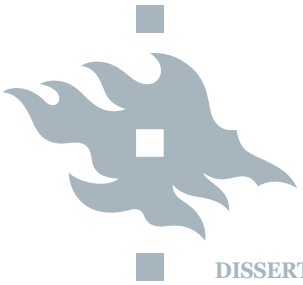

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Cortical Processes Related to Motor Stability and Proprioception in Human Adults and Newborns

Eero Smeds

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Auditorium F239a (Otakaari 3A, Espoo) on 24 March 2017, at 12 noon.

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Espoo, January 2017

Eero Smeds

Abstract

Accurate control of motor performance requires close co-operation between the motor and sensory functions of the human nervous system. Proprioceptive information about the positions and movements of one's own body parts needs to be carefully monitored to allow fine-tuning of motor output. At the same time, the brain needs to block the influence of distracting external stimuli, such as movements of other persons and various sounds, on the ongoing movements. My thesis focuses on the cortical processes related to these phenomena.

In the first studies of this thesis, we explored motor stability by recording brain and muscle activity with magnetoencephalography (MEG) and electromyography, respectively, from healthy adults who were maintaining a steady finger pinch. We analyzed the effects of simple auditory and visual distractors as well as observed movements of another person on the functional state of the primary motor (MI) cortex. All studied stimuli caused transient enhancement of the coupling between cortical and muscular activity at ~20 Hz, reflecting the maintenance of stable motor output. As expected based on earlier studies, movement observation also caused "mirror" activation in the MI cortex of the viewer, demonstrated by MEG-power suppression at ~7 and ~15 Hz. Importantly, these two simultaneous but opposite processes occurred at distinct frequency bands, suggesting that they were mediated by different populations of MI neurons. The results might explain how the human brain blocks the effects of external distractors on motor behavior and prevents unintentional imitation of observed movements.

The latter part of my thesis focuses on cortical activity evoked by proprioceptive afference in adults and newborns. In adults, we recorded MEG responses to proprioceptive input elicited by passive finger extensions and flexions. The amplitudes of the ~70-ms (extension) and ~90-ms (flexion) responses in the primary somatosensory cortex increased

by a factor of ~3 and ~6, respectively, when the interstimulus interval was prolonged from 0.5 to 8 s. These findings suggest an optimum interstimulus interval of 1.5–3.0 s for future applications in research and in the clinic. Finally, we showed using electroencephalography that proprioceptive stimulation with continuous passive hand movements elicits a prominent cortical response already at the neonatal phase. Such a passive-movement-based stimulation method could help assess the integrity of somatosensory pathways in neurologically impaired newborns.

This thesis improves understanding of the cortical mechanisms essential for proper motor control. The gained knowledge can ultimately benefit diagnostics, treatment, and follow-up of motor-system impairments ranging from movement disorders to neonatal cerebrovascular problems.

Tiivistelmä

Täsmällinen liikkeiden säätely edellyttää tiivistä yhteistyötä aivojen liike- ja aistitoimintojen välillä. Yhtäältä aivojen on tarkasti seurattava asentotunnon (proprioseptiikka) välittämää tietoa eri kehonosien asennoista ja liikkeistä, jotta motoriikan hienosäätely olisi mahdollista. Toisaalta taas aivojen täytyy välttää ulkoisten ärsykkeiden, kuten erilaisten äänten ja vaikkapa ympärillä olevien ihmisten liikkeiden, liiallista vaikutusta ihmisen omiin liikkeisiin. Väitöskirjani paneutuu näihin ilmiöihin liittyviin aivokuoritason toimintoihin.

Ensimmäisissä osatöissä tutkimme motorista vakautta ulkoisten häiriöärsykkeiden aikana mittaamalla terveiden aikuisten koehenkilöiden aivo- ja lihastoimintaa magnetoenkefalografialla (MEG) ja elektromyografialla samalla kun he puristivat pinsettiotteella voima-anturia tasaisella, kevyellä voimalla. Esitimme koehenkilöille tehtävän aikana yksinkertaisia kuulo- ja näköärsykkeitä sekä näytimme toisen henkilön käden liikkeitä. Primaarilta liikeaivokuorelta (MI) ja käden lihaksista mitattujen signaalien välillä esiintyvä ~20 Hz:n taajuinen niin kutsuttu kortikomuskulaarinen koherenssi voimistui kaikkien esitettyjen häiriöärsykkeiden jälkeen merkkinä MI alueen toiminnan vakauttamisesta. Toisen henkilön käden liike aiheutti lisäksi ”peilautumista” katsojan omalla MI alueella, kuten jo aiemmissa tutkimuksissa on näytetty. Tästä peilautumisesta osoituksena oli MEG:n tehon vaimeneminen ~7 ja ~15 Hz:n taajuuksilla. Nämä samanaikaiset mutta vastakkaiset prosessit esiintyivät eri taajuuksilla viitaten siihen, että ne olivat lähtöisin eri hermosolupopulaatioista. Tuloksemme voivat selittää sen, kuinka aivot torjuvat ulkoisten häiriöärsykkeiden suorat vaikutukset ihmisen omiin liikkeisiin ja estävät muiden ihmisten liikkeiden tahattoman matkimisen.

Väitöskirjani jälkimmäinen osa tarkastelee proprioseptiivisten ärsykkeiden herättämää aivoaktivaatiota aikuisilla ja vastasyntyneillä. Mittasimme aikuisilta passiivisten

sormen ojennus- ja koukistusliikkeiden synnyttämiä MEG-vasteita tutkien erityisesti sitä, kuinka liikeärsykkeiden antotiheys vaikuttaa vasteiden voimakkuuteen. Voimakkaimmat vastehuiput esiintyivät primaarilla tuntoaivokuorella ~70 (ojennus) ja ~90 ms (koukistus) liikkeen alun jälkeen, ja niiden amplitudi kasvoi noin kolmin- (ojennus) ja kuusinkertaisiksi (koukistus), kun peräkkäisten liikkeiden välistä aikaa pidennettiin 0.5 sekunnista 8 sekuntiin. Tulosten perusteella optimaalinen liikeärsykkeiden välinen aika näiden aivovasteiden mittaamiseen on 1.5–3 s. Tietoa voidaan hyödyntää tulevissa sovelluksissa niin tutkimuksessa kuin kliinisessäkin työssä. Viimeisessä osatyössä osoitimme, että elektroenkefalografialla voi mitata passiivisen liikkeen synnyttämiä aivovasteita myös vastasyntyneiltä. Tällaisilla mittauksilla voidaan kenties tulevaisuudessa selvittää vastasyntyneiden potilaiden tuntojärjestelmän toimintaa aivovaurioiden ja muiden neurologisten häiriöiden yhteydessä.

Väitöskirjani edistää ymmärrystä liikkeiden säätelyyn liittyvistä aivokuoritason mekanismeista. Uusi tieto voi lopulta johtaa parempaan diagnostiikkaan, hoitoon ja seurantaan esimerkiksi liikehäiriöissä sekä vastasyntyneiden aivoverenkiertohäiriöissä.

List of original publications

This thesis is based on the original publications listed below. They have been reprinted with the permission of their copyright holders.

P1: Hari R, Bourguignon M, Piitulainen H, **Smeds E**, De Tiège X, Jousmäki V: Human primary motor cortex is both activated and stabilized during observation of other person's phasic motor actions. *Philos Trans R Soc Lond B Biol Sci* 2014, 369: 20130171. doi: 10.1098/rstb.2013.0171.

P2: Piitulainen H, Bourguignon M, **Smeds E**, De Tiège X, Jousmäki V, Hari R: Phasic stabilization of motor output after auditory and visual distractors. *Hum Brain Mapp* 2015, 36: 5168–5182. doi: 10.1002/hbm.23001.

P3: **Smeds E**, Piitulainen H, Bourguignon M, Jousmäki V, Hari R: Effect of interstimulus interval on cortical proprioceptive responses to passive finger movements. *Eur J Neurosci* 2016, 45: 290–298. doi: 10.1111/ejn.13447.

P4: **Smeds E**, Vanhatalo S, Piitulainen H, Bourguignon M, Jousmäki V, Hari R: Corticokinematic coherence as a new marker for somatosensory afference in newborns. *Clin Neurophysiol* 2017. In press. doi: 10.1016/j.clinph.2017.01.006.

Author's contribution

P1: I participated in collecting and analyzing the data. I contributed to writing the manuscript as a coauthor.

P2: I participated in designing the experiment as well as collecting and analyzing the data. I contributed to writing the manuscript as a coauthor.

P3: I participated in designing the experiment and collecting the data. I was in charge of analyzing the data and writing the manuscript with contributions from my coauthors.

P4: I participated in designing the experiment and performing the pilot measurements. I was in charge of analyzing the data and writing the manuscript with contributions from my coauthors.

Abbreviations

CKC	corticokinematic coherence
CMC	cortex–muscle coherence
ECD	equivalent current dipole
EEG	electroencephalography
EMG	electromyography
F0	fundamental frequency
F1	first harmonic frequency
HUH	Helsinki University Hospital
ISI	interstimulus interval
MEG	magnetoencephalography
MI	primary motor (cortex)
MRI	magnetic resonance imaging
NICU	neonatal intensive care unit
PAM	pneumatic artificial muscle
SEP	somatosensory evoked potential
SI	primary somatosensory (cortex)
SMI	primary sensorimotor (cortex)
SNR	signal-to-noise ratio

1 Introduction

Imagine being a mountain climber. Your life depends on your ability to sense, without seeing, the positions and movements of your whole body. Thus, you need to rely on your proprioceptive sense. Furthermore, you need to stay alert to any external events, such as sudden sounds or moving objects, while simultaneously minimizing their direct influence on your movements.

Despite their importance for our everyday life, these elements of motor control—namely, proprioception and the ability to maintain stable motor output in the face of environmental distractors—are poorly known, especially in terms of the involvement of the primary sensorimotor (SMI) cortex. How does the brain block the effects of external distractors on motor behavior at the level of the primary motor (MI) cortex? How is proprioceptive afference reflected in the primary somatosensory (SI) cortex and how can proprioceptive cortical responses be evoked and measured most efficiently?

My thesis aims to fill these gaps (1) by exploring the effects of external distractors on the functional state of the MI cortex and its output during a precision-demanding motor task and (2) by characterizing cortical responses to proprioceptive input elicited by passive movements in adults and newborns. The results offer novel insight into cortical mechanisms supporting motor stability in healthy and diseased individuals. Furthermore, the improved understanding of proprioceptive cortical processing can be exploited in the development of new diagnostic tools in clinical neurophysiology.

2 Background

2.1 Magnetoencephalography

Magnetoencephalography (MEG) is a functional brain imaging method to study electrical activity of the brain by measuring the associated magnetic fields noninvasively outside the subject's head with magnetometers placed close to the scalp. As an electrophysiological method—similar to, for example, electroencephalography (EEG)—MEG has excellent temporal resolution, better than 1 ms. The spatial resolution of MEG can reach a few millimeters (for a review, see Hämäläinen et al., 1993).

2.1.1 History

The development of MEG over the past decades has been thoroughly reviewed by Hari and Salmelin (2012). The first MEG signals were measured with a single copper-coil magnetometer in the late 1960s (Cohen, 1968). The measured signals were ~10-Hz alpha oscillations, which were averaged time-locked to a certain phase in the simultaneously measured EEG signal. Several thousand epochs were required to detect the extremely weak MEG signals buried in the many times stronger noise, which mainly originated from the coil itself. Over a decade later, the MEG method was greatly improved by the introduction of new magnetic-field sensors, the superconducting quantum interference devices (SQUIDs), with low intrinsic noise and exquisite sensitivity to the weak brain signals (Cohen, 1972). With SQUIDs, cortical magnetic signals were finally detectable without averaging.

The early single-sensor MEG devices could measure the magnetic field only at one location at a time. Every task typically had to be repeated multiple times, moving the device between the replications, to cover the area of interest. Hence, recordings were very time-consuming, and studying the interplay between multiple brain regions was practically

impossible. Accordingly, MEG studies in the 1970s and 1980s focused on evoked responses in primary sensory areas (Brenner et al., 1975; Reite et al., 1978; Hari et al., 1980; 1983b; Teszner et al., 1983). To address the limitations of the single-sensor setup, multi-channel MEG devices started to be developed in the 1980s, eventually leading to the construction of the first whole-scalp system with 122 SQUID sensors in 1992. Current MEG systems typically contain 150–300 sensors arranged in a helmet-shaped array. The development of whole-head MEG devices has shifted the focus of the field to larger cortical areas and their connections, and enabled the study of complex brain functions such as those related to language processing and social interaction (for a review, see Hari and Salmelin, 2012).

2.1.2 Physiological basis

The primary origin of MEG signals is the synchronous activation of tens of thousands of cortical pyramidal neurons. During such activation electric currents flow in the neurons' apical dendrites, which are oriented parallel to each other. The net current within the active neuronal population is also oriented along the apical dendrites and generates a magnetic field that can be detected outside the head with MEG sensors. This current, called the primary current, is associated with opposite volume currents that close the electrical circuit and thus balance the accumulation of electric charge. When viewed from a distance, the circuit can be modeled as a point-like current dipole (representing the primary current) and return currents (volume currents) flowing in the surrounding conducting medium. When identifying cortical sources based on MEG signals, the aim is to solve the 'inverse problem', that is, to infer the primary-current distribution given the magnetic field on the surface of the head.

One crucial issue to consider here is the shape of the volume conductor. A sphere is a feasible first approximation for the head. In an ideally spherical conductor, the orientation of the primary current is decisive in whether or not a magnetic field can be detected outside the sphere. The strongest magnetic fields are generated by primary currents oriented tangentially with respect to the sphere's surface. In contrast, radially oriented primary currents and the corresponding volume currents counterbalance each other's effects on the magnetic field outside the sphere. In other words, radial currents do not generate magnetic fields outside a spherical volume conductor. Although the head is not an ideal sphere, also in MEG, the sensitivity is markedly better for tangential than radial cortical currents. Thus, MEG is most suited for measuring activity of cortical areas located in the walls of sulci,

where primary currents, oriented perpendicular to the cortical surface, run mostly tangentially to the head surface. In that sense, MEG is complementary to EEG, which is most sensitive to superficial radial currents, although it also picks up activity from tangential and deep currents. Unlike the electric potentials that are picked up by EEG, magnetic fields permeate the different tissue types between the cortex and the sensors (the cerebrospinal fluid, the skull, and the scalp) practically unaltered. This gives MEG an important advantage in the accuracy of source localization.

2.1.3 Magnetoencephalography in the study of the primary sensorimotor cortex

The SMI cortex comprises the SI cortex in the parietal lobe, posterior to the central sulcus, and the MI cortex in the frontal lobe, anterior to the central sulcus. The walls of the central sulcus contain both somatosensory and motor areas. The MI cortex, along with other motor areas, sends motor commands to spinal motoneurons via the pyramidal tract, whereas the SI cortex is responsible for the primary processing of somatosensory afference. The SI cortex further comprises several cytoarchitectonic areas: area 3b, which forms the largest part of the posterior bank of the central sulcus; area 3a, which covers the lower part of the posterior bank as well as the bottom of the sulcus; area 1, which covers the apex of the postcentral gyrus; and area 2, which lies immediately posteriorly from area 1. Areas 3b and 1 receive cutaneous afference, whereas areas 3a and 2 receive mostly proprioceptive afference. Areas 1 and 2 receive also abundant input from the more anterior areas 3b and 3a. In addition to having distinct cytoarchitectures, the subdivisions of SI also exhibit different receptor distributions (Geyer et al., 1997).

In the walls of cortical sulci, currents in apical dendrites run tangentially to the head surface. Thus, activity in the central sulcus can be readily explored with MEG (except in the special case where the magnetic fields produced by simultaneous oppositely oriented currents on the opposite walls of the sulcus cancel each other). Indeed, the SMI cortex has been one of the main focus areas in the history of MEG research. Numerous studies on somatosensory evoked fields in response to electrical or tactile stimulation have advanced our understanding of the processing of somatosensory afferent information (Brenner et al., 1978; Kaufman et al., 1981; Hari et al., 1984; Huttunen, 1986; Pihko et al., 2009; for reviews, see Hari and Forss, 1999; Kakigi and Forss, 2010). Also movement-related MEG activity has been extensively studied (Deecke et al., 1982; Hari et al., 1983a; Cheyne and

Weinberg, 1989; Salmelin et al., 1995; Cheyne et al., 1997; for a review, see Kakigi and Forss, 2010).

Studies on the spontaneous sensorimotor rhythm (mu rhythm), which comprises two main frequency components at ~10 and ~20 Hz, form one important sector of MEG research on SMI functions (for a review, see Cheyne, 2013). The mu rhythm is also central in studies on the coupling between the SMI cortex and muscular activity during stable muscle contraction (cortex–muscle coherence; CMC; Conway et al., 1995; Salenius et al., 1997a). Similar coherence analysis has been applied to evaluate coupling between cortical activity and kinematic signals (e.g. acceleration) from active or passive movements (Bourguignon et al., 2011; Piitulainen et al., 2013). This corticokinematic coherence (CKC) is observed at the movement frequency and its harmonics. I will discuss the sensorimotor mu rhythm as well as CMC and CKC in more detail in Sections 2.3, 2.4, and 2.5.3.

2.2 Motor stability in the presence of external distractors

Afferent input from all sensory modalities can have bottom-up effects on cortical motor areas. Abundant parietofrontal connections form the basis of sensorimotor transformations, which enable stereotypical and fast motor actions (such as relevant hand or eye movements) to specific types of stimuli (for a review, see Rizzolatti et al., 1998). Another special case of sensory information affecting cortical motor areas occurs when a person is observing another person's actions. Activation in the observer's brain extends to premotor and parietal areas that are active also during own movements (mirroring system; for reviews, see Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2010), and even to the MI cortex (Hari et al., 1998; Caetano et al., 2007; for a review, see Hari, 2015). This vicarious activation is thought to support understanding of observed actions and their goals, as well as learning through imitation (Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2010).

The literature presented above shows that sensory information has access to motor areas to enable proper actions. However, not all sensory input should affect the motor behavior. Indeed, it is neither appropriate nor practical to react to every stimulus or imitate all observed movements. To enable proper motor performance, the brain must be able to block the influence of an enormous amount of irrelevant stimuli.

One part of the solution to this problem seems to involve multi-level top-down suppression from the frontal lobes to more posterior brain areas. In a visual search task, strong activity in the premotor cortex reduced the level of behavioral interference caused by a visual distractor, suggesting that the premotor cortex controls parietal areas to facilitate a shift of attention towards the target stimulus and away from the distractor (de Fockert et al., 2004). The prevention of automatic imitation also relies on inhibition from frontal to more posterior brain areas, as is indicated by a patient study linking frontal lesions to pathological imitation behavior (Lhermitte et al., 1986) as well as by a combined functional magnetic resonance imaging and transcranial magnetic stimulation study in healthy subjects (Bien et al., 2009). Also the subthalamic nucleus contributes to the prevention of unintended motor reactions and imitation (Aron and Poldrack, 2006; Ray et al., 2012). It participates in suppressing already initiated movements, possibly by inhibiting thalamocortical output (Aron and Poldrack, 2006).

Despite these previous reports on brain mechanisms preventing undesired motor reactions, the end effects on the MI cortex and the corticospinal pathway remain largely unknown. Studies P1 and P2 of my thesis attempt to elucidate these issues.

2.3 Sensorimotor rhythms

The SMI cortex, like many other cortical areas, expresses characteristic spontaneous rhythmic activity visible both in EEG (Gastaut, 1952) and MEG (Tiihonen et al., 1989b). This mu rhythm has an arch-shaped waveform, and it comprises both alpha (~10 Hz) and beta (~20 Hz) frequencies. The mu rhythm is prominent at rest but is suppressed transiently by active (Jasper and Penfield, 1949; Gastaut, 1952; Salmelin and Hari, 1994b) and passive (Chatrian et al., 1959; Alegre et al., 2002) movements, as well as by electrical median-nerve (Salmelin and Hari, 1994a; Salenius et al., 1997b) and tactile (Chatrian et al., 1959; Cheyne et al., 2003) stimulation. After the initial suppression, the mu rhythm typically increases in amplitude exceeding the pre-suppression level for a brief period (rebound) before returning to baseline (Salmelin and Hari, 1994b; Alegre et al., 2002; Cheyne et al., 2003). However, the rebound following median-nerve stimulation is abolished by simultaneous manipulation of an object (Salenius et al., 1997b; Schnitzler et al., 1997; Hari et al., 1998) and, to a lesser extent, by finger movements and tactile stimulation (Salenius et al., 1997b).

Visual and auditory stimuli can also modulate the mu rhythm. A change in the percept of a non-biological visual stimulus is associated with enhanced alpha-band mu oscillations (Vanni et al., 1999), whereas verbal instructions to move suppress the mu rhythm (Chatrian et al., 1959). Action-related sounds cause a similar but weaker rebound in the beta-band mu rhythm compared with own actions (Caetano et al., 2007), while movement observation (Hari et al., 1998; Caetano et al., 2007) and even motor imagery (Schnitzler et al., 1997) suppress the beta-band mu rhythm.

2.4 Cortex–muscle coherence

During weak–intermediate isometric muscle contraction electromyographic (EMG) signals are coherent with SMI-cortex activity at ~20 Hz, as has been shown in previous MEG (Conway et al., 1995; Salenius et al., 1997a; Gross et al., 2000) and EEG (Halliday et al., 1998) recordings. At higher contraction forces, this cortex–muscle coherence (CMC) peaks at ~40 Hz (Salenius et al., 1996; Brown et al., 1998). CMC seems to reflect the corticospinal drive from the MI cortex to the motoneuron pool, as it is predominantly driven by efferent signaling (Salenius et al., 1997a; Gross et al., 2000; Lim et al., 2014), with a negligible contribution by afferent sensory feedback from the muscles to the cortex (Baker, 2007; Witham et al., 2011; Lim et al., 2014). Furthermore, in the efferent CMC component, the lags between the cortical signals and the EMG signals correspond to the conduction times from the MI cortex to the muscles (Salenius et al., 1997a; Gross et al., 2000).

Like the mu rhythm, CMC typically responds to changes in the sensorimotor state with a transient suppression and a subsequent rebound. Such situations include movements (Kilner et al., 1999; 2000) and electrical median-nerve stimulation (Hari and Salenius, 1999; Tecchio et al., 2006) as well as electrical cutaneous stimulation and mechanical perturbation (McClelland et al., 2012). Thus, CMC seems to be linked to achieving and maintaining stable MI output (Kilner et al., 2000). During stable contraction CMC is modulated also by visual stimulation (Safri et al., 2006; 2007), indicating adjustments in motor output in response to visual distractors.

In P1 and P2, we used CMC to monitor the corticospinal drive during an isometric finger-pinch task. With this approach, we studied the effect of various external distractors on the motor output.

2.5 Cortical responses to proprioceptive stimuli

2.5.1 Proprioception

The proprioceptive sense enables a person to feel the positions and movements of one's own body parts as well as the forces acting upon them (for a review, see Proske and Gandevia, 2012), thus constituting an essential part of the motor-control system. The different types of proprioceptors are sensitive to changes in the mechanical state of muscles, joints, tendons, and even the skin. Studies P3 and P4 of this thesis focus on proprioceptive afference evoked by unresisted passive movements, which mainly activate muscle receptors (Proske and Gandevia, 2012). These receptors reside inside the muscles in specific proprioceptive organs, muscle spindles, which consist of specialized muscle fibers (intrafusal fibers) and sensory nerve endings wrapped around them. During movements muscle stretch causes the intrafusal fibers to stretch, too, activating the sensory nerve endings and resulting in a neural afferent signal. The primary cortical target of this proprioceptive information is area 3a of the SI cortex (Kaas, 1993), although positron emission tomography studies indicate activation of the MI cortex as well (Naito et al., 1999; Naito and Ehrsson, 2001). The MI cortex seems to receive also some direct proprioceptive input because a subset of motor-cortex neurons in monkeys responds to muscle stretch at similar short latencies as neurons in area 3a (Lucier et al., 1975; Colebatch et al., 1990). Proprioceptive information is further processed in area 2 of the SI cortex, in the secondary somatosensory (SII) cortex, and in somatosensory association areas (Kaas, 1993).

2.5.2 Responses to transient passive movements

Proprioceptive cortical processing has been studied by using transient passive-movement stimuli and recording either EEG (Rodin et al., 1969; Papakostopoulos et al., 1974; Shibasaki et al., 1980; Mima et al., 1996) or MEG (Xiang et al., 1997; Lange et al., 2001; Alary et al., 2002; Druschky et al., 2003) responses. Such stimuli have consistently elicited in the contralateral SMI cortex prominent responses that peak ~70–80 ms after the movement onset. Some MEG studies have pinpointed the exact source of the response to be in the MI cortex (Lange et al., 2001) and others in the SI cortex (Alary et al., 2002). The cortical responses to passive movements are resilient against cutaneous anesthesia, strongly suggesting that they indeed represent proprioceptive rather than tactile afference (Starr et al., 1981; Abbruzzese et al., 1985; Mima et al., 1996).

Shortening the interstimulus interval (ISI) leads to attenuation of cortical evoked responses, regardless of the sensory modality. In other words, the cortical activity traces due to the previous stimuli affect the processing of the following ones. The duration of these traces is reflected in the decay constant or "lifetime" of the exponential saturation function that accurately describes the ISI dependence of the response amplitude (Lu et al., 1992b). Different responses have different lifetimes depending on the sensory modality, cortical area, and latency. In general, responses peaking at longer latencies and originating at higher stages of cortical processing have longer lifetimes than those at shorter latencies and lower stages, supporting the idea that individual brain areas as well as complete cortical processing streams operate on multiple hierarchically organized timescales (for a review, see Hari et al., 2010).

The effects of ISI on response amplitude have been studied in detail for the auditory ~100-ms responses (Hari et al., 1982; Lu et al., 1992b; 1992a; Mäkelä et al., 1993; Sams et al., 1993), for visual responses peaking between 90 and 440 ms (Uusitalo et al., 1996; 1997), for somatosensory responses between 20 and 100 ms (Tiihonen et al., 1989a; Hari et al., 1993; Wikström et al., 1996), and for nociceptive responses between 150 and 330 ms (Raij et al., 2003). However, studies on the influence of ISI on proprioceptive responses are few (Starr et al., 1981; Abbruzzese et al., 1985), and no reports exist on the lifetimes of these responses. In P3, we characterized in detail the ISI dependence of proprioceptive MEG responses to learn about the temporal operating scales underlying proprioceptive cortical processing and to find the optimum ISI yielding the maximum signal-to-noise ratio (SNR) in a given measurement time.

2.5.3 Steady-state response to continuous movements: corticokinematic coherence

Apart from transient movements, proprioceptive afference can be studied also using continuous repetitive movements. Such stimulation evokes cortical steady-state responses, which can be analyzed by estimating the coherence between cortical activity and the movement signal (corticokinematic coherence; CKC; Bourguignon et al., 2011; Piitulainen et al., 2013). Previous MEG studies have shown that CKC indeed illustrates afferent proprioceptive signaling, as (1) it can be elicited with about equal strength by both passive and active movements (Piitulainen et al., 2013), (2) it is stronger in the afferent than efferent direction (Bourguignon et al., 2015), and (3) it is detected regardless of the level of

cutaneous input during the stimulation (Piitulainen et al., 2013). CKC seems to enable efficient identification of the SMI cortex: in healthy adults, one minute of passive finger movements is sufficient to reliably locate the hand area of the contralateral SMI cortex in an MEG measurement (Piitulainen et al., 2015). P4 of my thesis shows that CKC can be reliably measured in newborn infants as well.

3 Aims

The aim of this thesis was to improve our understanding of cortical processes related to motor stability and proprioception, which are essential for proper motor control. By characterizing proprioceptive cortical responses in adults and newborns, we aimed at providing novel tools for neurophysiological diagnostics. Specific goals of the individual studies were as follows:

- to examine brain mechanisms preventing unintentional imitation of observed movements at the level of the MI cortex (P1).
- to investigate the effects of external distractors on the functional state of the MI cortex and on the motor output (P1 and P2).
- to characterize the ISI dependence of proprioceptive cortical responses and determine the most efficient ISI for proprioceptive stimulation (P3).
- to evaluate whether proprioceptive stimuli (produced by passive hand movements) elicit reliable cortical responses in newborn infants and could thus be used for straightforward assessment of somatosensory function (P4).

4 Materials and methods

4.1 Participants

Altogether 51 healthy adult volunteers (24 women, 27 men; age 19–38 years) took part in P1, P2, and P3. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), except for two who were ambidextrous. All subjects gave written informed consent prior to participation, and the studies were approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

In Study P4, scalp EEG was recorded from 14 newborn patients of the neonatal intensive care unit (NICU) of the Helsinki University Hospital (HUH) during clinically indicated EEG measurements. One infant had to be excluded from all analyses due to jitteriness that was related to a hypoxic-ischemic insult and caused excessive artifacts in the EEG signals. The study was part of a project that develops novel diagnostics at the Department of Children's Clinical Neurophysiology, and it was approved by the Ethics Committee of the Children's Hospital of HUH.

4.2 Tasks and stimuli

4.2.1 Isometric contraction tasks

Participants of P1 and P2 were asked to maintain a steady finger pinch with the right index finger and thumb against a force transducer in 5-min blocks repeated 2 (P1) or 4 (P2) times. Figure 1A illustrates a subject performing the task. The target force level was 10 ± 2% (P1) or 6 ± 1% (P2) of the individual maximum voluntary contraction. A continuous 500-Hz feedback tone was presented whenever the force drifted out of the target range to help subjects maintain stable force.

4.2.2 Visual and auditory stimuli

In P1, the subjects observed an experimenter performing transient right-hand pinching movements every 3–6 s against a similar force transducer as the one that the subject was using. The subjects viewed the hand from a ~2-m distance. Only the hand of the experimenter was visible to the subject. In P2, visual checkerboard and auditory beep stimuli were presented as distractors in a random order every 3.5–5 s. The duration of both stimuli was 100 ms. The frequency of the beeps (1 kHz) was clearly distinguishable from that of the feedback tone.

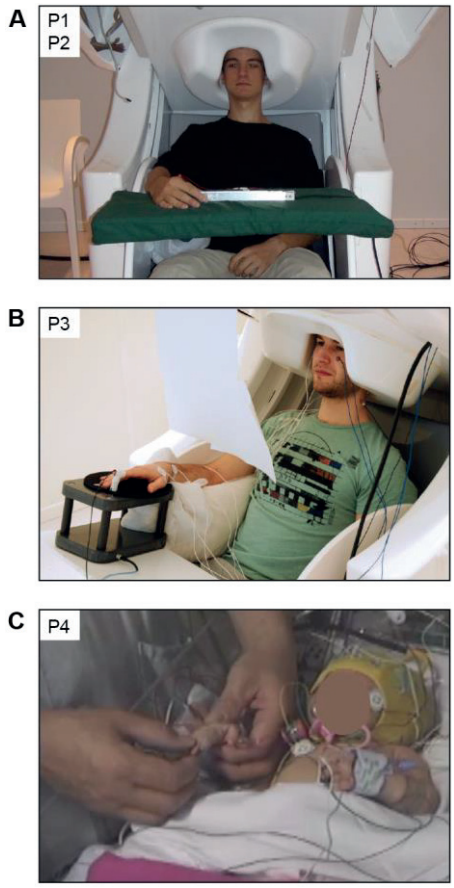

Figure 1. Measurement settings. **A.** P1 and P2: The subject is sitting with his head inside the MEG helmet and pinching the force transducer with his right hand. Adapted from Fig. 1 of P1. **B.** P3: The subject's right index finger is attached to the PAM stimulator that generates transient passive movements during the MEG recording. Adapted from Fig. 1 of P3. **C.** P4: The experimenter is moving the infant's right hand during an EEG recording. Adapted from Supplementary Video 1 of P4.

4.2.3 Passive-movement stimuli

In P3, the right index finger of the subjects was passively moved with a pneumatic artificial muscle (PAM) stimulator developed by our research team (Piitulainen et al., 2015). Figure 1B shows the measurement setting. The movements were transient alternating flexions and extensions occurring at the metacarpophalangeal joint at regular intervals. The total range of movement was ~5 mm, and the velocity during the initial 50 ms after movement onset was ~25 and ~15 mm/s for extension and flexion movements, respectively. We applied the passive movements at ISIs of 0.5, 1, 2, 4, 8, and 16 s. Here, ISI corresponded to the duration of one complete movement cycle, comprising one extension and one flexion movement. Between the extension and flexion, there was a pause, the duration of which depended on the ISI. The number of stimuli in one condition was 45–240, depending on the ISI (fewer stimuli at longer ISIs). The movements were blocked from subjects' view with a sheet of paper. Subjects also wore earplugs to avoid hearing any acoustic noise from the movement actuator.

In P4, passive movements were applied to newborn subjects. An experimenter manually generated continuous flexion–extension movements of the infant's wrist or fingers at 1 or 2 Hz for ~5–10 min at a time. The right and left hands were stimulated separately. Figure 1C shows a snapshot of the continuous stimulation of the infant's hand.

4.2.4 Somatosensory evoked potentials

In P4, somatosensory evoked potentials (SEPs) were measured, for clinical indications, from 9/13 newborns by stimulating the median nerve at both wrists separately with a pair of disk electrodes and a battery-powered portable electrical peripheral nerve stimulator (ENERGY Light integrated stimulator, Micromed, Mogliano Veneto, Italy). The ISI was 2 s and each hand was stimulated for ~10 min. The stimulation current was individually adjusted so that it produced a small twitch of the thumb of the infant.

4.3 Measurements

4.3.1 Magnetoencephalography

Magnetoencephalographic brain signals were recorded in P1, P2, and P3. The measurements were carried out with a 306-channel whole-head neuromagnetometer (Elekta Neuromag™,

Elekta Oy, Helsinki, Finland) in a magnetically shielded room (Imedco AG, Hägendorf, Switzerland) in the MEG Core of Aalto NeuroImaging, Aalto University. Table 1 indicates the sampling rates and online filters of MEG as well as all other recordings. During the measurements the head position was continuously monitored by feeding currents into 4–5 head-tracking coils attached to the scalp. The locations of the coils were digitized with respect to anatomical fiducials with an electromagnetic tracker (Fastrak®, Polhemus, Colchester, VT, USA).

4.3.2 Electroencephalography

In P4, EEG signals were measured from newborn infants with a NicoletOne™ EEG system (Natus Medical Inc., Pleasanton, CA, USA) and 19 sintered Ag/AgCl electrodes attached to an EEG cap (Waveguard™, ANT Neuro, Enschede, The Netherlands). EEG signals were recorded with reference to the Cz electrode at the vertex. The measurements were part of clinical EEG recordings carried out in the NICU of HUH by the staff of the Department of Children's Clinical Neurophysiology.

Table 1. Sampling rates and online and offline filters of different signals in individual publications. The notch filter was set at 50 Hz and its harmonics. Acc. = acceleration; LP = low-pass filter.

Study	Signal	Sampling (Hz)	Online filter (Hz)	Offline filter (Hz)
P1	MEG	1000	0.1–330	1–195 & notch
	EMG	1000	0.1–330	CMC: 20–195 & notch Averaging: 5 (LP)
	Force	1000	330 (LP)	5 (LP)
P2	MEG	1000	0.1–330	1–195 & notch
	EMG	1000	0.1–330	CMC: 5–195 & notch Averaging: 5 (LP)
	Force	1000	330 (LP)	5 (LP)
P3	MEG	1000	0.1–330	40 (LP)
	EMG	1000	10–330	20–295
	Acc.	1000	0.1–330	1–195
P4	EEG	2000	0.053–500	–
	Acc.	2000	0.053–500	0.5–500

4.3.3 Electromyography, force, and acceleration

In P1, P2, and P3, we recorded EMG signals with surface electrodes placed over muscles of the right hand and arm: first dorsal interosseous (P1 and P2), flexor digitorum superficialis (P2), flexor carpi radialis (P2 and P3), and extensor carpi ulnaris (P3). In P1 and P2, EMG was measured with a bipolar configuration with two electrodes over the target muscle, whereas in P3, there was only one electrode over each muscle and a common reference electrode on the distal radial bone.

Before the isometric contraction tasks (P1 and P2), the maximum voluntary contraction force was measured with a rigid load cell (1042, Vishay Precision Group, Malvern, PA, USA) that the subjects pinched between the right thumb and index finger with maximum force for 3–4 s. This force level was used to adjust the individual target force range for the contraction tasks. During the actual measurements the subjects steadily (isometrically) pinched the aluminum handles of a force transducer (Honeywell International Inc., Morristown, NJ, USA) that measured their contraction force.

Acceleration from finger (P3) and hand (P4) movements was monitored with a 3-axis accelerometer (ADXL335 iMEMS Accelerometer, Analog Devices Inc., Norwood, MA, USA). Acceleration signals were used to detect movement onsets (P3) and evaluate CKC (P4).

4.3.4 Magnetic resonance imaging

We acquired anatomical 3D-T1 magnetic resonance images (MRIs) from all subjects in studies P1, P2, and P3 to co-register the functional MEG results and the brain structure. The MRIs were obtained with a 3.0T Signa VH/i (General Electric, Milwaukee, WI, USA) or a 3T MAGNETOM Skyra (Siemens Healthcare, Erlangen, Germany) whole-body MRI scanner at the AMI Center of Aalto NeuroImaging, Aalto University.

4.4 Analyses

The analyses were performed with custom-made scripts in MATLAB® (MathWorks, Natick, MA, USA) unless stated otherwise. To simplify the text, offline filters are given only in Table 1.

4.4.1 Preprocessing and signal averaging

4.4.1.1 MEG

To suppress artifacts and to correct for head movements, we preprocessed the MEG signals offline using the signal space separation method (Taulu et al., 2004) in P1 and P2, and the temporal signal space separation method (Taulu and Simola, 2006) in P3.

MEG responses to passive movements (P3) were averaged with an analysis period from −500 to 1000 ms with respect to movement onsets determined from the acceleration signals. We discarded from the analysis all responses during the first 4 s of the measurement, as the first responses are typically stronger than the following ones. We also rejected all epochs where MEG signal variation—filtered to 1–95 Hz for this step only—exceeded 3 pT in magnetometers or 0.7 pT/cm in gradiometers, indicating movement or other artifacts. Finally, the averaged responses were baseline-corrected with respect to the mean between −150 and 0 ms.

4.4.1.2 EEG

An experienced clinical neurophysiologist (coauthor SV) visually screened the EEG recordings (P4), annotating periods of major movement artifacts, which were then excluded from further analyses. Before the coherence analysis, the EEG signal from each channel was re-referenced to the weighted average of the surrounding channels using the current-source-density transformation (for a review, see Kayser and Tenke, 2015) to enhance the spatial specificity of the results.

The SEPs were analyzed with BESA® Research (BESA GmbH, Gräfelfing, Germany) following routine procedures of the Department of Children's Clinical Neurophysiology. As the SEPs were acquired and analyzed for clinical purposes, and used in P4 only as supplementary data, I will not discuss the details of the analysis here.

4.4.1.3 EMG, force, and acceleration

In P1 and P2, force signals and rectified EMG signals were averaged time-locked to the visual and auditory stimuli to reveal stimulus-induced changes in the contraction. Here, the force and EMG signals were normalized to the mean of the baseline period (−2000 to −500 ms) of the averaged response (P1) or already at the single-trial level to the mean of the trial (P2).

In P3, we computed the root mean square of the whole-length EMG signal as an index of how well the subjects were able to relax during the passive-movement stimulation. Additionally, EMG signals were rectified and averaged from the same epochs as the MEG signals to check for possible stimulus-locked EMG activity.

In P3 and P4, we combined the three acceleration signals—corresponding to the three orthogonal spatial directions—in one signal by calculating their Euclidean norm, which represents the magnitude of acceleration independent of its direction. The Euclidean norm of the acceleration signals was used to determine movement onsets (P3) and to evaluate CKC (P4).

4.4.2 Coherence analyses

Coherence between MEG and EMG signals (P1 and P2) as well as between EEG and acceleration signals (P4) was evaluated according to the formulation of Halliday and collaborators (1995).

4.4.2.1 Cortex–muscle coherence

First, we ignored all external stimuli and computed CMC between MEG and rectified (P1) or unrectified (P2) EMG signals from 1024-ms epochs—corresponding to a ~1-Hz frequency resolution—with 80% overlap. We rejected all epochs in which MEG signal excursion exceeded 3 pT (P1) or 6 pT (P2) in magnetometers or 0.7 pT/cm (P1) or 1.4 pT/cm (P2) in gradiometers. For further analyses, we chose the gradiometer channel, among 18 gradiometers over the left SMI cortex, showing the highest CMC peak in the typical CMC frequency range of 10–30 Hz (Conway et al., 1995; Salenius et al., 1997a). Subjects who did not express statistically significant CMC ($N = 5$ in P1 and $N = 1$ in P2) were excluded from further analyses.

Next, we evaluated the modulation of CMC and MEG power by the external stimuli. We evaluated CMC and MEG power from the selected gradiometer channel in 1024-ms windows sliding in 100-ms steps from −2000 to 3000 ms with respect to the stimulus onset and constructed time–frequency maps from the data (see e.g. Fig. 2A and 2C). Individual MEG-power maps were normalized, each frequency bin separately, to the mean power in the baseline period from −2000 to −500 ms. The individual maps were averaged across subjects.

To locate cortical sources of the CMC and MEG-power modulations (P1 and P2), we first segmented the cortical surface from the individual MRIs with the FreeSurfer software (Martinos Center for Biomedical Imaging, Charlestown, MA, USA; Dale et al., 1999) and co-registered them with the corresponding MEG data using the Elekta Neuromag™ software. Next, we computed the MEG forward model for two orthogonal tangential current dipoles in a homogeneous volumetric (5-mm grid) source space that covered the whole brain (MNE suite; Gramfort et al., 2014). We used the signals from all 306 MEG channels to build individual CMC and MEG-power maps within the computed source space with a minimum-variance beamformer. These maps were computed at the frequencies of the observed sensor-level modulations and for a series of time windows to reveal the spatiotemporal evolution of the stimulus effects.

To obtain group-level cortical maps, the individual MRIs were transformed to the standard Montreal Neurological Institute brain using the spatial-normalization algorithm implemented in the SPM software package (SPM8, Wellcome Trust Centre for Neuroimaging, UCL, London, UK), and this transformation was applied also to individual maps. Individual MEG-power maps were normalized to the mean of their baseline. Finally, group-level cortical CMC and MEG-power maps were computed by averaging the individual maps across subjects.

4.4.2.2 Corticokinematic coherence

In P4, we evaluated CKC between neonatal EEG signals and acceleration signals from passive hand movements. First, we determined the optimum epoch length (in number of movement cycles) yielding statistically significant CKC with the least amount of data. Here, we performed the CKC analysis with epoch lengths of 1–10 movement cycles and found that, at group level, 2 cycles was the optimum epoch length. Thus, we performed the final analysis with 2- and 1-s epochs for 1- and 2-Hz movements, respectively. Epoch overlap was 80%. We computed CKC on all 19 EEG channels and extracted the maximum value across 6 channels that covered the contralateral central area, and across 2 frequencies (movement frequency F0 and the first harmonic frequency F1).

4.4.3 Source-space analysis of cortical responses to passive movements

Cortical sources of the responses to passive movements (P3) were modeled with equivalent current dipoles (ECDs) using the Elekta Neuromag™ software. First, we fitted an ECD to

the response obtained with the 8-s ISI. For this step, we used a selection of 18 planar gradiometers covering the left SMI cortex. We then used this ECD to model the responses also at the other ISIs. This procedure was done separately for each subject and for extension and flexion movements.

To examine the effect of ISI on response amplitude, we extracted the peak value of the source waveform for each ISI, normalized these values by dividing them by the individual's mean across ISIs, averaged these normalized values across subjects, and plotted the averages (the group-level source strengths) against ISI. The effect of ISI on source strength was modeled with the exponential saturation function:

$$A(ISI) = A_{\max}\left(1 - e^{-\frac{ISI}{\tau}}\right),$$

where A is the normalized source strength, A_{max} is the highest A that can be reached for arbitrarily long ISIs, and τ is the lifetime of the response.

4.4.4 Statistical analyses

The statistical significance of the observed CMC (P1 and P2) and CKC (P4) levels was evaluated by comparing these levels with those obtained with surrogate signals (Faes et al., 2004). Such a surrogate signal has spectral properties identical to the original signal but the phase of each frequency is randomized. Coherence was regarded as statistically significant if it exceeded the 95th percentile of the maximum coherence values of 1000 surrogate coherence analyses (corresponding to $p < 0.05$).

In the CMC studies (P1 and P2), a similar surrogate-based method was used also for statistical analysis of the stimulus-induced effects. We computed 1000 surrogate group-level CMC maps using the original signals, but replacing the stimulus onsets with dummy stimulus-onset series that were not temporally linked to the actual stimuli. We estimated the threshold for a statistically significant increase (or decrease) as the 95th percentile (or 5th percentile) of the surrogate coherence values separately for each resel (resolution element; equivalent to a pixel in a time–frequency map). A cluster of resels above (or below) this threshold was regarded as statistically significant if its size exceeded the 97.5th percentile of the maximum cluster sizes of the 1000 surrogate maps (corresponding to $p < 0.05$, Bonferroni-corrected for the two comparisons). The same dummy onset series were used to evaluate the effects of the stimuli on MEG power and averaged force and EMG signals.

In P3 and P4, additional statistical testing was performed with standard parametric and nonparametric tests in IBM SPSS Statistics 22 (IBM, Armonk, NY, USA).

5 Experiments

5.1 Publication 1: Observing another person's movements both activates and inhibits the viewer's primary motor (MI) cortex

5.1.1 Motivation

The MI cortex is activated during observation of another person's movements (Hari et al., 1998; Caetano et al., 2007). Yet, healthy people do not automatically imitate every action they see. This study was designed to find out how the brain prevents unintended imitation. More specifically, what mechanisms in the MI cortex might be responsible for stabilizing the motor output during action observation?

5.1.2 Methods

We measured MEG and surface EMG signals from 14 healthy adults while they were maintaining a steady pinch between their right thumb and index finger. Simultaneously, the subjects observed transient hand movements performed by an experimenter. We monitored the CMC between the MEG and the EMG signals to reveal the effects of the visual stimuli on the corticospinal drive from the MI cortex to the muscles. Furthermore, to assess the stimulus-induced changes in MI-cortex activity, we analyzed the modulation of the MEG power.

5.1.3 Results

Statistically significant ($p < 0.05$) CMC was found in 9 of 14 subjects, with a peak at 15–23 Hz. Figures 2A and 2C show that in these 9 subjects, CMC was enhanced and MEG power suppressed in the left SMI area after the observed movements. The CMC enhancement occurred between 0.1 and 1.0 s and the MEG-power suppression between −0.3 and 2.1 s

with respect to the stimulus onset. Here, it should be noted that the start of the effect before the zero line is erroneous and a result of the poor time-resolution of the time–frequency analysis where the value of each time point was obtained from a ~1-s time window centered at that time point. The modulations also had distinct frequency distributions with the CMC increase centered at 18 Hz, and the MEG-power suppression exhibiting one peak around 7 Hz and another around 15 Hz. Figures 2B and 2D, illustrating the modulations on a global scale, show that the CMC increase occurred quite focally in the left MI cortex, whereas the MEG-power suppression covered a broad area, including central and parieto-occipital regions. Contraction force or EMG activity were not modulated by the observed movements ($p > 0.1$ for both comparisons).

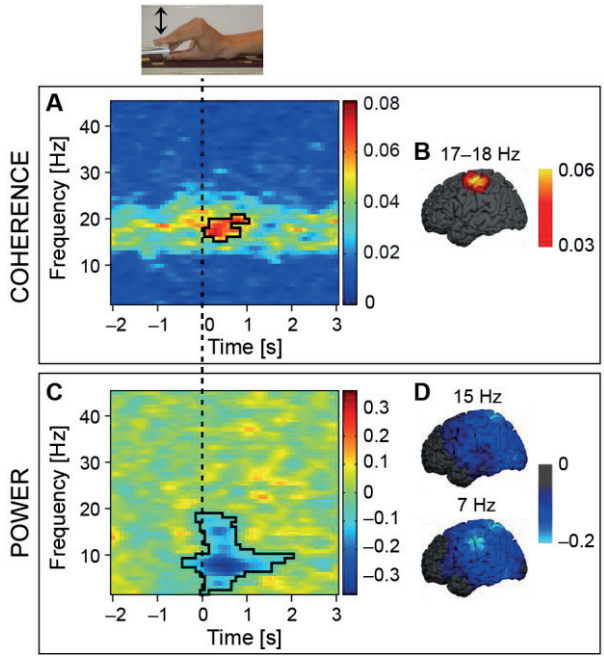

Figure 2. Group-level modulations of CMC (top) and MEG power (bottom) related to observed hand movements. **A.** Time–frequency representation of CMC modulations in a single gradiometer over the left SMI cortex. The area inside the black borders corresponds to significant ($p < 0.05$) modulation. The vertical dashed line indicates onset of the observed movement. **B.** Cortical distribution of CMC within 0.5 s from stimulus onset. **C.** Time–frequency representation (as in A) of normalized MEG power. **D.** Cortical distribution of normalized MEG power within 0.5 s (15-Hz power) and between 0.5 and 1.0 s (7-Hz power) after stimulus onset. Note that in A and C, each time point reflects data from a ~1-s time window centered at that time point, explaining the apparent beginning of the MEG-power suppression (C) already before stimulus onset. Adapted from Figs. 1, 3, and 4 of P1.

5.1.4 Conclusions

Observing another person's hand movements caused simultaneous CMC enhancement and MEG-power suppression in the viewer's MI cortex in the mu-rhythm frequency range. This finding was unexpected as CMC and mu-rhythm level typically follow each other: Both are, for example, suppressed by active movements (mu rhythm: Salmelin and Hari, 1994b; CMC: Kilner et al., 1999; 2000). Importantly, the opposite CMC and mu-rhythm modulations in the current study occurred at distinct frequency bands, suggesting that they reflect different aspects of action observation mediated by different populations of MI-cortex neurons.

The mu-rhythm suppression is in line with previous MEG studies (Hari et al., 1998; Caetano et al., 2007) and likely indicates vicarious cortical activation. The CMC increase, in contrast, likely reflects stabilization of the motor output, as suggested by a previous MEG study (Kilner et al., 2000), and this finding might thus explain how unintended imitation can be avoided despite vicarious MI-cortex activation. Thus, action observation seems to cause activation of one population of MI-cortex neurons and inhibition of another, manifested as mu-rhythm suppression and CMC increase, respectively.

5.2 Publication 2: Motor output stabilizes after simple auditory and visual distractors

5.2.1 Motivation

In P1 discussed above, we examined brain mechanisms preventing automatic imitation of observed movements at the level of the MI cortex. However, the motor system must carefully control also the effects of other types of external distractors to maintain proper motor performance. Here, we studied how this task is reflected in the function of the MI cortex when simple auditory and visual stimuli are presented during a precision-demanding motor task.

5.2.2 Methods

We measured MEG and surface EMG signals from 22 healthy adults who were performing a similar steady contraction task as in P1. This time, we presented brief auditory (pure tones) and visual (checkerboard) stimuli to the subjects during the task. We analyzed stimulus-

related modulations in CMC, MEG power, contraction force, and EMG activity similarly as in P1 to find out how the M1 cortex reacts to distractors.

5.2.3 Results

Of the 22 subjects, 20 showed statistically significant CMC ($p < 0.05$; peak frequencies 11–29 Hz) and were able to maintain the contraction force within the task limits. Figures 3A and 3C illustrate that both CMC and MEG power were enhanced in the SMI cortex at frequencies around 20 Hz after both auditory and visual stimuli. The visual stimuli were also followed by an MEG-power enhancement at frequencies above 30 Hz. These modulations occurred between 0.3 and 1.7 s for auditory stimuli and between −0.1 and 1.5 s for visual stimuli. Additionally, MEG power showed early suppression at 15–33 Hz between −0.3 and 0.8 s with respect to the auditory stimuli (Fig. 3C, left panel). Again, the start of the effect before the zero line pertains to the fact that in the time–frequency representation each time point reflects data from a ~1-s time window around that time point. Figures 3B and 3D demonstrate that the CMC and MEG-power enhancements were most prominent in the left MI cortex.

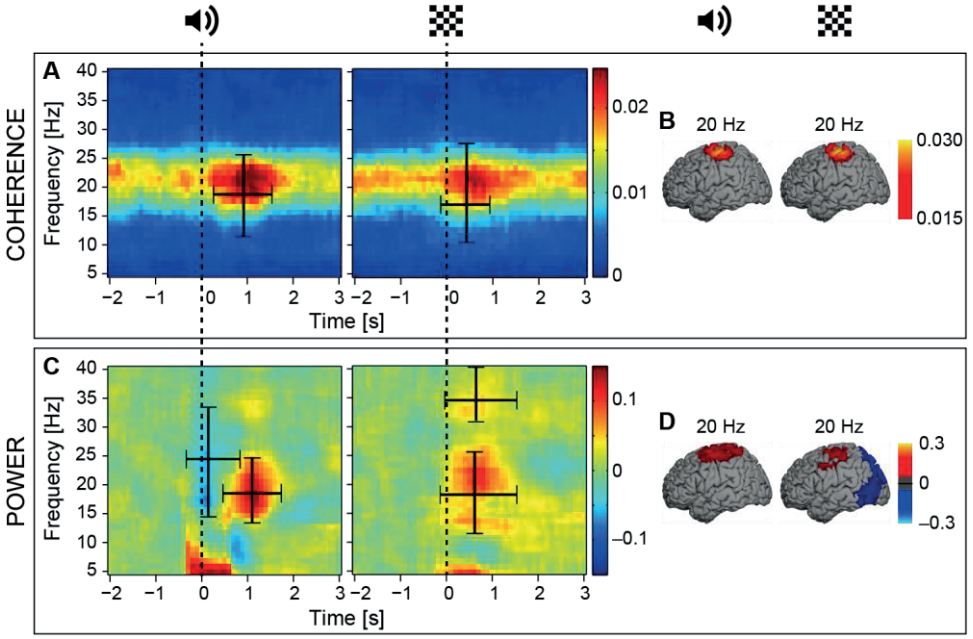

Figure 3. Group-level modulations of CMC (top) and MEG power (bottom) in response to simple auditory and visual stimuli. **A.** Time–frequency representations of single-channel CMC modulations related to auditory (left panel) and visual (right panel) stimuli. The temporal and spectral ranges of significant ($p < 0.05$) changes are indicated with black horizontal and vertical bars, respectively. The vertical dashed lines indicate stimulus onset. **B.** Cortical distribution of CMC within 0.5 s from stimulus onset. **C.** Time–frequency representations (as in A) of normalized MEG power. **D.** Cortical distribution of normalized MEG power between 0.5 and 1.0 s after stimulus onset. Note that in A and C, each time point reflects data from a ~1-s time window centered at that time point, explaining the apparent beginning of some modulations already before stimulus onset. Adapted from Figs. 3 and 4 of P2.

Figure 4 shows that the distractors also caused tiny force and EMG modulations beginning within tens of milliseconds from stimulus onset. At the group level, all modulations were statistically significant ($p < 0.001$). At the individual level, they exceeded significance level ($p < 0.05$) in 8/20 (force) and 13/20 (EMG) subjects for auditory stimuli and in 3/20 (force) and 3/20 (EMG) subjects for visual stimuli. The modulations were well within the task limits (6 ± 1% of the force of maximum voluntary contraction), and their amplitudes were only about half of the signals' background fluctuations.

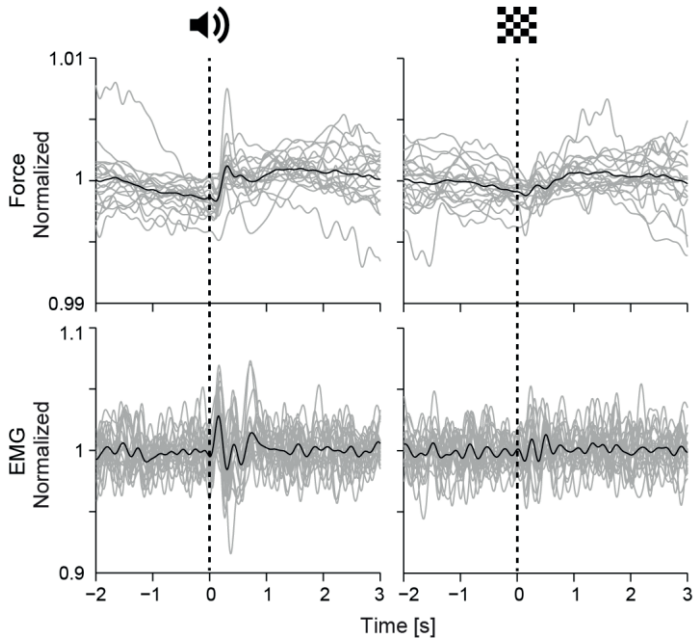

Figure 4. Individual (grey; $N = 20$) and group-level (black) normalized force (top) and EMG (bottom) signals averaged with respect to stimulus onset. Adapted from Fig. 3 of P2.

5.2.4 Conclusions

The observed enhancements of CMC and MEG power after auditory and visual distractors indicate inhibition of the MI cortex and stabilization of its output. The exact mechanism giving rise to this effect is not certain, but may be speculated based on our observations.

First, the tiny variations in force and EMG suggest that the stimuli triggered covert startle-like responses. These responses and the ensuing proprioceptive afferent signals could have contributed to the observed CMC and MEG-power increases, as movements are typically followed by rebounds in mu rhythm (Salmelin and Hari, 1994b; Alegre et al., 2002) and CMC (Kilner et al., 2000). Such covert motor responses might also explain the early MEG-power suppression immediately following the auditory, but not the visual stimuli. In line with this view, the auditory distractors seemed to be associated with slightly stronger force and EMG modulations than the visual distractors. Yet, even in the case of auditory distractors, these modulations were very small and well below the spontaneous fluctuations in the signals during the contraction task. Stimulus intensities were not matched

across modalities, so our data do not allow further conclusions to be drawn regarding the differences between the two stimulus types.

Second, the distractors might have caused a transient shift of attention from the motor task to auditory and visual sensory processing, leading to inhibition and stabilization of the MI cortex. This interpretation is in line with previous evidence of increased mu rhythm during a visual task and reciprocal enhancement in posterior alpha during a motor task (Pfurtscheller, 1992), as well as with findings of increased EEG–EMG coherence during unattended visual stimulation (Safri et al., 2006; 2007).

5.3 Publication 3: Cortical proprioceptive responses to passive finger movements increase in amplitude as a function of the interstimulus interval

5.3.1 Motivation

A typical feature of cortical responses to sensory stimulation is that response amplitudes decrease when the ISI is shortened. This relationship has been studied in detail with MEG in the visual (e.g. Uusitalo et al., 1996), auditory (e.g. Lu et al., 1992b), and somatosensory (e.g. Hari et al., 1993) systems. However, in the study of proprioceptive responses the effect of ISI has remained largely unexplored. In this study, we characterized the ISI dependence of proprioceptive cortical responses to learn about the temporal scales of the underlying cortical processes and to optimize stimulation parameters for efficient assessment of proprioceptive afference both in research and in the clinic.

5.3.2 Methods

We measured MEG signals from 15 healthy adults during transient, passive flexion–extension movements of the right index finger. The passive movements were generated automatically by a PAM stimulator (Piitulainen et al., 2015; see also Fig. 1B in Section 4.2.3 of this thesis) at ISIs of 0.5, 1, 2, 4, 8, and 16 s. We also recorded surface EMG from the flexor and extensor sides of the right antebrachium to verify that subjects remained relaxed during the stimulation and to detect possible stimulus-locked, reflexive EMG activity.

We averaged the MEG signals time-locked to the stimuli and modeled with ECDs the locations and orientations of the sources of the responses evoked by the 8-s ISI

stimulation. For each subject, we thus obtained one ECD model that we then applied for all ISIs to determine the source waveforms. We extracted the peak amplitudes of these waveforms and normalized them within subjects to the individual mean across ISIs. We modeled the relationship between ISI and the normalized source strength with an exponential saturation function of the form $A(ISI) = A_{\max}\left(1 - e^{-\frac{ISI}{\tau}}\right)$, where A is the normalized source strength, A_{max} is the highest A that can be reached for arbitrarily long ISIs, and τ is the lifetime of the response.

5.3.3 Results

The passive finger extensions and flexions evoked prominent responses peaking in planar gradiometers above the contralateral SMI area at ~70 and ~90 ms, respectively. Figure 5A shows for one representative subject that these responses were generated by posteriorly oriented sources in the posterior bank of the central sulcus corresponding to areas 3a and 3b of the SI cortex. Similar sources in the SI cortex were detected also in the rest of the group. Source location and orientation did not differ between extension and flexion movements ($p < 0.05$ for both comparisons). The root-mean-square values of the EMG signals from the stimulation conditions did not exceed rest levels, suggesting that the subjects were able to remain relaxed during the measurements. Stimulus-locked EMG responses were detected after flexions in 14/15 subjects and after extensions in 1/15 subjects. The EMG responses peaked 100–200 ms after movement onset.

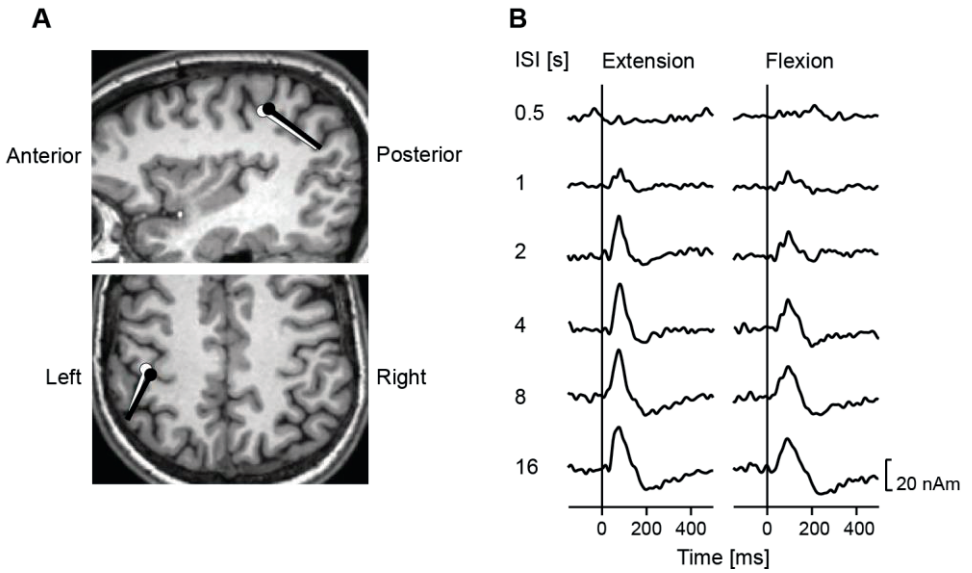

Figure 5. A. Cortical sources of the responses to passive finger extensions (black) and flexions (white) in one representative subject. **B.** Source waveforms of the same subject for extensions and flexions at all ISIs. Adapted from Fig. 3 of P3.

The single-subject source waveforms in Figure 5B show that the responses were practically undetectable at the shortest ISI of 0.5 s but increased in amplitude towards longer ISIs. Figure 6 shows that a similar effect was observed also at group level. Source strength was markedly enhanced when ISI was prolonged, and reached a plateau at an ISI of 8 s. The ISI dependence followed closely the exponential saturation function fitted to the data. The estimated response lifetimes were 1.3 s for extension and 2.2 s for flexion movements.

With signal averaging, the residual noise in the averaged response is decreased by a factor of $\sqrt{n}$, where n is the number of stimuli. When the measurement time is fixed, n is inversely proportional to the ISI, meaning that prolonging the ISI increases the residual noise by a factor of $\sqrt{ISI}$. Also response amplitude is increased, when ISI is prolonged, by a factor of $\left(1 - e^{-\frac{ISI}{\tau}}\right)$, as indicated by our model. It follows that the SNR of an averaged response is highest when ISI ≈ 1.26 τ. Knowing the response lifetime τ, we can calculate that an ISI of 1.7 s for extension and 2.8 s for flexion movements will yield maximum SNR in a given measurement time (Fig. 6).

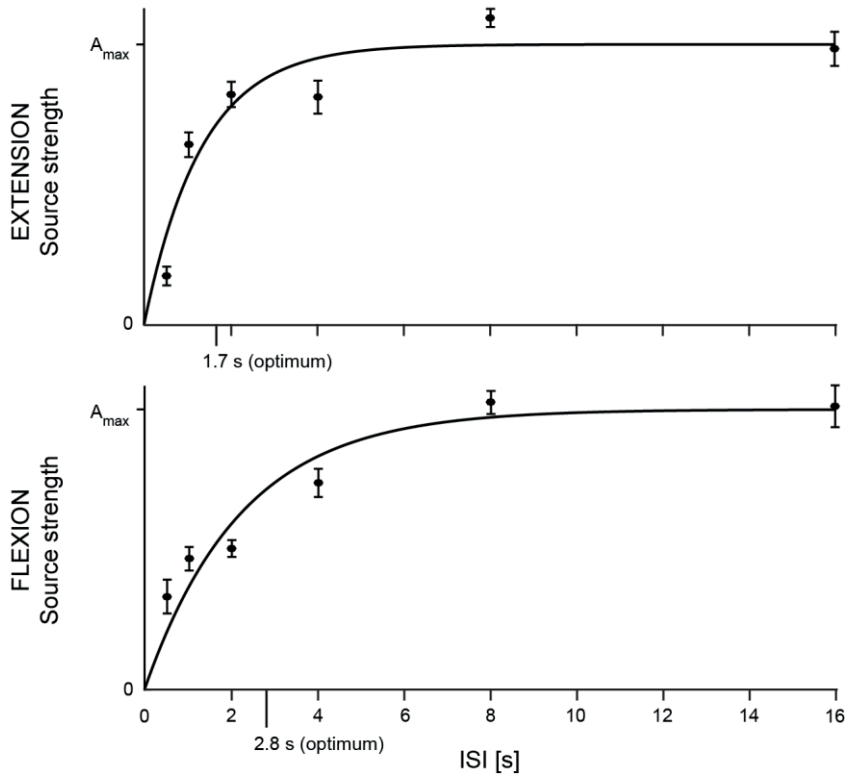

Figure 6. Normalized source strength plotted against ISI for extensions (top panel) and flexions (bottom panel). The black dots represent group-average values with error bars indicating the standard error of the mean. The black curve illustrates the exponential saturation function fitted to the data. Adapted from Fig. 4 of P3.

5.3.4 Conclusions

The amplitudes of passive-movement-evoked proprioceptive responses in the SI cortex increase as a function of ISI, reaching a plateau at an ISI of 8 s. The estimated response lifetimes resemble those obtained earlier for the auditory N100 responses (Hari et al., 1982; Lu et al., 1992b) and SII responses at ~100 ms (Hari et al., 1993). Due to the stimulation procedure, each movement cycle, corresponding to one ISI, in fact included two movements (one extension and one flexion), and the reported lifetimes are based on the assumption that the resulting proprioceptive feedback (from finger flexor and extensor muscles) is processed in distinct populations of cortical neurons. However, if both responses stem from the same neuronal population, then the cortical recovery of the responses would be twice as fast, that is, the lifetimes would be only half of the ones reported here. Nevertheless, with the current

type of stimulation an ISI of 1.5–3.0 s will maximize the SNR of the measured proprioceptive responses and can thus be recommended for both clinical and research applications.

5.4 Publication 4: Cortical responses to passive movements can be measured already in newborn infants

5.4.1 Motivation

In this study, we explored whether passive movements can be used to evoke detectable cortical responses also in newborns. Such measurements could be exploited in neonatology not only to specifically assess proprioceptive function but also to evaluate the integrity of somatosensory pathways in general. In neonatal brain injury, early assessment of somatosensory function can improve diagnostics and guide treatment, thus benefiting the outcome (for a review, see Majnemer and Rosenblatt, 1996). However, the current standard method of measuring SEPs in response to electrical median-nerve stimulation requires specialized technical expertise (e.g. in stimulating the nerve at the tiny wrist), limiting its use as a bedside test. Passive-movement stimulation is a completely noninvasive alternative that could be readily performed in the NICU.

5.4.2 Methods

We included in the study 13 newborn patients who underwent a clinical EEG examination in the NICU. The most frequent EEG indications in the group were birth asphyxia and suspected seizures. During the EEG measurements an experimenter manually moved the infant's hand at wrist or metacarpophalangeal level for 5–10 min at a time. In separate stimulation runs, either the left or the right hand was moved continuously at either 1 or 2 Hz. As part of the clinical EEG recordings, SEPs were acquired from 9/13 infants.

We analyzed the CKC between the EEG signals and the Euclidean norm of the three orthogonal acceleration signals picked up by an accelerometer that was attached to the infant's hand. To see whether the infants' functional brain state affects CKC, we determined, from each stimulation run, the sleep stage as well as the ratio of slow (0.5–4 Hz) and fast (5–10 Hz) activity in the occipital area. The level of newborns' occipital slow EEG activity—occurring around the studied CKC frequencies—varies considerably depending on the momentary brain state.

5.4.3 Results

All 13 infants showed statistically significant CKC ($p < 0.05$) at F1 in the contralateral central area or its surroundings. Out of the 36 individual stimulation runs, a significant result was found in 33. Across those 33 runs, the median of CKC peak values was 0.067 (range 0.020–0.511) and the required data length to obtain statistically significant CKC was 73 s (7–371 s). The measures of functional brain state (sleep stage and occipital slow/fast ratio) did not show significant correlations with CKC peak value or the required data length ($p >$ 0.05 for all comparisons). There was interhemispheric asymmetry in the spontaneous EEG activity of five infants. These asymmetries were not systematically reflected as interhemispheric differences in the CKC results.

Figure 7A illustrates, for one representative subject, the scalp distribution of CKC; during right-hand movements the maximum CKC occurred in the left central area. The individual CKC spectra in Figure 7B show that CKC peaked consistently at F1, agreeing with a previous adult study using similar methodology (Piitulainen et al., 2013). The finding that CKC peaked at F1 instead of F0 was expected, given the evidence from an earlier EEG study that during a manual tracking task, signals from the SMI cortex reflect the absolute hand velocity independent of movement direction (O'Suilleabhain et al., 1999). Also the reference signal (Euclidean norm of the acceleration signals), with its power peaking at F1, likely contributed to the prominent CKC observed at this frequency. The spectra of the original single-axis acceleration signals peaked at F0 as expected.

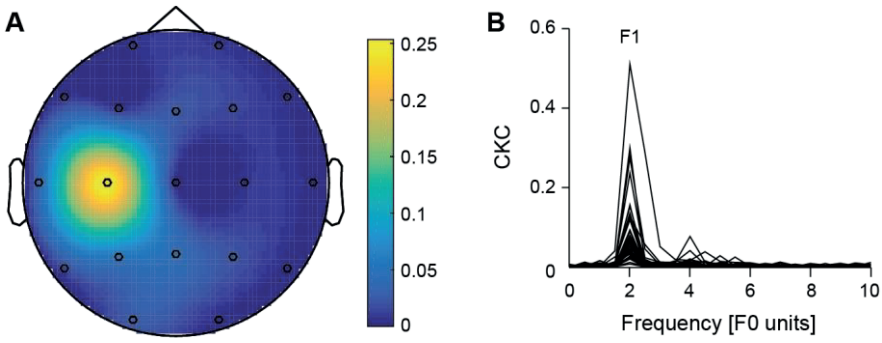

Figure 7. A. Scalp distribution of CKC at F1 in one representative subject during right-hand movements at 1 Hz. The head is viewed from above with the nose pointing upwards. The small circles indicate electrode locations. **B.** CKC spectra from all 36 measurements from the channel showing maximum CKC. The horizontal axis is scaled to F0 units with the value 2 corresponding to F1. Adapted from Figs. 2 and 3 of P4.

SEPs were normal in 8 of the 9 tested infants, with scalp distributions similar to those observed for CKC. In one infant with statistically significant CKC on both sides, SEPs were delayed and attenuated in the right hemisphere, but normal in the left. Another infant had statistically significant CKC only in the right hemisphere, but normal SEPs on both sides.

5.4.4 Conclusions

We were able to measure cortical activity evoked by passive movements from critically ill newborns in the noisy NICU environment. The infants' functional brain state did not seem to affect the results. Some inconsistencies between the CKC results and the clinical EEG and SEP findings might result from slight irregularities in the movement stimulation impeding comparison between stimulation runs. To improve the situation in future studies, the manual movements should be replaced with an automatic passive-movement stimulator. In fact, the device used in Study P3 of this thesis has already been applied successfully to study CKC in adults (Piitulainen et al., 2015).

In the future, CKC could complement conventional SEP measurements in neonatology, as the stimulation is easy to perform and completely noninvasive. Furthermore, the frequencies of interest in CKC analysis are clearly below those of typical interference in the NICU (e.g. power-line noise, muscular activity of the infant), giving the method high resilience against common interference sources. Our results pave the way for new studies exploring the clinical value of CKC in different neonatal patient groups and comparing the results with those of other diagnostic tests.

6 Discussion

6.1 Maintaining stable motor output despite external distractors

6.1.1 Modulations of cortex–muscle coherence and mu-rhythm power reflect stabilization of the MI cortex

We showed in P1 and P2 that external auditory and visual stimuli enhance CMC temporarily during a precision-demanding isometric contraction task. This effect was evident after observed transient hand movements as well as after simple beeps and checkerboard stimuli. The CMC enhancement reflects stabilization of the MI cortex, which likely helps to prevent unintended motor reacting to the distractors. This view is supported by earlier studies on the relationship between CMC and voluntary movements. CMC is suppressed during movements and phasically enhanced when stable contraction is resumed (Kilner et al., 2000). Conversely, voluntary movements are slowed down during periods of strong 13–35-Hz corticospinal synchrony (Gilbertson et al., 2005). Furthermore, corticospinal synchrony, reflected as coherence between EEG and finger microtremor, is enhanced before anticipated mechanical finger stretch that the subject is supposed to resist (Androulidakis et al., 2007). Thus, CMC seems to be associated with the maintenance of the existing motor and postural state. Accordingly, CMC enhancements after external distractors likely reflect prevention of unintended movements. The mechanism possibly involves inhibition of a specific neuronal population in the MI cortex, as discussed below in more detail. But first, I will consider the other part of the results of P1 and P2: the modulations of mu-rhythm power.

The sensorimotor mu rhythm and CMC are closely related. Indeed, as discussed above for CMC, also the beta-range mu rhythm seems to reflect stability of the motor state and promotion of the *status quo* (for a review, see Engel and Fries, 2010). Accordingly, mu rhythm and CMC typically co-vary in experimental settings; both measures are attenuated

and then transiently enhanced by, for example, active movements (mu rhythm: Salmelin and Hari, 1994b; CMC: Kilner et al., 1999; 2000) and electrical median nerve stimulation (Hari and Salenius, 1999). Given this background, the results from Study P2 are expected as they show similar modulation of CMC and mu-rhythm power in response to the stimuli. Both measures were enhanced at ~20 Hz within a 2-s time window following the stimuli, suggesting stabilization of the MI cortex to maintain steady contraction. Additionally, the auditory stimuli caused early suppression of mu-rhythm power, likely related to a covert startle response. This finding is discussed in more detail below in Section 6.1.2.

In contrast to the simple auditory and visual stimuli in P2, the observed hand movements in P1 had the opposite effects on mu-rhythm power and CMC, suppressing the former and enhancing the latter. However, as these modulations occurred at distinct frequency bands, they can be interpreted as two opposing processes taking place simultaneously in the MI cortex. According to this view, the mu-rhythm suppression reflects vicarious activation of one neuronal population, whereas the CMC increase is related to inhibition of another. Indeed, it has been shown in monkeys that some pyramidal tract neurons in the MI cortex are activated by observed movements while others are inhibited, possibly preventing overt actions (Vigneswaran et al., 2013). The reported mu-rhythm suppression after observed movements in Study P1 is in line with previous MEG studies (Hari et al., 1998; Caetano et al., 2007) and with transcranial magnetic stimulation studies showing increased excitability during movement observation (Fadiga et al., 1995; Strafella and Paus, 2000). Accordingly, the absence of mu-rhythm suppression, indicating a lack of MI-cortex activation, was expected in Study P2, as the stimuli were not related to human movements or to the isometric contraction task.

In summary, the results presented in this thesis suggest that external distractors lead to transient MI-cortex inhibition that blocks any undesirable effects on the motor output. In the special case of observing another person's movements, the MI cortex also exhibits vicarious activation, yet simultaneous inhibition of a different neuronal population successfully stabilizes the motor output, thus preventing unintended imitation of the movements. But what causes this stabilization effect in the MI cortex? Our findings, combined with earlier knowledge, permit some speculations presented in the following section.

6.1.2 Possible mechanisms supporting MI-cortex stabilization

Preventing unwanted effects of sensory input on motor behavior involves top-down control from the frontal lobes, likely inhibiting more posterior brain areas (Lhermitte et al., 1986; de Fockert et al., 2004; Bien et al., 2009). Our results (P1 and P2) suggest that this inhibition is conveyed also to a subset of MI-cortex neurons, as reflected by enhanced CMC (and mu-rhythm power in Study P2) after various sensory distractors during isometric contraction. As a result, the existing postural state is favored and new movements are discouraged.

As discussed already in Section 5.2.4, covert startle-like responses and attentional disengagement are also potential contributors to the observed effects. The tiny startle-like responses, evoked by the auditory and visual stimuli in Study P2, could be mediated by a fast subcortical loop via the reticulospinal tract, as reported for the classical auditory startle (for a review, see Yeomans and Frankland, 1995) and suggested also for rapid-onset coordinated finger movements following a startling auditory 'go' signal (Honeycutt et al., 2013). The proprioceptive afference elicited by these responses could partly explain the CMC and mu-rhythm modulations found in P2. However, they cannot alone explain all of the results, as in Study P1 CMC was enhanced despite the absence of startle-like responses. Another possible mechanism is that the distractors cause a shift of attention from the motor to the sensory systems leading to inhibition and stabilization of the MI cortex. Such disengagement from the motor task would not require the sensory stimuli to have direct access to the MI cortex, but could rather be mediated at the thalamic level, although these subcortical mechanisms cannot be confirmed based on our data.

The relative contributions of the suggested mechanisms of MI-cortex stabilization are beyond the scope of this thesis and remain to be elucidated in future studies.

6.2 Proprioceptive afference to the adult and newborn cerebral cortex

In P3 and P4, we shifted focus from the efferent link between the cortex and the muscles to the reciprocal afferent signaling that conveys proprioceptive feedback about movements and postures, thus constituting an important part of proper motor control. We successfully measured reliable cortical responses to passive movements in both adults and newborns. In adults, responses to transient passive movements are already fairly well established (Rodin et al., 1969; Papakostopoulos et al., 1974; Shibasaki et al., 1980; Mima et al., 1996; Xiang

et al., 1997; Lange et al., 2001; Alary et al., 2002; Druschky et al., 2003). Our findings in Study P3 extend the existing literature by providing a detailed characterization of the effect of ISI on these cortical responses. In newborns, in contrast, cortical responses to passive movements have, to my knowledge, not been reported before. In Study P4, we showed that such responses can indeed be recorded, which can greatly benefit neonatal intensive care (see Section 6.3).

6.2.1 Proprioceptive cortical responses and their lifetimes in healthy adults

In P3, we observed prominent responses in the adult SMI cortex following passive finger extensions and flexions, consistent with previous studies (Xiang et al., 1997; Lange et al., 2001; Alary et al., 2002; Druschky et al., 2003; Onishi et al., 2013; Piitulainen et al., 2013; 2015). As discussed already in Section 2.5, cortical responses to passive movements truly reflect proprioceptive signaling as they are (1) unaffected by cutaneous anesthesia (Starr et al., 1981; Abbruzzese et al., 1985; Mima et al., 1996), (2) elicited similarly by both active and passive movements (Piitulainen et al., 2013), and (3) observed regardless of the level of tactile stimulation during the movements (Piitulainen et al., 2013). Based on earlier knowledge of the proprioceptive system (for a review, see Proske and Gandevia, 2012), the cortical responses in P3 mainly reflect afferent signals from muscle receptors of finger extensors and flexors. We localized the sources of the proprioceptive responses to area 3a or 3b of the SI cortex. Previous evidence about the functional organization of the SI cortex (Kaas, 1993) would suggest area 3a as the likely origin.

Shortening the ISI of the passive finger movements dramatically decreased the amplitude of the cortical responses. Such an ISI effect seems to be universal for cortical sensory processing, as similar observations have been made in many sensory modalities (Hari et al., 1982; Uusitalo et al., 1996; Wikström et al., 1996). The period of reduced cortical responsiveness following a sensory stimulus might reflect a decrease in the number of active neurons due to transient active inhibition of some neuronal populations (Loveless et al., 1989). The duration of this period can be characterized with the response lifetime (Lu et al., 1992b).

The ISI effect has been reported earlier for EEG responses to wrist extensions (Abbruzzese et al., 1985) and ankle flexions (Starr et al., 1981). The novelty of the results presented in this thesis lies in the models that were used to accurately describe this effect and to determine the response lifetimes. We also used a novel pneumatic passive-movement

stimulator capable of producing stimuli with extremely good accuracy and repeatability. Similar exponential saturation models, as presented in Study P4, have been applied successfully also to auditory (Lu et al., 1992b), visual (Uusitalo et al., 1996), and nociceptive (Raij et al., 2003) cortical responses. The estimated lifetimes of proprioceptive responses were 1.3 and 2.2 s for extension and flexion movements, respectively. The results integrate nicely into the existing literature, as similar cortical recovery rates have been observed also for other responses of comparable latency, namely, the supratemporal auditory N100 response (Hari et al., 1982; Lu et al., 1992b) and the ~100-ms SII response to electrical median nerve stimulation (Hari et al., 1993).

As a further outcome of P3, we were able to determine that, within a fixed measurement time, maximum SNR of the averaged cortical responses to passive finger movements will be reached with ISIs of 1.5–3.0 s. This finding can be exploited to optimize stimulation protocols for both scientific and clinical use. The practical significance of this finding is discussed in more detail in Section 6.3.

6.2.2 Proprioceptive stimulation as a probe for somatosensory function in newborns

In P4, we demonstrated that cortical responses to passive movements can be detected already in newborns by analyzing the coherence between EEG and movement kinematics (CKC). Highest CKC was observed at F1 in the contralateral central area in line with an earlier adult study that also employed manual passive-movement stimulation (Piitulainen et al., 2013).

As pointed out in Section 2.5.3, there is strong evidence that CKC in adults reflects mainly cortical processing of proprioceptive afference (Piitulainen et al., 2013; Bourguignon et al., 2015). Also in newborns, CKC is probably mainly driven by proprioceptive input. However, since we did not specifically explore the peripheral origin of the CKC in Study P4, we cannot exclude the possibility of tactile contribution. Yet, it should be noted that regardless of the relative proprioceptive and tactile contributions, CKC offers a valuable tool for assessing the integrity of somatosensory pathways in newborns.

6.3 Clinical relevance and future prospects

Certain motor-system disorders are characterized by involuntary movements in response to irrelevant external stimuli. Such conditions include hyperekplexia, caused by a genetic defect in the glycine-signaling system and characterized by an exaggerated startle reflex, and echopraxia, automatic imitation of other persons' movements associated with, for example, frontal-cortex lesions and Tourette syndrome. The disease mechanisms of these disorders involve reduced inhibition in the motor system (Lhermitte et al., 1986; Zhou et al., 2002). Studies P1 and P2 of this thesis give new insight into the role of the MI cortex in suppressing such aberrant reactions in healthy individuals. Further investigations are required to clarify how these cortical processes operate in individuals suffering from a hyperreactive motor system associated with, for instance, frontal-lobe lesions, hyperekplexia, or excessive distractibility occurring in attention-deficit disorder.

Proprioception is compromised, at different levels of the nervous system, in various neurological disorders such as stroke, cerebellar degeneration, myelopathies, and cerebral palsy (Rowland et al., 2010). Clinical assessment of proprioceptive function currently relies on moving the patients' fingers or toes and asking them to report, without looking, the perceived changes in position. There is thus a clear need for objective, neurophysiological tests—based on, for example, EEG or MEG—to measure proprioceptive afference to the cortex. Study P3 of this thesis contributes to the development of such a standardized method by demonstrating that ISIs of 1.5–3.0 s will maximize the SNR of proprioceptive cortical responses. Thus, the ISI should be set within this range to achieve the most efficient electrophysiological assessment of proprioceptive afference.

Passive-movement stimulation can prove useful also in newborn patients. Brain injuries in the peri- and neonatal phase, due to, for example, preterm birth and perinatal asphyxia, are a major cause of infant mortality and lifelong neurological impairment (for a review, see Lawn et al., 2014). A key challenge to improve the treatment and outcome of this patient group is to monitor the brain function objectively and quickly with bedside tests already in the NICU. The conventional SEPs, elicited by median-nerve stimulation, can predict neurological outcome at a very early stage (for reviews, see Majnemer and Rosenblatt, 1996; Vanhatalo and Lauronen, 2006). However, the stimulation method requires technical expertise, especially when studying newborn patients, and can thus be used in the NICU only if specialized personnel is available.

Passive-movement stimulation, as successfully applied in Study P4, offers a complementary approach to assess somatosensory afference in newborns. The stimulation is simple and totally noninvasive, permitting flexible use in neuromonitoring in the NICU. Furthermore, when evaluating the afference using CKC analysis between passive movements and cortical activity, the frequencies of interest are clearly below those of typical noise in the NICU, such as the main-line noise and the infant's muscular activity, rendering the method highly insensitive to these artifacts. Indeed, despite the noisy recording environment, we were able to obtain decent CKC from all 13 studied infants without off-line artifact removal other than rejecting periods of major spontaneous movements of the infants based on visual inspection of the data. According to Study P4, CKC did not depend on the infant's vigilance (as judged on the basis of sleep stage and occipital background activity), which is a desirable quality for a reliable clinical test that should be sensitive to neurological abnormalities rather than physiological fluctuations.

The robustness of the CKC method can be further improved with automatized stimulation using a device analogous to the one applied in Study P3 and in a previous adult CKC study (Piitulainen et al., 2015). The extremely good reproducibility provided by such a stimulator, compared with manual stimulation, would reduce the amount of data required in individual measurements and improve the repeatability between measurements. According to earlier functional magnetic resonance imaging studies, automatic movement stimulation can be successfully used to elicit BOLD responses in newborns (Arichi et al., 2010; Allievi et al., 2013). We are currently developing a stimulator compatible with newborn EEG measurements to be used in future studies that will explore, in detail, the possibilities of passive-movement stimulation and CKC in severe neonatal brain injuries such as hypoxic-ischemic encephalopathy. It will also be important to assess CKC in healthy infants to obtain reference values for patient studies and to learn about the normal development of the cortical responses. Furthermore, the assessment method could benefit diagnostics and follow-up of cerebral palsy in pediatric patients as well as in older patients, as the disease involves, among other manifestations, marked dysfunction of the proprioceptive sense (Wingert et al., 2009). Passive-movement stimulation combined with CKC analysis thus opens many possibilities for clinical applications that can help a large group of patients.

7 Conclusions

In this thesis work, I explored how the SMI cortex is affected by a number of different stimuli, either relevant or irrelevant to motor control. More specifically, I attempted to answer the following questions: (1) how does the MI cortex participate in securing stable motor performance in the presence of external distractors *irrelevant* to the ongoing motor task and (2) how does the activity of the SI cortex reflect *relevant* proprioceptive feedback about one's own movements.

In answer to the first question, this thesis shows that the output from the MI cortex to the spinal cord is stabilized transiently after distracting auditory and visual stimuli, thus likely preventing unintended motor reactions. In the special case of observing another person's movements, a distinct subset of the viewer's MI cortex is also simultaneously activated.

As for the second question, this thesis expands our knowledge about cortical proprioceptive processing in two ways. First, it sheds new light on the temporal scales of the associated cortical processes by characterizing how fast the SI cortex is able to recover after transient proprioceptive stimulation in healthy adults. Second, the results show that cortical responses to proprioceptive stimulation (continuous passive hand movements) can be detected already in newborn infants. Both of these findings can directly benefit the development of novel diagnostic tools for clinical neurophysiology.

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