengths between T_0 and $T_{1\text{-year}}$ measurements. The beta suppression and rebound strengths to tactile and proprioceptive stimuli correlated significantly between the measurements; the Spearman's correlation coefficients (r) for the suppression and rebound are 0.47–0.88 and 0.47–0.94, respectively. More detailed correlation values are shown in Table 2.

In summary, the strength of beta rhythm suppression and rebound to tactile and proprioceptive stimuli both in MEG and EEG were highly reproducible in the 1-year follow-up period.

Reproducibility within 1 month.

Strength of beta suppression and rebound. The additional 1-month follow-up recordings were performed for a subgroup of our participants to confirm that the reliability of beta rhythm modulation was similar for both the 1-month and 1-year follow up. Figure 3*B* shows group averaged (n = 8)

Table 1. *Relative peak strengths and latencies of the beta rhythm suppression and rebound in three follow-up MEG/EEG measurements*

	Tactile Stimulation				Proprioceptive Stimulation			
	MEG		EEG		MEG		EEG	
	LH	RH	LH	RH	LH	RH	LH	RH
Suppression								
T_0								
Relative amplitude, %	−29 ± 2	−25 ± 2	−19 ± 2	−19 ± 2	−31 ± 2	−23 ± 3	−20 ± 2	−20 ± 2
SD ±	10	10	9	10	11	12	9	8
CV, %	34	40	47	47	35	52	45	40
Peak latency, ms	260 ± 17	296 ± 17	247 ± 22	263 ± 17	320 ± 22	316 ± 20	304 ± 27	299 ± 17
$T_{1\text{-month}}$								
Relative amplitude, %	−28 ± 4	−23 ± 5	−21 ± 3	−15 ± 4	−30 ± 4	−23 ± 5	−23 ± 4	−22 ± 3
SD ±	12	14	9	10	12	14	12	10
CV, %	42	61	45	67	40	61	52	45
Peak latency, ms	213 ± 24	250 ± 38	224 ± 36	248 ± 39	232 ± 29	247 ± 29	339 ± 37	250 ± 26
$T_{1\text{-year}}$								
Relative amplitude, %	−30 ± 2	−27 ± 2	−20 ± 2	−23 ± 2	−33 ± 2	−21 ± 3	−22 ± 2	−20 ± 2
SD ±	9	10	9	7	10	13	7	8
CV, %	30	37	45	30	30	62	32	40
Peak latency, ms	255 ± 22	255 ± 15	291 ± 21	250 ± 21	341 ± 24	311 ± 19	361 ± 18	281 ± 22
Rebound								
T_0								
Relative amplitude, %	47 ± 8	37 ± 6	34 ± 4	30 ± 4	41 ± 7	36 ± 6	29 ± 4	27 ± 4
SD ±	35	29	20	19	31	28	17	17
CV, %	74	78	59	63	76	78	59	63
Peak latency, ms	729 ± 38	785 ± 57	703 ± 38	750 ± 47	893 ± 56	891 ± 58	845 ± 42	792 ± 37
$T_{1\text{-month}}$								
Relative amplitude, %	59 ± 16	50 ± 17	45 ± 9	46 ± 8	53 ± 10	53 ± 14	41 ± 7	35 ± 8
SD ±	45	48	24	22	30	39	19	23
CV, %	76	96	53	48	57	74	46	66
Peak latency, ms	765 ± 47	690 ± 85	724 ± 81	618 ± 66	866 ± 97	855 ± 91	813 ± 71	739 ± 60
$T_{1\text{-year}}$								
Relative amplitude, %	54 ± 8	40 ± 8	34 ± 5	33 ± 5	43 ± 7	37 ± 6	35 ± 4	30 ± 4
SD ±	35	34	20	24	32	27	17	18
CV, %	65	85	59	73	74	73	49	60
Peak latency, ms	711 ± 38	854 ± 82	722 ± 43	719 ± 57	889 ± 47	900 ± 68	897 ± 64	849 ± 46

Values (mean ± SE) are presented for contralateral responses to stimulated hand (LH, left hand; RH, right hand) for both tactile and proprioceptive stimulation. In addition, standard deviation (SD) and coefficient of variation (CV) are shown for the suppression and rebound strengths. The number of subjects is n (T_0) = 21, n ($T_{1\text{-month}}$) = 8, n ($T_{1\text{-year}}$) = 19. EEG, electroencephalography; MEG, magnetoencephalography; T_0, baseline; $T_{1\text{-month}}$, follow-up after 1 month; $T_{1\text{-year}}$, follow-up after 1 year.

TSEs in the T_0 and $T_{1\text{-month}}$ measurements. The relative peak strengths of suppression and rebound (seen in Table 1) did not differ significantly (P = 1.0) between the T_0 and $T_{1\text{-month}}$ measurements.

Intersession correlations. The beta suppression and rebound relative peak strengths between T_0 and $T_{1\text{-month}}$ measurements correlated strongly in MEG, but correlations were weaker in EEG. The ICC and Spearman's correlation coefficient values between T_0 and $T_{1\text{-month}}$ measurements are shown in Table 2.

Reproducibility of Baseline Beta Power

Baseline beta rhythm power, and Spearman's correlation and ICC coefficients for tactile and proprioceptive stimulation in MEG and EEG are shown in Table 3. Baseline beta power between T_0 and $T_{1\text{-month}}$ or T_0 and $T_{1\text{-year}}$ measurements did not show significant differences.

ICC coefficients were good or excellent between T_0 and $T_{1\text{-month}}$ (0.76–0.99) and T_0 and $T_{1\text{-year}}$ (0.72–0.95) measurements, and corresponding Spearman's correlations coefficients were 0.57–0.99 (T_0 vs. $T_{1\text{-month}}$) and 0.57–0.96 (T_0 vs. $T_{1\text{-year}}$).

Interindividual Variation of Beta Suppression and Rebound

Interindividual variation (coefficient of variation) for the relative strength of beta suppression was 30%–67% and for rebound was 46%–96% at T_0, $T_{1\text{-month}}$, and $T_{1\text{-year}}$. The coefficient of variation (in %) are shown in Table 1.

DISCUSSION

These novel results indicate that the beta rhythm modulation, i.e., suppression and rebound are highly reproducible over a long 1-year follow-up period. This information is essential for the usability of these biomarkers in longitudinal follow-up experiments. In addition, the absolute baseline beta power remained at stable level throughout the follow-up period. We used fixed and well repetitive tactile and proprioceptive stimuli to modulate the beta rhythm. Hence, the effects of instabilities, typical for active volitional movements, were eliminated and did not affect the assessment of reproducibility. Our study proves that the reproducibility of beta suppression and rebound within 1 year is good or

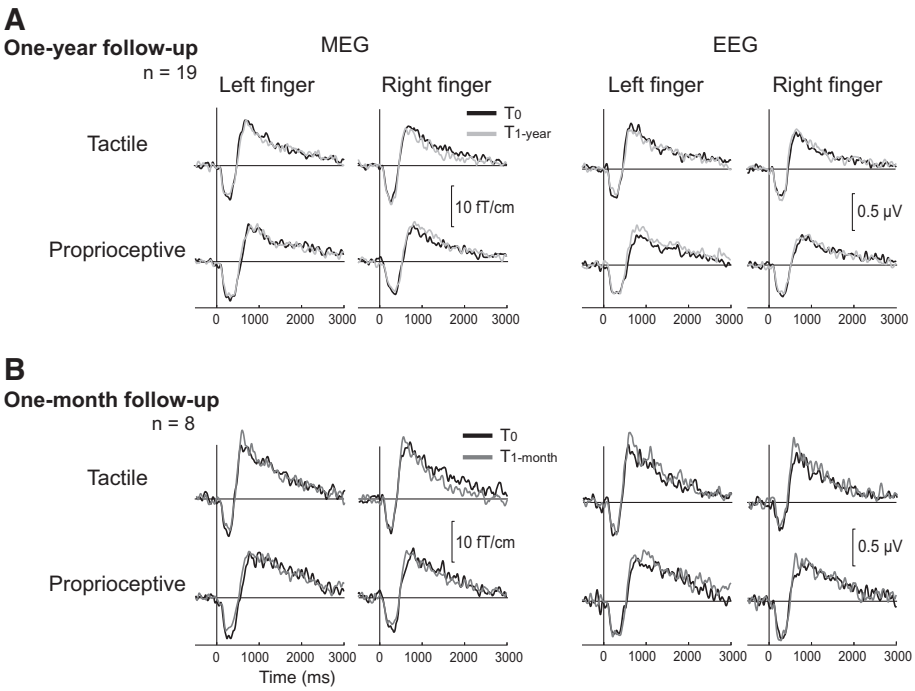

Figure 3. Grand averaged beta rhythm modulation to tactile and proprioceptive stimuli in the baseline and follow-up measurements. One-year ($T_{1\text{-year}}$, n = 19) (*A*) and 1-month ($T_{1\text{-month}}$, n = 8) (*B*) follow-up measurements are compared with the baseline (T_0) measurement, not showing significant differences between the measurements. Temporal spectral evolution (TSE) curves are showing the peak modulation of the most representative magnetoencephalography (MEG) and electroencephalography (EEG) channels over the sensorimotor cortex contralateral to the stimulated hand. Trigger onsets are shown as vertical lines at zero time; *n*, Number of subjects.

excellent both when using MEG or EEG, and therefore, the beta rebound can be reliably used as a biomarker to reflect the functional state of the sensorimotor cortex in follow-up studies.

Reproducibility of Beta Rhythm Modulation

In the current study, the reproducibility of beta suppression and rebound were verified to be good or excellent. Previous studies have reported that the beta rhythm modulation to active movement to be well reproducible within days or weeks in EEG (34, 46).

Beta suppression versus rebound.

The beta suppression is mainly thought to reflect the excitation of the SMI cortex to sensory input, whereas the rebound appears later, lasts longer, and is regulated by more complex inhibitory interneuron networks, and is thus more sensitive to alterations in the stimulus or environment. The beta suppression and rebound are generated in slightly different locations in the SMI cortex, with the rebound more anteriorly in the primary motor cortex (MI) (16, 47, 48). The rebound appears to be stronger in the contralateral hemisphere with respect to stimulus, whereas the suppression is similarly strong in both hemispheres (49). Due to these spatiotemporal differences in beta suppression and rebound, they are thought to reflect distinct functional roles in the sensorimotor cortical processing. Consequently, the beta rebound has been shown to be altered in different neurological conditions, such as stroke and schizophrenia, whereas the suppression has shown to remain relatively stable in these conditions and during follow-up (11, 32, 33). It may be that the suppression is more like all-or-nothing type of response, whereas the rebound is more prone to changes in the functional state of the sensorimotor cortex.

Active movement versus tactile and proprioceptive stimulation.

Although beta rhythm modulation has been reported to be reproducible for well-controlled active movement (34, 46), active movement-induced beta rebound is susceptible for various factors, such as speed and intensity of movement (48, 50, 51). Movement preparation has been seen to induce the beta rhythm suppression before movement onset (1, 52), and even motor imaging has been shown to cause beta rhythm modulation (4), which can hamper the evaluation of its reproducibility. In patient studies, in particular, slight changes in the performance of the active movement may affect the assessment of the reproducibility of beta modulation and thus interfere in the interpretation of changes in sensorimotor cortex function. Proprioceptive and tactile stimulation are easy to standardize and remain the same throughout the measurement, which is especially important in clinical studies that are otherwise more prone to subject-related disturbances. Taken together, especially in patient studies, tactile or proprioceptive stimulation should preferably be used to study longitudinal changes in sensorimotor cortex function, since it is advisable to keep the measurement settings as stable as possible.

1-month versus 1-year.

The reproducibility of beta modulation has earlier been studied within few weeks (34), and there is no certainty about its reproducibility in longer term. We examined the reproducibility of beta rhythm modulation within 1-year period, to ensure its feasibility for long-term follow-up studies. This is

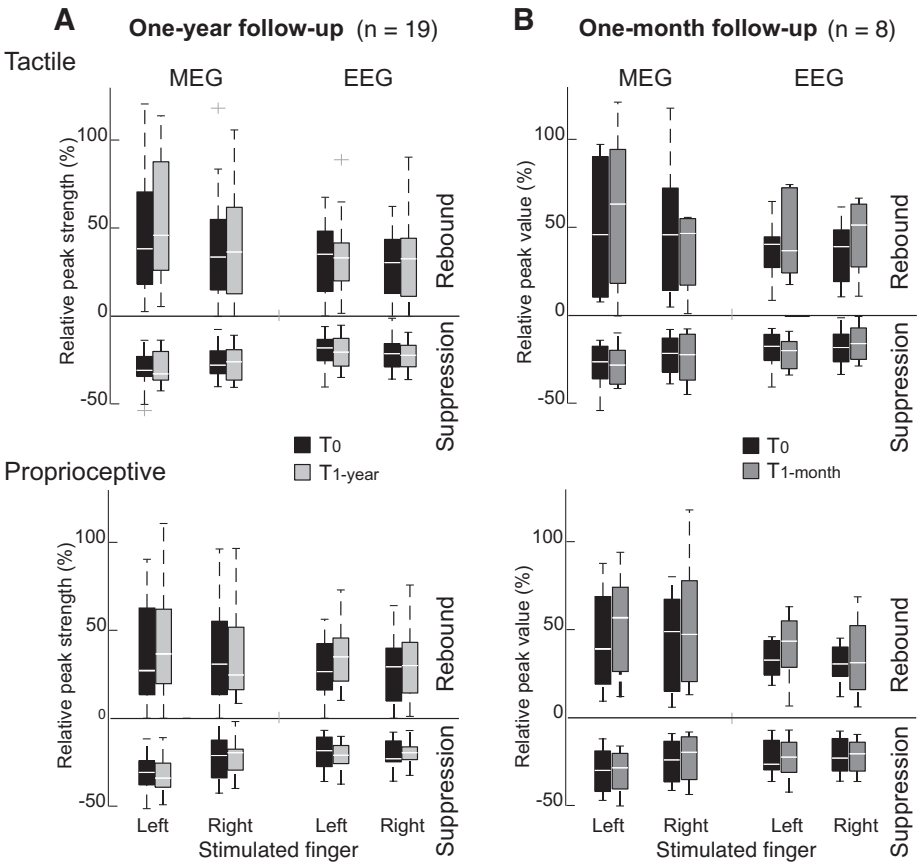

Figure 4. Peak strength of beta rhythm suppression and rebound to tactile and proprioceptive stimuli relative to baseline value for 1-year (*A*) and 1-month (*B*) follow-up measurement. Fifty percent of strength values are included in the box, horizontal lines indicate median value, and whiskers indicate variability outside the upper and lower quartiles. Outlier values are shown as crosses. EEG, electroencephalography; MEG, magnetoencephalography; *n*, number of subjects.

especially important, since the beta rhythm rebound has been proposed to be a biomarker reflecting functional recovery of the SMI cortex after acute stroke, whereas no clear association between suppression and motor recovery has been found (11, 32, 33). The beta power and the strength of beta modulation have been shown to increase in relation to aging (6, 47). However, such changes seem not to occur within a 1-year follow-up period, at least in relatively young adult participants. In older individuals, the aging effect may be more significant, and need to be clarified in future studies. Nevertheless, the present results encourage the use of beta rebound/modulation to evaluate the effectiveness of rehabilitation and drug interventions in short- or long-term follow-up studies. In addition, in well-recovering patients with stroke, the rebound in the affected hemisphere recovered to the level of the unaffected hemisphere within 1 year, although it was diminished in the acute phase and at 1 month (53).

Interindividual and intersession variations of beta suppression and rebound.

Beta rhythm suppression and rebound typically show high interindividual variation and are weak and even undetectable in some individuals. The higher interindividual variation likely arises from individual differences in the functional anatomy of the sensorimotor strip. For example, the sensorimotor rhythm generator may be located more on the gyral or fissural cortex affecting the depth and orientation of the strength of the source detected with MEG outside the skull (54). However, the beta suppression has proved to be more stable than the rebound, which is more sensitive to, for example, changes in stimulus properties, such as speed and intensity of movement. In addition, the state of the subject's alertness may also effect on the strength of beta rhythm modulation. For most of our participants, the beta modulation remained stable at individual level during the 1-year follow-up (on average suppression $< 9\%$ and rebound $< 26\%$ change), although some participants showed a greater intersession variability (suppression 0.1%–30% and rebound 0%–98%). It is noteworthy to mention that the interindividual variation of beta modulations were ~30%–62%, but the intersession variation was on average less than <26%. This further indicates that beta modulations are reproducible at group level, but in some individuals the variability can be substantial. Therefore, it is important to standardize the recording design as well as possible, e.g., to pay attention to the homogeneity of the stimuli and the state of the participants alertness during the MEG/EEG registration.

MEG versus EEG.

Our study showed high or excellent reproducibility both for MEG and EEG, but ICC values appeared to be higher for MEG than EEG. This is likely to be due to MEG's better sensitivity to detect beta rhythm modulation. However, the relative suppression and rebound strengths correlated well

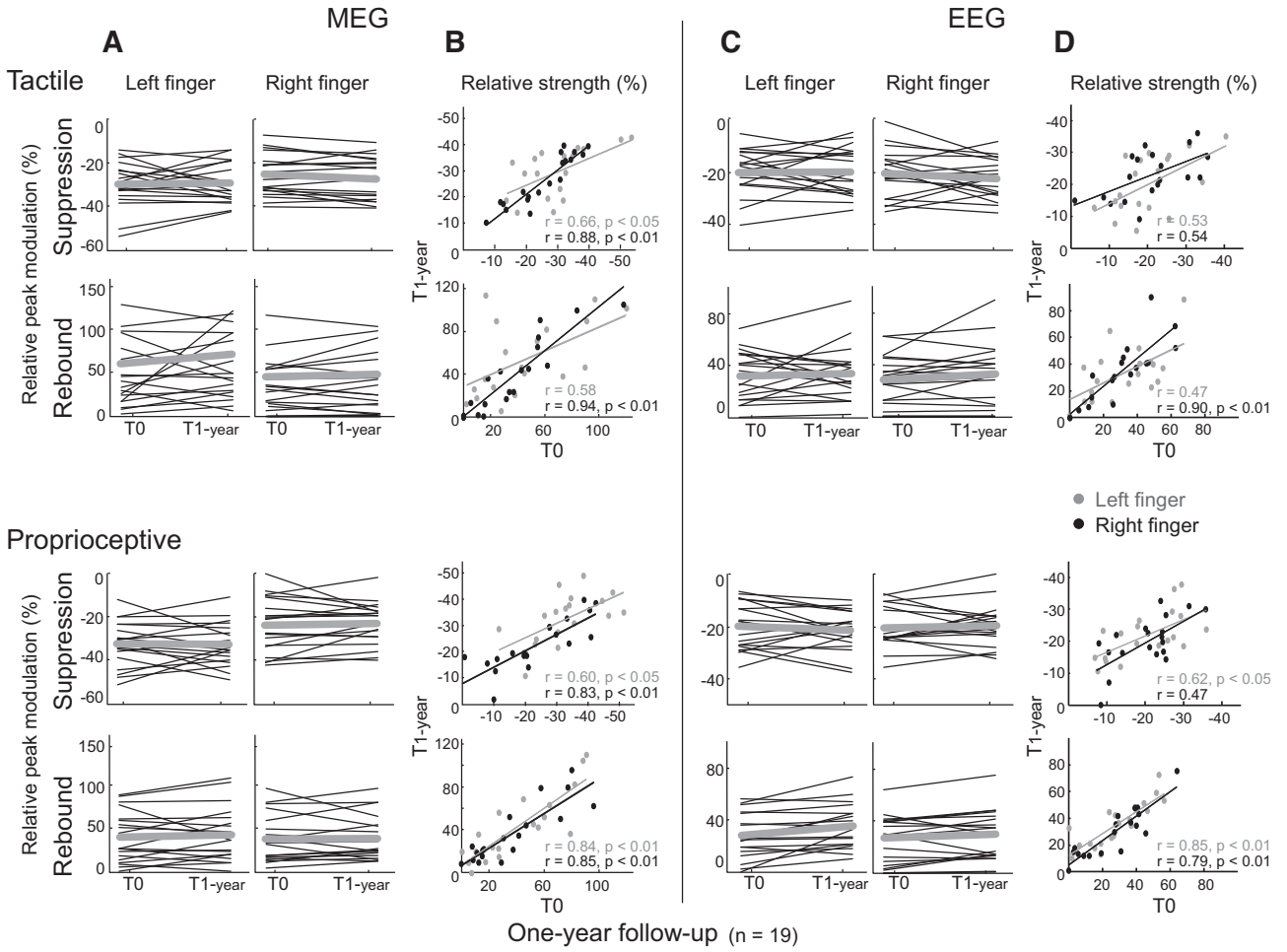

Figure 5. Individual subjects' beta suppression and rebound strengths in the baseline (T_0) and 1-year follow-up measurements (n = 19) to tactile and proprioceptive stimulations in magnetoencephalography (MEG) and electroencephalography (EEG). Relative peak modulations for each subject in the baseline (T_0) and 1-year follow-up ($T_{1\text{-year}}$) measurements for left and right hand stimuli for MEG (*A*) and EEG (*C*). Thin black lines represent direction of change for each subject separately, and gray lines the group-mean changes. Scatterplots and Spearman's correlation coefficients for the relative peak modulation strengths between the T_0 and $T_{1\text{-year}}$ measurements for MEG (*B*) and EEG (*D*). The gray color represents left and black color right hand stimulation.

between MEG and EEG measurements, and therefore both methods are valid for measuring beta modulation (5). Since mainly EEG has been adopted as a standard method in clinical trials, it is important that a neurophysiological biomarker can be reliably and reproducibly detected with it. The present study indicated the feasibility of both MEG- and EEG-based detection of the beta rhythm modulation and utilization in long-term follow-up studies.

Factors Affecting the Baseline or Induced Beta Power

In healthy individuals, the Rolandic beta power at rest has been shown to be highly reproducible both when assessed with MEG and EEG (34, 55, 56). Typically, the beta suppression and rebound are computed relative (in percentage) to the baseline beta power. For this reason, alterations in baseline beta power during a study may also affect induced beta suppression and rebound strengths (18, 57, 58). There are several factors (major ones are discussed in the following sections) that may alter the baseline level of the beta rhythm power, and hence should be taken into account when using baseline normalized modulation of beta suppression and rebound. However, previous studies have shown that baseline beta power remain the same during stroke recovery (59, 60), although the beta modulation amplitudes show prominent changes during the recovery period (11). In other words, the beta rhythm resting power and induced modulation strength appear to be distinct phenomena likely reflecting different aspects in cortical sensorimotor processing.

Age.

The beta rhythm has been shown to be age dependent. In children, the beta power has shown to be reduced than in adults (61). Concomitantly, several studies have shown that in elderly subjects the beta power at rest is increased than in younger subjects, leading to an increase of beta suppression (6, 47, 57, 62, 63), with the exception of Alzheimer's disease, where the resting-state beta power has been shown to

Table 2. *Intersession correlations of the beta rhythm suppression and rebound relative strengths for both tactile and proprioceptive stimulation in MEG and EEG*

	MEG				EEG			
	Left Hand		Right Hand		Left Hand		Right Hand	
	ICC	*r*	ICC	*r*	ICC	*r*	ICC	*r*
Tactile stimulus								
Suppression								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.75	0.66*	0.96	0.88**	0.73	0.53	0.72	0.54
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.84	0.74	0.96	0.91*	0.87	0.71	0.46	0.50
Rebound								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.70	0.58	0.95	0.94**	0.75	0.47	0.90	0.90**
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.91	0.74	0.95	0.91*	0.74	0.71	0.82	0.83
Proprioceptive stimulus								
Suppression								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.76	0.60*	0.88	0.83**	0.76	0.62*	0.80	0.47
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.88	0.79	0.96	0.86*	0.79	0.76	0.87	0.74
Rebound								
T_0 vs. $T_{1\text{-year}}$ (n = 19)	0.92	0.84**	0.93	0.85**	0.87	0.85**	0.93	0.79**
T_0 vs. $T_{1\text{-month}}$ (n = 8)	0.90	0.81	0.93	0.95**	0.75	0.60	0.83	0.95**

Intraclass (ICC) and Spearman's (r) correlation coefficient values are presented for contralateral responses to stimulated hand. EEG, electroencephalography; MEG, magnetoencephalography; T_0, baseline; $T_{1\text{-month}}$, follow-up after 1 month; $T_{1\text{-year}}$, follow-up after 1 year. *$P < 0.05$; **$P < 0.01$.

decrease (64). The frequency of the beta rhythm has also been shown to be lower with increasing age (63).

Circadian rhythm.

The circadian rhythm is known to affect the level of the beta rhythm power, being lower in the morning and increasing toward the afternoon (46, 65). Also the strength of beta suppression has been shown to increase toward the afternoon, but no such effect has been observed for the beta rebound (46).

Drugs.

Drugs that affect the GABAergic neurotransmitter system have been observed to alter the intensity of the beta rhythm. Benzodiazepine, a nonselective $GABA_A$ agonist elevates the beta rhythm power and increases the strength of beta suppression (19, 21, 66, 67). In contrast, tiagabine (GABA reuptake transporter, which affects both $GABA_A$ and $GABA_B$ subunits) has been shown to increase the beta power and amplitude of beta suppression, but decrease the amplitude of beta rebound (18).

Alertness and attention.

Mental fatigue caused by long-lasting attentive task and overload has been shown to enhance the beta power (68), whereas reduced alertness, for example, due to sleepiness decreases the beta power and the amplitude of beta suppression and rebound (43). Enhanced vigilance and active

Table 3. *Baseline beta power (means ± SE) and intraclass (ICC) and Spearman's (r) correlation coefficient values on the sensorimotor cortex in three follow-up MEG/EEG measurements for contralateral responses to stimulated hand*

Tactile Stimulation					
MEG, fT/cm	Left hand	Right hand	EEG, μV	Left hand	Right hand
T_0	36.2 ± 3	42.0 ± 4		2.3 ± 0.2	2.4 ± 0.2
$T_{1\text{-month}}$	33.3 ± 3	41.8 ± 5		2.4 ± 0.4	2.3 ± 0.4
$T_{1\text{-year}}$	35.5 ± 4	43.2 ± 4		2.3 ± 0.2	2.3 ± 0.2
ICC					
T_0 vs. $T_{1\text{-year}}$	0.87	0.81		0.95	0.91
T_0 vs. $T_{1\text{-month}}$	0.84	0.86		0.95	0.96
Spearman's (r)					
T_0 vs. $T_{1\text{-year}}$	0.80**	0.75**		0.96**	0.88**
T_0 vs. $T_{1\text{-month}}$	0.81*	0.91**		0.98**	0.99**
Proprioceptive Stimulation					
MEG, fT/cm	Left hand	Right hand	EEG, μV	Left hand	Right hand
T_0	32.4 ± 3	39.1 ± 4		2.4 ± 0.2	2.3 ± 0.2
$T_{1\text{-month}}$	31.0 ± 4	37.6 ± 5		2.4 ± 0.5	2.6 ± 0.5
$T_{1\text{-year}}$	33.2 ± 4	41.1 ± 4		2.4 ± 0.2	2.3 ± 0.2
ICC					
T_0 vs. $T_{1\text{-year}}$	0.72	0.91		0.94	0.90
T_0 vs. $T_{1\text{-month}}$	0.76	0.92		0.99	0.95
Spearman's (r)					
T_0 vs. $T_{1\text{-year}}$	0.57*	0.85**		0.93**	0.87**
T_0 vs. $T_{1\text{-month}}$	0.57	0.79*		0.96**	0.83*

EEG, electroencephalography; MEG, magnetoencephalography. *$P < 0.05$; **$P < 0.01$.

attention to stimuli have also been shown to increase the beta power (69, 70), and either to increase (70, 71) or decrease (72) the intensity of beta suppression and rebound. In addition, cortical proprioceptive processing is altered when attention is directed to the proprioceptive stimuli, increasing the sustained-evoked field amplitude but reducing the beta power (73).

In the present study, all these confounding factors were strived to standardize as accurately as possible; measurements were taken at the same time of day, age distribution of the subjects was even, the subjects had no CNS medication, and they were instructed to keep good vigilance and not to pay attention to the stimuli during the recordings.

Conclusions

Our study demonstrates that the beta rhythm suppression and rebound to tactile and proprioceptive stimulation are reproducible both in MEG and EEG recordings within a 1-year period. This finding suggests that the beta modulation is a suitable tool for longitudinal studies to monitor changes in the level of sensorimotor cortex activation and inhibition. Such a need has arisen, for example, in evaluation of the effectiveness of rehabilitation and drug intervention in neurological patients. Our results encourage a wider use of beta rhythm modulation, especially the beta rebound, as a biomarker to study and follow-up the function of sensorimotor cortex.

SUPPLEMENTAL DATA

Supplemental Fig. S1: https://doi.org/10.6084/m9.figshare.17032178.v1.

ACKNOWLEDGMENTS

The authors thank staff scientist Mia Liljeström, Ph.D., at the Department of Neuroscience and Biomedical Engineering for help with the data analysis.

GRANTS

This work was supported by the SalWe Research Program for Mind and Body, Tekes—the Finnish Funding Agency for Technology and Innovation under Grant Number 1104/10; Academy of Finland under Grant Numbers 296240, 307250, 326988, 327288; Aalto NeuroImaging, Aalto Brain Center; and Jane and Aatos Erkko Foundation Grant number 602.274.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.I., K.L., and H.P. conceived and designed research; M.I. performed experiments; M.I. analyzed data; M.I., H.P., and K.L. interpreted results of experiments; M.I. prepared figures; M.I. drafted manuscript; M.I., K.L., V.J., N.F., and H.P. edited and revised manuscript; M.I., K.L., V.J., N.F., and H.P. approved final version of manuscript.

REFERENCES

1. **Pfurtscheller G**, **Lopes da Silva FH.** Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* 110: 1842–1857, 1999. doi:10.1016/s1388-2457(99)00141-8.
2. **Alegre M**, **Labarga A**, **Gurtubay IG**, **Iriarte J**, **Malanda A**, **Artieda J.** Beta electroencephalograph changes during passive movements: sensory afferences contribute to β event-related desynchronization in humans. *Neurosci Lett* 331: 29–32, 2002. doi:10.1016/s0304-3940(02)00825-x.
3. **Cassim F**, **Monaca C**, **Szurhaj W**, **Bourriez JL**, **Defebvre L**, **Derambure P**, **Guieu JD.** Does post-movement β synchronization reflect an idling motor cortex? *Neuroreport* 12: 3859–3863, 2001. doi:10.1097/00001756-200112040-00051.
4. **Schnitzler A**, **Salenius S**, **Salmelin R**, **Jousmäki V**, **Hari R.** Involvement of primary motor cortex in motor imagery: a neuromagnetic study. *Neuroimage* 6: 201–208, 1997. doi:10.1006/nimg.1997.0286.
5. **Illman M**, **Laaksonen K**, **Liljeström M**, **Jousmäki V**, **Piitulainen H**, **Forss N.** Comparing MEG and EEG in detecting the ∼20-Hz rhythm modulation to tactile and proprioceptive stimulation. *NeuroImage* 215: 116804, 2020. doi:10.1016/j.neuroimage.2020.116804.
6. **Walker S**, **Monto S**, **Piirainen JM**, **Avela J**, **Tarkka IM**, **Parviainen TM**, **Piitulainen H.** Older age increases the amplitude of muscle stretch-induced cortical β-band suppression but does not affect rebound strength. *Front Aging Neurosci* 12: 117, 2020. doi:10.3389/fnagi.2020.00117.
7. **Salmelin R**, **Hari R.** Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience* 60: 537–550, 1994. doi:10.1016/0306-4522(94)90263-1.
8. **Parkkonen E**, **Laaksonen K**, **Piitulainen H**, **Parkkonen L**, **Forss N.** Modulation of the reverse similar 20-Hz motor-cortex rhythm to passive movement and tactile stimulation. *Brain Behav* 5: e00328, 2015. doi:10.1002/brb3.328.
9. **Houdayer E**, **Labyt E**, **Cassim F**, **Bourriez JL**, **Derambure P.** Relationship between event-related β synchronization and afferent inputs: analysis of finger movement and peripheral nerve stimulations. *Clin Neurophysiol* 117: 628–636, 2006. doi:10.1016/j.clinph.2005.12.001.
10. **Gaetz W**, **Cheyne D.** Localization of sensorimotor cortical rhythms induced by tactile stimulation using spatially filtered MEG. *Neuroimage* 30: 899–908, 2006. doi:10.1016/j.neuroimage.2005.10.009.
11. **Laaksonen K**, **Kirveskari E**, **Mäkelä JP**, **Kaste M**, **Mustanoja S**, **Nummenmaa L**, **Tatlisumak T**, **Forss N.** Effect of afferent input on motor cortex excitability during stroke recovery. *Clin Neurophysiol* 123: 2429–2436, 2012. doi:10.1016/j.clinph.2012.05.017.
12. **Pfurtscheller G.** Functional brain imaging based on ERD/ERS. *Vision Res* 41: 1257–1260, 2001. doi:10.1016/S0042-6989(00)00235-2.
13. **Neuper C**, **Wortz M**, **Pfurtscheller G.** ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Prog Brain Res* 159: 211–222, 2006. doi:10.1016/S0079-6123(06)59014-4.
14. **Salmelin R**, **Hämäläinen M**, **Kajola M**, **Hari R.** Functional segregation of movement-related rhythmic activity in the human brain. *Neuroimage* 2: 237–243, 1995. doi:10.1006/nimg.1995.1031.
15. **Pfurtscheller G**, **Stancak A Jr**, **Neuper C.** Post-movement β synchronization. A correlate of an idling motor area? *Electroencephalogr Clin Neurophysiol* 98: 281–293, 1996. doi:10.1016/0013-4694(95)00258-8.
16. **Jurkiewicz MT**, **Gaetz WC**, **Bostan AC**, **Cheyne D.** Post-movement β rebound is generated in motor cortex: evidence from neuromagnetic recordings. *NeuroImage* 32: 1281–1289, 2006. doi:10.1016/j.neuroimage.2006.06.005.
17. **Parkes LM**, **Bastiaansen MC**, **Norris DG.** Combining EEG and fMRI to investigate the post-movement β rebound. *NeuroImage* 29: 685–696, 2006. doi:10.1016/j.neuroimage.2005.08.018.
18. **Muthukumaraswamy SD**, **Myers JF**, **Wilson SJ**, **Nutt DJ**, **Lingford-Hughes A**, **Singh KD**, **Hamandi K.** The effects of elevated endogenous GABA levels on movement-related network oscillations. *NeuroImage* 66: 36–41, 2013. doi:10.1016/j.neuroimage.2012.10.054.
19. **Hall SD**, **Stanford IM**, **Yamawaki N**, **McAllister CJ**, **Ronnqvist KC**, **Woodhall GL**, **Furlong PL.** The role of GABAergic modulation in motor function related neuronal network activity. *NeuroImage* 56: 1506–1510, 2011. doi:10.1016/j.neuroimage.2011.02.025.
20. **Gaetz W**, **Edgar JC**, **Wang DJ**, **Roberts TP.** Relating MEG measured motor cortical oscillations to resting γ-aminobutyric acid (GABA) concentration. *Neuroimage* 55: 616–621, 2011. doi:10.1016/j.neuroimage.2010.12.077.

21. **Yamawaki N**, **Stanford IM**, **Hall SD**, **Woodhall GL.** Pharmacologically induced and stimulus evoked rhythmic neuronal oscillatory activity in the primary motor cortex in vitro. *Neuroscience* 151: 386–395, 2008. doi:10.1016/j.neuroscience.2007.10.021.
22. **Rossiter HE**, **Boudrias MH**, **Ward NS.** Do movement-related β oscillations change after stroke? *J Neurophysiol* 112: 2053–2058, 2014. doi:10.1152/jn.00345.2014.
23. **Espenhahn S**, **Rossiter HE**, **van Wijk BCM**, **Redman N**, **Rondina JM**, **Diedrichsen J**, **Ward NS.** Sensorimotor cortex β oscillations reflect motor skill learning ability after stroke. *Brain Commun* 2: fcaa161, 2020. doi:10.1093/braincomms/fcaa161.
24. **Liddle EB**, **Price D**, **Palaniyappan L**, **Brookes MJ**, **Robson SE**, **Hall EL**, **Morris PG**, **Liddle PF.** Abnormal salience signaling in schizophrenia: the role of integrative β oscillations. *Hum Brain Mapp* 37: 1361–1374, 2016. doi:10.1002/hbm.23107.
25. **Uhlhaas PJ**, **Linden DE**, **Singer W**, **Haenschel C**, **Lindner M**, **Maurer K**, **Rodriguez E.** Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci* 26: 8168–8175, 2006. doi:10.1523/JNEUROSCI.2002-06.2006.
26. **Degardin A**, **Houdayer E**, **Bourriez JL**, **Destee A**, **Defebvre L**, **Derambure P**, **Devos D.** Deficient "sensory" β synchronization in Parkinson's disease. *Clin Neurophysiol* 120: 636–642, 2009. doi:10.1016/j.clinph.2009.01.001.
27. **Hall SD**, **Prokic EJ**, **McAllister CJ**, **Ronnqvist KC**, **Williams AC**, **Yamawaki N**, **Witton C**, **Woodhall GL**, **Stanford IM.** GABA-mediated changes in inter-hemispheric β frequency activity in early-stage Parkinson's disease. *Neuroscience* 281: 68–76, 2014. doi:10.1016/j.neuroscience.2014.09.037.
28. **Heida T**, **Poppe NR**, **de Vos CC**, **van Putten MJ**, **van Vugt JP.** Event-related mu-rhythm desynchronization during movement observation is impaired in Parkinson's disease. *Clin Neurophysiol* 125: 1819–1825, 2014. doi:10.1016/j.clinph.2014.01.016.
29. **Pihko E**, **Nevalainen P**, **Vaalto S**, **Laaksonen K**, **Mäenpää H**, **Valanne L**, **Lauronen L.** Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: a magnetoencephalographic study. *Hum Brain Mapp* 35: 4105–4117, 2014. doi:10.1002/hbm.22462.
30. **Hoffman RM**, **Wilson TW**, **Kurz MJ.** Hand motor actions of children with cerebral palsy are associated with abnormal sensorimotor cortical oscillations. *Neurorehabil Neural Repair* 33: 1018–1028, 2019. doi:10.1177/1545968319883880.
31. **Kurz MJ**, **Proskovec AL**, **Gehringer JE**, **Heinrichs-Graham E**, **Wilson TW.** Children with cerebral palsy have altered oscillatory activity in the motor and visual cortices during a knee motor task. *Neuroimage Clin* 15: 298–305, 2017. doi:10.1016/j.nicl.2017.05.008.
32. **Parkkonen E**, **Laaksonen K**, **Piitulainen H**, **Pekkola J**, **Parkkonen L**, **Tatlisumak T**, **Forss N.** Strength of ~20-Hz rebound and motor recovery after stroke. *Neurorehabil Neural Repair* 31: 475–486, 2017. doi:10.1177/1545968316688795.
33. **Tang CW**, **Hsiao FJ**, **Lee PL**, **Tsai YA**, **Hsu YF**, **Chen WT**, **Lin YY**, **Stagg CJ**, **Lee IH.** β-Oscillations reflect recovery of the paretic upper limb in subacute stroke. *Neurorehabil Neural Repair* 34: 450–462, 2020. doi:10.1177/1545968320913502.
34. **Espenhahn S**, **de Berker AO**, **van Wijk BCM**, **Rossiter HE**, **Ward NS.** Movement-related β oscillations show high intra-individual reliability. *NeuroImage* 147: 175–185, 2017. doi:10.1016/j.neuroimage.2016.12.025.
35. **Piitulainen H**, **Illman M**, **Laaksonen K**, **Jousmäki V**, **Forss N.** Reproducibility of corticokinematic coherence. *Neuroimage* 179: 596–603, 2018. doi:10.1016/j.neuroimage.2018.06.078.
36. **Piitulainen H**, **Illman M**, **Jousmäki V**, **Bourguignon M.** Feasibility and reproducibility of electroencephalography-based corticokinematic coherence. *J Neurophysiol* 124: 1959–1967, 2020. doi:10.1152/jn.00562.2020.
37. **Oldfield RC.** The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9: 97–113, 1971. doi:10.1016/0028-3932(71)90067-4.
38. **Piitulainen H**, **Bourguignon M**, **Hari R**, **Jousmäki V.** MEG-compatible pneumatic stimulator to elicit passive finger and toe movements. *Neuroimage* 112: 310–317, 2015. doi:10.1016/j.neuroimage.2015.03.006.
39. **Taulu S**, **Simola J.** Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Phys Med Biol* 51: 1759–1768, 2006. doi:10.1088/0031-9155/51/7/008.
40. **Gramfort A**, **Luessi M**, **Larson E**, **Engemann DA**, **Strohmeier D**, **Brodbeck C**, **Goj R**, **Jas M**, **Brooks T**, **Parkkonen L**, **Hämäläinen M.** MEG and EEG data analysis with MNE-Python. *Front Neurosci* 7: 267, 2013. doi:10.3389/fnins.2013.00267.
41. **Uusitalo MA**, **Ilmoniemi RJ.** Signal-space projection method for separating MEG or EEG into components. *Med Biol Eng Comput* 35: 135–140, 1997. doi:10.1007/BF02534144.
42. **David O**, **Kilner JM**, **Friston KJ.** Mechanisms of evoked and induced responses in MEG/EEG. *NeuroImage* 31: 1580–1591, 2006. doi:10.1016/j.neuroimage.2006.02.034.
43. **Illman M**, **Laaksonen K**, **Liljeström M**, **Piitulainen H**, **Forss N.** The effect of alertness and attention on the modulation of the β rhythm to tactile stimulation. *Physiol Rep* 9: e14818, 2021. doi:10.14814/phy2.14818.
44. **Pfurtscheller G**, **Stancak A Jr**, **Edlinger G.** On the existence of different types of central β rhythms below 30 Hz. *Electroencephalogr Clin Neurophysiol* 102: 316–325, 1997. doi:10.1016/S0013-4694(96)96612-2.
45. **Tallon-Baudry C**, **Bertrand O**, **Delpuech C**, **Permier J.** Oscillatory γ-band (30-70 Hz) activity induced by a visual search task in humans. *J Neurosci* 17: 722–734, 1997. 15: doi:10.1523/JNEUROSCI.17-02-00722.1997.
46. **Wilson TW**, **Heinrichs-Graham E**, **Becker KM.** Circadian modulation of motor-related β oscillatory responses. *Neuroimage* 102: 531–539, 2014. doi:10.1016/j.neuroimage.2014.08.013.
47. **Bardouille T**, **Bailey L**, **CamCAN Group.** Evidence for age-related changes in sensorimotor neuromagnetic responses during cued button pressing in a large open-access dataset. *Neuroimage* 193: 25–34, 2019. doi:10.1016/j.neuroimage.2019.02.065.
48. **Fry A**, **Mullinger KJ**, **O'Neill GC**, **Barratt EL**, **Morris PG**, **Bauer M**, **Folland JP**, **Brookes MJ.** Modulation of post-movement β rebound by contraction force and rate of force development. *Hum Brain Mapp* 37: 2493–2511, 2016. doi:10.1002/hbm.23189.
49. **Hari R**, **Salmelin R.** Human cortical oscillations: a neuromagnetic view through the skull. *Trends Neurosci* 20: 44–49, 1997. doi:10.1016/S0166-2236(96)10065-5.
50. **Cassim F**, **Szurhaj W**, **Sediri H**, **Devos D**, **Bourriez J**, **Poirot I**, **Derambure P**, **Defebvre L**, **Guieu J.** Brief and sustained movements: differences in event-related (de)synchronization (ERD/ERS) patterns. *Clin Neurophysiol* 111: 2032–2039, 2000. doi:10.1016/s1388-2457(00)00455-7.
51. **Zhang X**, **Li H**, **Xie T**, **Liu Y**, **Chen J**, **Long J.** Movement speed effects on β-band oscillations in sensorimotor cortex during voluntary activity. *J Neurophysiol* 124: 352–359, 2020. doi:10.1152/jn.00238.2020.
52. **Derambure P**, **Defebvre L**, **Bourriez JL**, **Cassim F**, **Guieu JD.** Event-related desynchronization and synchronization. Reactivity of electrocortical rhythms in relation to the planning and execution of voluntary movement. *Neurophysiol Clin* 29: 53–70, 1999. doi:10.1016/s0987-7053(99)80041-0.
53. **Parkkonen E**, **Laaksonen K**, **Parkkonen L**, **Forss N.** Recovery of the 20 Hz rebound to tactile and proprioceptive stimulation after stroke. *Neural Plast* 2018: 7395798, 2018. doi:10.1155/2018/7395798.
54. **Hillebrand A**, **Barnes GR.** A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. *Neuroimage* 16: 638–650, 2002. doi:10.1006/nimg.2002.1102.
55. **Nikulin VV**, **Brismar T.** Long-range temporal correlations in α and β oscillations: effect of arousal level and test-retest reliability. *Clin Neurophysiol* 115: 1896–1908, 2004. doi:10.1016/j.clinph.2004.03.019.
56. **Martin-Buro MC**, **Garces P**, **Maestu F.** Test-retest reliability of resting-state magnetoencephalography power in sensor and source space. *Hum Brain Mapp* 37: 1: 179–190, 2016. doi:10.1002/hbm.23027.
57. **Heinrichs-Graham E**, **Wilson TW.** Is an absolute level of cortical β suppression required for proper movement? Magnetoencephalographic evidence from healthy aging. *Neuroimage* 134: 514–521, 2016. doi:10.1016/j.neuroimage.2016.04.032.
58. **Lemm S**, **Müller KR**, **Curio G.** A generalized framework for quantifying the dynamics of EEG event-related desynchronization. *PLoS Comput Biol* 5: e1000453, 2009. doi:10.1371/journal.pcbi.1000453.
59. **Laaksonen K**, **Helle L**, **Parkkonen L**, **Kirveskari E**, **Mäkelä JP**, **Mustanoja S**, **Tatlisumak T**, **Kaste M**, **Forss N.** Alterations in spontaneous brain oscillations during stroke recovery. *PLoS One* 8: e61146, 2013. doi:10.1371/journal.pone.0061146.

60. **Tecchio F**, **Zappasodi F**, **Pasqualetti P**, **Tombini M**, **Caulo M**, **Ercolani M**, **Rossini PM.** Long-term effects of stroke on neuronal rest activity in rolandic cortical areas. *J Neurosci Res* 83: 1077–1087, 2006. doi:10.1002/jnr.20796.
61. **Gaetz W**, **Macdonald M**, **Cheyne D**, **Snead OC.** Neuromagnetic imaging of movement-related cortical oscillations in children and adults: age predicts post-movement β rebound. *Neuroimage* 51: 792–807, 2010. doi:10.1016/j.neuroimage.2010.01.077.
62. **Xifra-Porxas A**, **Niso G**, **Larivière S**, **Kassinopoulos M**, **Baillet S**, **Mitsis GD**, **Boudrias MH.** Older adults exhibit a more pronounced modulation of β oscillations when performing sustained and dynamic handgrips. *Neuroimage* 201: 116037, 2019. doi:10.1016/j.neuroimage.2019.116037.
63. **Rossiter HE**, **Davis EM**, **Clark EV**, **Boudrias MH**, **Ward NS.** Beta oscillations reflect changes in motor cortex inhibition in healthy ageing. *Neuroimage* 91: 360–365, 2014. doi:10.1016/j.neuroimage.2014.01.012.
64. **Koelewijn L**, **Bompas A**, **Tales A**, **Brookes MJ**, **Muthukumaraswamy SD**, **Bayer A**, **Singh KD.** Alzheimer's disease disrupts α and β-band resting-state oscillatory network connectivity. *Clin Neurophysiol* 128: 2347–2357, 2017. doi:10.1016/j.clinph.2017.04.018.
65. **Toth M**, **Kiss A**, **Kosztolanyi P**, **Kondakor I.** Diurnal alterations of brain electrical activity in healthy adults: a LORETA study. *Brain Topogr* 20: 63–76, 2007. doi:10.1007/s10548-007-0032-3.
66. **Hall SD**, **Barnes GR**, **Furlong PL**, **Seri S**, **Hillebrand A.** Neuronal network pharmacodynamics of GABAergic modulation in the human cortex determined using pharmaco-magnetoencephalography. *Hum Brain Mapp* 31: 581–594, 2010. doi:10.1002/hbm.20889.
67. **Jensen O**, **Goel P**, **Kopell N**, **Pohja M**, **Hari R**, **Ermentrout B.** On the human sensorimotor-cortex β rhythm: sources and modeling. *Neuroimage* 26: 347–355, 2005. doi:10.1016/j.neuroimage.2005.02.008.
68. **Boksem MA**, **Meijman TF**, **Lorist MM.** Effects of mental fatigue on attention: an ERP study. *Brain Res Cogn Brain Res* 25: 107–116, 2005. doi:10.1016/j.cogbrainres.2005.04.011.
69. **Kamiński J**, **Brzezicka A**, **Gola M**, **Wróbel A.** Beta band oscillations engagement in human alertness process. *Int J Psychophysiol* 85: 125–128, 2012. doi:10.1016/j.ijpsycho.2011.11.006.
70. **Bardouille T**, **Picton TW**, **Ross B.** Attention modulates β oscillations during prolonged tactile stimulation. *Eur J Neurosci* 31: 761–769, 2010. doi:10.1111/j.1460-9568.2010.07094.x.
71. **Dockstader C**, **Cheyne D**, **Tannock R.** Cortical dynamics of selective attention to somatosensory events. *Neuroimage* 49: 1777–1785, 2010. doi:10.1016/j.neuroimage.2009.09.035.
72. **Bauer M**, **Oostenveld R**, **Peeters M**, **Fries P.** Tactile spatial attention enhances γ-band activity in somatosensory cortex and reduces low-frequency activity in parieto-occipital areas. *J Neurosci* 26: 490–501, 2006. doi:10.1523/JNEUROSCI.5228-04.2006.
73. **Piitulainen H**, **Nurmi T**, **Hakonen M.** Attention directed to proprioceptive stimulation alters its cortical processing in the primary sensorimotor cortex. *Eur J Neurosci* 54: 4269–4282, 2021. doi:10.1111/ejn.15251.

IV

ALTERED EXCITATION-INHIBITION BALANCE IN THE PRIMARY SENSORIMOTOR CORTEX TO PROPRIOCEPTIVE HAND STIMULATION IN CEREBRAL PALSY

by

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