Department of Radiology
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# Reactivity of the human primary motor cortex during observation of action

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*To be publicly discussed by permission of the Faculty of Medicine of the University of Helsinki, in the Auditorium F1 at the Helsinki University of Technology, on March 8, 2005, at 12 noon.*

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# Abstract

"Mirror neurons" are visuomotor neurons which are activated both when the individual is observing and performing an action. These cells were originally discovered in the ventral premotor cortex (area F5) of monkeys by Rizzolatti and collegues. Mirror neurons directly match observed actions and their motor counterparts and probably have a role in action understanding, as well as learning and imitation of action.

Brain imaging and electrophysiological studies have recently shown that a similar system exist also in the human brain. Areas comprising the human mirror-neuron system (MNS) include at least the inferior frontal gyrus and the adjacent premotor area, the primary motor cortex (MI), and possibly the superior temporal sulcus and the inferior parietal lobule, as well. Motor cortex involvement was first shown in our laboratory using magnetoencephalography (MEG).

In this thesis I studied with my colleagues the reactivity of the human primary motor and somatosensory areas during observation of action using magnetoencephalography. A neuromagnetic ~20-Hz rhythm was used as an indicator of the functional state of MI. In Study I, we showed the ~20-Hz rhythm was dampened more when the subjects observed live than videotaped hand movements, indicating stronger activation of the primary motor cortex and this result suggests that the human mirror neuron system is sensitive to differentiating natural and artificially presented movements. In Study III we found that the human MI is activated during observation of tool use, in contrast to monkeys. MI was activated more strongly during observation of goal-directed than non-goal-directed tool use. This difference could be related to the observer's ability to understand and imitate the perceived goal-directed actions. Study II showed that ~20-Hz reacts differently to electrical stimulation of thumb and middle finger. Post-stimulus rebounds were stronger after thumb stimuli, suggesting that the sensorimotor processing differs for thumb and middle finger in the human primary motor and somatosensory cortices. This result might be due to larger and more complex cortical representation of thumb.

The somatosensory cortices are considered to contribute to the MNS . In Study IV we showed that somatosensory evoked fields after tactile lip stimulation are somatotopically enhanced in primary somatosensory cortex during silent lip-reading. This enhancement could reflect simulation of other person's action-related sensations and hence could enable the observer to experience what the other person feels while performing motor acts.

In Study V we investigated the reactivity of MI in schizophrenic patients and their healthy co-twins during action observation. We found that the reactivity of the motor-cortex rhythm

was weaker in schizophrenic subjects than in their healthy twins, both in observation and execution conditions. The weakened reactivity of the primary motor cortex suggests a dysfunction of motor cognition in schizophrenia, and might partly explain the difficulties of these patients in differentiating actions of self and others.

# Abbreviations

| | |
|---|---|
| AP | action potential |
| ANOVA | analysis of variance |
| BA | Brodmann's area |
| CNS | central nervous system |
| ECD | equivalent current dipole |
| EEG | electroencephalography |
| EMG | electromyography |
| EOG | electro-oculography |
| ERP | event-related potential |
| fMRI | functional magnetic resonance imaging |
| IF | inferior frontal area |
| IPL | inferior parietal lobule |
| ISI | interstimulus interval |
| MI | primary motor cortex |
| MEG | magnetoencephalography |
| MN | median nerve |
| MNS | mirror-neuron system |
| MRI | magnetic resonance imaging |
| PET | positron emission tomography |
| PPC | posterior parietal cortex |
| SEF | somatosensory evoked field |
| SEM | standard error of mean |
| SI | primary somatosensory cortex |
| SII | secondary somatosensory cortex |
| SMA | supplementary motor cortex |
| SQUID | superconducting quantum interference device |
| STS | superior temporal sulcus |
| TMS | transcranial magnetic stimulation |
| TSE | temporal spectral evolution |

# List of publications

This thesis is based on the following five publications which are referred to in the text by their Roman numerals I–V

I **Järveläinen J**, Schürmann M, Avikainen S and Hari R. Stronger reactivity of the human primary motor cortex during observation of live rather than video motor acts. NeuroReport 2001, 12: 3493–3495.

II **Järveläinen J**, Schürmann M. The motor cortex ~20-Hz rhythm reacts differently to thumb and middle finger stimulation: an MEG study. NeuroReport 2002, 13:1243–1246.

III **Järveläinen J**, Schürmann M, Hari R. Activation of the human primary motor cortex during observation of tool use. NeuroImage 2004, 23: 187–192.

IV Möttönen R, **Järveläinen J**, Sams M, Hari R. Viewing speech modulates activity in the left SI mouth cortex. NeuroImage, NeuroImage. 2005, 24: 731–737.

V **Järveläinen J**, Schürmann M, Avikainen S, Cannon TD, Lönnqvist J, Huttunen M and Hari R. Disease-specific decrease in reactivity of the primary motor cortex during action observation and execution in twins discordant for schizophrenia. Submitted.

**Contributions of the author**

I was the principal author in Studies I–III and V, carrying out the measurements with co-authors, analyzing the data and writing the publications with input from my co-authors. I had a major contribution in the acquisition and the analysis of the data in Study IV. I also participated in writing of this manuscript. In all studies, I actively participated in the planning of the experiments.

# 1. Introduction

*"The movements of expression in the face and body ... serve as the first means of communication between the mother and her infant; she smiles approval, and thus encourages her child on the right path, or frowns disapproval. We readily perceive sympathy in others by their expression; our sufferings are thus mitigated and our pleasures increased; and mutual good feeling is thus strengthened."*

Charles Darwin (*The Expression of Emotions in Man and Animals*, 1872)

How do we understand other people's behaviour? How can we interpret people's intentions, goals, feelings and states of mind from simple gestures, gaze, facial expressions and movements? In monkey brain, the frontal cortex contains neurons that discharge both when the monkey performs or observes another monkey or human to execute similar movements. These "mirror neurons" seem to be a core part of a system that directly matches observed and executed actions. Recent neurophysiological and neuroimaging studies indicate that similar mirror neurons exist also in several parts of the human brain. This "mirror-neuron system" (MNS) could have an important role in understanding, imitating and learning of actions. The aim of this thesis was to study the reactivity of the human primary motor (and the somatosensory) cortex, which is part of MNS, during observation of human motor action. Whole-scalp magnetoencephalography (MEG) allowed totally non-invasive monitoring of brain reactivity related to these functions. MEG has excellent temporal resolution combined with reasonable spatial resolution and made possible to study cortical activations in different sites of the brain simultaneously.

Recent studies have indicated that human MNS might subserve broader functions than motor action understanding and imitation, interacting closely with e.g. somatosensory system. Considering the homology of the monkey F5 area and the human Broca's area, where the mirror neurons were found, it has been suggested that MNS could have role in evolution of language (Arbib and Rizzolatti, 1998). Simple manual and orofacial gestures have evolved into complex sequences of communication and finally converted to auditory modality. Also empathy for pain and expressions of emotions might be mediated by a system similar to the motor MNS. The dysfunction of the MNS could contribute to symptoms of certain neuropsychiatric syndromes, such as

Asperger's syndrome, autism spectrum disorders and schizophrenia which involve disturbances in social communication and the agency of action.

The present work aims to extend the knowledge of functions of the MI and SI-parts of the human MNS during different action observation conditions using MEG. In Studies I–IV subjects were healthy adults and in Study V schizophrenic patients and their unaffected co-twins. The study was performed at the Brain Research Unit of the Low Temperature Laboratory of Helsinki University of Technology.

# 2. Review of literature

## 2.1. Motor cortices and pathways

The movements of the body are controlled by a motor system that involves cerebral cortex, basal ganglia, brain stem and cerebellum. The motor cortices are located anterior to the central sulcus, occupying about one third of the frontal lobes. The motor cortex can be divided into three separate areas: the primary motor cortex, the premotor area and the supplementary motor cortex. These areas have topographical representations of all the muscle groups of the body. The cortical motor system is needed for the execution of skilled voluntary movements and for planning of complex movements. The following introduction to the structure and function of the sensorimotor system is mainly based on reviews by Kandel and Jessel (1991), Guyton and Hall ( 1996) and Rizzolatti and Luppino (2001).

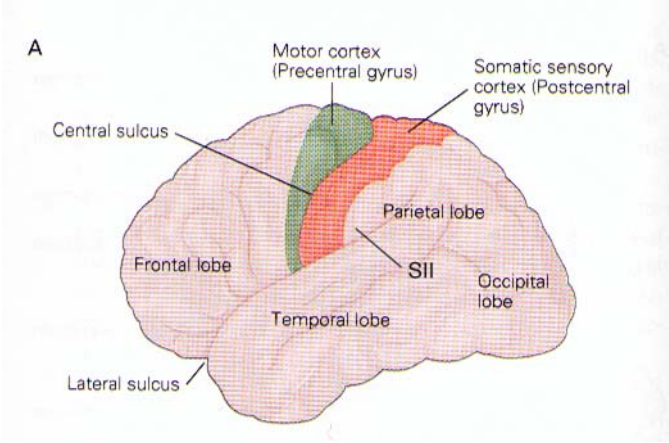


Figure 1. Human motor and somatosensory cortices. Modified from Kandel and Jessel (1991).

### 2.1.1. Motor areas

The primary motor cortex (MI) is located anterior to the central sulcus, beginning laterally in the sylvian fissure and spreading cranially to the uppermost part of the brain and then dipping into the longitudinal fissure (see Fig. 1). The MI is somatotopically arranged containing a contralateral motor map of the body. The representation of the head is located laterally, close by the lateral fissure, and the hands, limbs and trunk lie more medially. Areas of the body that require

greater precision of movement, such as the face, thumb, fingers and hands have much larger representation areas than do the trunk or the limbs. Stimulation of MI elicits relatively precise and simple muscle twitches in the contralateral side of the body. The ablation of primary motor cortex results in paralysis or hypotonia of the represented muscles. In humans, the adjacent cortical areas and deeper structures are usually also damaged (*i.e*. by stroke), resulting spasticity in the muscles due to disinhibition of the vestibular and reticular brain stem nuclei.

The premotor cortex (PMC) lies immediately anterior to the MI, extending inferiorly into the sylvian fissure and superiorly into the longitudinal fissure. The PMC is also somatotopically organized. The neurons of PMC project directly to MI, the red nucleus, the reticular formation, the basal ganglia and indirectly to cerebellum. The direct monosynaptic connections to lower areas suggest that PMC can control movements independently of the MI. PMC receives major input from posterior parietal and prefrontal areas. Electrical stimulation of the PMC results in patterns of movements involving muscle groups that are used to perform specific tasks.

Supplementary motor area (SMA) is located anterior and superior to PMC. The stimulation of SMA often elicits complex bilateral movements such as grasping, and this area participates in planning and organizing of complex movements.

### 2.1.2. Corticospinal tract

The most important pathway from MI to periphery is the corticospinal tract, also called the pyramidal tract. The corticospinal tract originates mostly from MI, PMC and SMA. Also somatosensory areas SI and SII and the cingulate cortices contribute to the corticospinal tract. The axons from cortex pass through the posterior limb of the internal capsule and then downwards through the brain stem and medulla, where most of the fibers cross to the opposite side. The fibers then descend in the lateral corticospinal tract and terminate on the interneurons in the intermediate regions of the cord gray matter. Some of the axons also synapse on the sensory relay neurons in the dorsal horn and some directly on the anterior motor neurons. A small part of fibers do not cross in the medulla. These fibers form the ventral corticospinal tracts and have a role in controlling postural movements. The corticospinal tract is crucial for discrete and fine-tuned movements, especially those of distal segments of the limbs, particularly the hands and the fingers.

Also other pathways participate in cortical control of movement, namely routes that involve basal ganglia, cerebellum and several brain stem nuclei.

## 2.2. Somatosensory cortices and pathways

The somatosensory system collects sensory information from skin, joints, muscles and subcutaneous tissue. Somatosensation consist of touch, proprioception, thermal sensation and pain and these submodalities are mostly conveyed separately. Somatosensory pathways from periphery to brain are somatotopically organized. The tactile and proprioseptive signals ascend to the somatosensory cortex via the dorsal column-medial lemniscal pathway. The nerve fibers synapse in the cuneate and gracile nuclei in medulla. After decussating to the opposite side, the fibers continue to thalamus and after that to the somatosensory cortex. Pain and temperature information is mainly carried by the anterolateral pathway.

### 2.2.1. Primary somatosensory cortex

The primary somatosensory cortex (SI) is located in the posterior bank of the central sulcus in the postcentral gyrus. SI consist of four different cytoarchitectonic areas: the Brodmann areas 3a, 3b, 1, and 2. Most of the thalamic sensory projections terminate in the areas 3a and 3 b which are connected to areas 1 and 2. Areas 3b and 1 are specialized for processing of information coming from mechanoreceptors of the skin and areas 3a and 2 for processing the proprioceptic information arriving from muscles and joints. Similarly as the MI, SI is somatotopically organized so that the areas that have dense innervation, such as lips and fingertips, are disproportionately largely represented in SI (Penfield and Jasper 1954).

### 2.2.2. Secondary somatosensory cortex and other somatosensory areas

The secondary somatosensory cortex lies in the upper bank of the Sylvian fissure. The SII has a crude somatotopic organization so that the face is presented anteriorly, the arms centrally and the legs posteriorly (Penfield and Jasper 1954; Hari *et al.* 1993). The information to SII enters from both sides of the body via thalamus, from the SI, and also from other sensory areas such as visual and auditory cortices. Neurons of SII have projections to ipsilateral MI, SMA, PPC and to contralateral SII (Jones and Powell 1969; Burton and Carlson 1986). Direct electrical stimulation of SII in humans results in sensations of numbness, tingling and desire to move in contra-, ipsi- and bilateral body parts (Penfield and Jasper 1954; Blume *et al.* 1992).

Posterior parietal cortex (PPC) is a higher-order somatosensory association area which is located in the parietal lobe, comprising Brodmann areas 5 and 7. PPC has a role in the integration of the tactile, proprioceptive and visual information. PPC also codes visual and body-centred space: lesion in the (especially right) PPC result in a neglect syndrome so that the patients ignore contralateral visual, tactile, and auditory stimuli.

Some other cortical areas, such as the mesial side of frontal cortex and the parietal cortex participate in processing of tactile information (Penfield and Jasper 1954).

## 2.3. Mirror-neuron system

Mirror neurons were first discovered in the monkey brain by Rizzolatti and his collegues who showed that area F5 in the ventral premotor cortex of the monkey contains neurons that discharge both when the monkey perfoms goal-directed hand movements and when he observes another monkey or human execute similar movements (Pellegrino *et al.* 1992; Gallese *et al.* 1996; Rizzolatti *et al.* 1996a). These mirror neurons seem to be a core part of a system that directly matches observed and executed actions. Recent functional neuroimaging and electrophysiological studies indicate that mirror neurons exist also in the human brain.

### 2.3.1. Mirror neurons in monkeys

Area F5 in monkey frontal cortex (see Figure 2) contains two particular classes of visuomotor neurons: canonical and mirror neurons (Gallese *et al.* 1996). The former are activated both when monkey observes graspable objects, the latter when the monkey observes or executes certain hand action. The actions that typically activate mirror neurons are placing or taking an object, as well as grasping and manipulating objects (Gallese *et al.* 1996; Rizzolatti *et al.* 1996a). Some of the mirror neurons are activated during observation and execution of only one type of action, whereas others show broader congruence and their activation is defined by the goal of the action (Pellegrino *et al.* 1992). Interestly, the monkey mirror neurons are not activated at all or only very weakly when action is made with a tool (Gallese *et al.* 1996). Some of the mirror neurons are active also during observation of mouth actions and even when the monkey listens to sounds associated with actions (Gallese *et al.* 1996; Kohler *et al.* 2002). When the final part of the action was hidden behind the screen, mirror neurons were also activated, suggesting that the neurons have a role in understanding the goal of action (Umilta *et al.* 2001). When the object behind the screen was removed and the monkey was aware of that the mirror neurons were not activated.

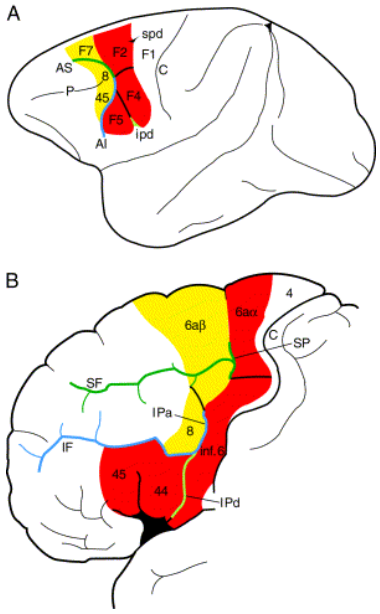


Figure 2. Brain of macaque monkey (A) and human (B) showing frontal areas which harbour the mirror neurons (areas F5 and BA 44). Brain regions with similar colours have anatomical and functional homologies (yellow: orientating behaviour, red: interacting with external world). Modified from Arbib and Rizzolatti (1998).

Mirror-neuron type behaviour has been found also in the other parts of the monkey brain. Neurons in inferior parietal lobule were activated both during observation and execution of hand actions (Kohler *et al.* 2002). Also neurons in monkey superior temporal sulcus area were activated during observation of goal-directed hand actions, but these neurons lack clear motor properties (Perrett *et al.* 1989).

### 2.3.2. Mirror-neuron system in humans

Taking into account the similarity between human and monkey brain, one would expect that similar mirror-neuron system could be found also in human brain. In recent years several functional neuroimaging and electrophysiological studies have provided evidence that mirror neurons exist also in the human brain. The first evidence came from transcranial magnetic stimulation study where human motor cortex was stimulated while subjects observed hand actions (Fadiga *et al.* 1995a). The motor evoked potentials were significantly increased during observation of movements involving the same muscles. However, this method did not define the level where the effect takes place. Later, positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and MEG studies demonstrated the existence of human mirror neuron system. Areas comprising the human MNS include at least the inferior frontal gyrus (see Figure 2) and the

primary motor cortex, and often the superior temporal sulcus and the inferior parietal lobule are activated as well (Fadiga *et al.* 1995b; Grafton *et al.* 1996; Rizzolatti *et al.* 1996b; Hari *et al.* 1998; Iacoboni *et al.* 1999; Nishitani and Hari 2000; Nishitani and Hari 2002). MNS could have an important role both in understanding the meaning of the observed actions and in motor learning and imitation (Gallese *et al.* 1996; Rizzolatti *et al.* 1996a).

The recent data indicate that the "motor MNS", which is activated qualitatively similarly by observed and executed motor acts, may be only one subsystem of the neural substrate for mirroring of other person's actions, feelings, sensations, and intentions (Gallese 2001; Rizzolatti *et al.* 2001; Gallese *et al.* 2004; Rizzolatti and Craighero 2004). For example, viewing other person's facial emotional reactions to unpleasant odorants activates those parts of the anterior insula that are also activated when the subject himself inhales the same odorants (Wicker *et al.* 2003). Furthermore, both imitating and observing of emotional facial expressions activate *e.g.* the right amygdala in addition to the MNS (Carr *et al.* 2003). Also on similar lines, viewing painful stimulation of other person's hand activates the affective (but not sensory-discriminative) pain processing matrix in the observer's brain (Singer *et al.* 2004). All these findings suggest that a widely distributed neural circuitry subserves simulation of other persons' acts and feelings.

## 2.4. Dysfunctional mirror neuron system in schizophrenia?

Dysfunction in distinguishing actions of self and others often occurs in schizophrenia, leading to delusions of control, thought insertion, and hallucinations (Frith 1987; Gray 1991; Frith 1992). Many patients with schizophrenia describe 'passivity' experiences in which actions, speech, thoughts or emotions are made for them by some external agent rather than by their own will (Frith 1987).

The motor system can be depicted as a network where the input is the motor command that produces a movement and the output is the sensory consequence of that movement. In order to produce a goal-directed movement the system must be able to estimate its current state, for example the position of the limb, and must also represent its goal. On the basis of these two representations the system can compute a sequence of motor commands that should generate the movement required to reach the goal (Frith 1992). In the patient with delusions of control the motor system concerned with the generation of a forward model and the representation of the predicted state of the system might be dysfunctional (Frith 1992). This could be true also when the motor system is

active in action observation and might cause difficulties in attributing the observed action to the right agent.

## 2.5. Magnetoencephalography

The neural currents in the brain produce weak magnetic fields that can be registered outside the head with MEG. This technique allows investigation of the cerebral electrical activity totally noninvasively, with excellent temporal and reasonable spatial resolution. The MEG technique has seen great development from the first recordings made in 1968 to introduction of the whole-scalp 122-channel device in 1993 and the 306-channel neuromagnetometer in 1997 in our laboratory. The following introduction to MEG is largely based on the review by Hämäläinen *et al.* (1993).

### 2.5.1. Origin of magnetic fields

Electric currents in the cortical pyramidal cells of the fissural cortex are assumed to be the primary generators of the magnetic fields measured outside the head. The dendrites of these cells are oriented orthogonal to the cortical surface and parallel to each other, which permits summation of magnetic fields with minimal cancellation.

The magnetic fields are probably produced by the post-synaptic excitatory or inbitory currents which are dipolar in contrast to quadrupolar currents associated with action potentials. The magnetic field of a quadrupolar current diminishes as $1/r^3$ with the distance r. Instead, the magnetic field of a dipolar current decreases more slowly as $1/r^2$. Also the duration of action potential is only one millisecond whereas the duration of a postsynaptic potential is at least 5–10 ms (typically 30–100 ms), which allows summation of several impulses.

### 2.5.2. Instrumentation

Magnetic fields produced by the brain are very weak compared with the earth's magnetic field and environmental noise. Therefore MEG measurements in our laboratory are performed in a magnetically shielded room consisting of layers of mu-metal and aluminium, combined with active cancellation of the background magnetic noise.

The cerebral magnetic are registered by SQUID (superconducting quantum interference device) sensors, which are kept immersed in liquid helium at the temperature of 4 Kelvin. Magnetic

field is first registered with the pickup coils which convert the magnetic flux into electric current. The pickup coils form closed loops with input coils that are coupled to the SQUIDs.

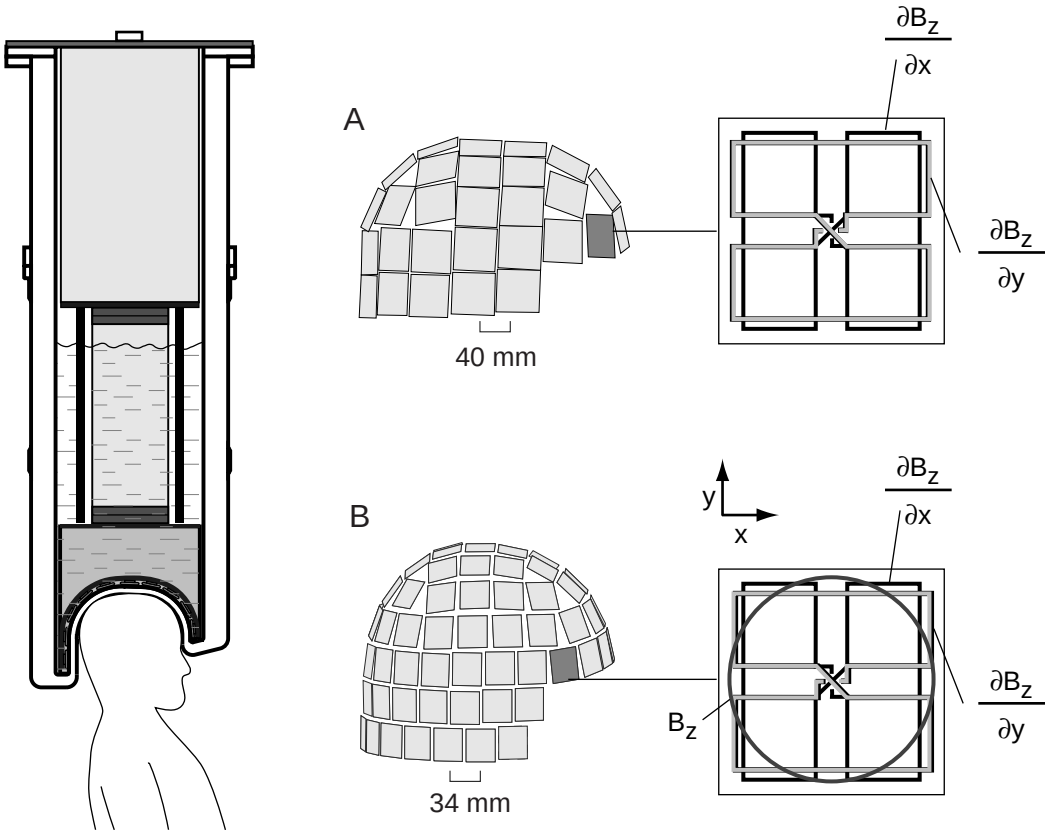


Figure 3. Schematic view of the Neuromag-122™ neuromagnetometer (left) and helmet-shaped sensor arrays of Neuromag-122™ (right, A) and Vectorview™ (right, B). Neuromag-122™ consists of 122 first-order gradiometers covering the whole scalp. The 61 sensor units measure the two orthogonal derivates $\partial B_z/\partial x$ and $\partial B_z/\partial y$ of the magnetic field component $B_z$ normal to the helmet surface. Vectorview™ system contains 102 identical triple sensors, each comprising two orthogonal first-order planar gradiometers and one magnetometer. Adapted from Vectorview™ Users Guide.

The sensitivity of the system depends on the configuration of the pickup coils. Magnetometers have only one loop and they are easily disturbed by the environmental noise and the signals from the heart. First-order gradiometers have an additional compensation coil wound in the opposite direction. These gradiometers record the difference between the field strength recorded by the pickup and the compensation coils, and they are effective in measuring magnetic fields produced by the nearby sources. The planar gradiometers have a pickup coil and the compensation coil coupled in a figure-of-eight structure, which measures the tangential derivative of the magnetic field. They detect the largest signal just above the local source area, facilitating the interpretation of the measured signals.

The helmet shaped whole-scalp neuromagnetometer Vectorview™ (see Fig. 3) used in the present work comprises 204 planar gradiometers and 102 magnetometers.

### 2.5.3. Source analysis

Calculation of current sources from the measured magnetic fields, called the inverse problem, has no unique solution. When interpreting the MEG data, biological knowledge can be used to limit the amount of solutions. Currents in the brain can be approximated with equivalent current dipoles (ECDs), assuming that the activated cortical area is relatively small to appear as a point when viewed from a distance. The ECD model has five parameters: *x*-, *y*- and *z*-coordinates orientation in the tangential plane, and strength. The ECD which best explains the measured field distribution may be determined by a least-squares search, and the adequacy of the model may be expressed by the goodness-of-fit (*g*) value, which indicates how much of the measured field variance is accounted for by the dipole model.

Multidipole models can be used to model the activity of several brain areas simultaneously. Temporally or spatially separated dipoles can be first determined individually, employing the single-dipole model, and thereafter be introduced simultaneously into a multidipole model, where their strenghts are allowed to change as a function of time whereas their locations and orientations are kept fixed.

## 2.6. Cortical rhythms

Cerebral cortex exhibits prominent rhythmic activity in electrical and magnetic recordings. It is assumed that thalamus plays important role in generation of cortical rhythms. *In vitro* studies have shown that certain thalamic cells have intrinsic oscillatory activity due to their intrinsic membrane properties (Llinas 1988). It has been suggested that thalamus has ‘pacemakers’ that drive the cortical oscillatory activity (Lopes da Silva 1991). Despite the extensive animal and human research, the functional significance of the rhythms has remained relatively unknown.

Several regions of the human cortex diplay their own intrinsic rhythms with modality and frequency-specific reactivity to certain tasks (Hari *et al.* 1997). The best known rhythms are posterior alpha rhythm and the rolandic mu rhythm. The alpha rhythm is dampened by opening of the eyes and mu rhythm by somatosensory stimulation or limb movements.

### 2.6.1 Mu rhythm

The rolandic mu rhythm is closely related to the sensorimotor functions. The mu rhythm consist of two frequency components at about 10 Hz and 20-Hz with nearly harmonic relationship, resulting "the comb-shape" of the rhythm (Tiihonen *et al.* 1989).

Both components of the mu rhythm react with a transient "rebound" after a limb movement or a somatosensory stimulation. The ~20-Hz reacts about 0.3 s faster and clearly stronger than the ~10-Hz rhythm (Salenius *et al.* 1997b). The different location, timing and strength of the rebounds suggest that these two frequency components are generated by the different neural networks. The ~20–Hz rhythm seems to reflect functions of the motor system, whereas the 10 Hz component is related more strongly to the somatosensory system.

Several lines of evidence suggest that the ~20-Hz rhythm originates predominantly in the precentral primary motor cortex (Hari *et al.* 1997). First, oscillatory activity of similar frequency has been recorded intraoperatively from the anterior wall of the human central sulcus (Jasper 1949). Second, the sources of the ~20-Hz component of the rolandic MEG rhythm are slightly more anterior to sources of the ~10-Hz component that arises in the postcentral somatosensory cortex (Salmelin and Hari 1994). Third, the ~20-Hz rhythm is coherent with motor unit firing during isometric muscle contraction which also supports motor–cortex origin of the ~20-Hz rhythm (Salenius *et al.* 1997a). After electrical median nerve stimulus, the ~20-Hz motor-cortex rhythm is first transiently, and bilaterally, suppressed and then 200–400 ms later strongly enhanced (Salmelin and Hari 1994). This rebound likely reflects cortical inhibition, as has been argued on the basis of both MEG and transcranial magnetic stimulation studies (Salmelin and Hari 1994; Chen *et al.* 1999; Abbruzzese *et al.* 2001). Consequently, the rebound has been used as an indicator of the functional state of the primary motor cortex (Schnitzler *et al.* 1997; Hari *et al.* 1998; Silen *et al.* 2000). The rebound is abolished during action execution (Salenius *et al.* 1997c; Schnitzler *et al.* 1997) and significantly suppressed during action observation (Hari *et al.* 1998).

## 2.7. Somatosensory evoked responses

Somatosensory cortex and pathways can be studied by measuring somatosensory evoked potentials (SEPs) with EEG or somatosensory evoked fields (SEFs) by MEG. Evoked responses are averaged time-locked to the stimuli to distinguish them from the background activity. Both electrical and tactile stimuli can be used; the electric stimuli produce clear and reproducible responses and are easy to apply, but the tactile stimuli are more physiological. The electric stimuli

are usually applied on the peripheral nerves such as median or tibial nerves, at intensities just above the motor threshold.

The earliest somatosensory response to median nerve stimulation peaks at 20 ms (N20m). It is mainly generated by the current from deep towards the superficial layers of area 3b of the SI cortex. The next deflection is of opposite polarity and peaks at 30–35 ms (P35m). The SEFs follow the homuncular organization in SI cortex (Hari *et al.* 1993).

Somatosensory responses from the SII cortex were first demonstrated with MEG (Hari *et al.* 1993). They peak at around 100 ms after upper-limb stimuli and they are bilateral even to unilateral stimuli. Additional activation of the posterior parietal cortex has been found in MEG studies (Forss *et al.* 1994).

# 3. Aims of the study

The aim of this thesis was to investigate, by means of magnetoencephalographic recordings, the reactivity of the human primary motor cortex during action observation. The specific aims in each study were:

I To find out whether videotaped and live hand movements would differ in their effectiveness to activate the human primary motor cortex.

II To study whether the reactivity of the motor cortex would differ to thumb and middle finger stimuli.

III To find out whether the motor-cortex part of the human MNS would be activated by observation of tool use.

IV To explore whether speech viewing and listening would affect cortical somatosensory processing.

V To investigate whether schizophrenic subjects would show abnormalities in the motor-cortex part of their MNS during observation and execution of finger movements, compared with their healthy co-twins.

# 4. Subjects and methods

## 4.1. Subjects

A total of 64 subjects were studied in five experiments (ages 22–58, 35 males, 29 females). Subjects of Studies I–IV were healthy adults and in Study V, 11 schizophrenic patients were studied with their healthy co-twins.

## 4.2. Stimulation

| | | Stimulation | |
|---|---|---|---|
| Study | N | Stimulation site | Stimulus type |
| I | 10 | Median nerve + visual | Electric + video + live movement |
| II | 12 | Thumb + middle finger | Electric |
| III | 10 | Median nerve + visual | Electric + live movement |
| IV | 8 | Median nerve + lower lip | Electric + tactile + live movement + auditory |
| V | 22 | Median nerve + visual | Electric + live movement |

Table 1. Stimulation in Studies I to V.

**Visual stimuli**

The visual stimuli in Studies I, III, and V were produced by the experimenter who was performing live actions in the front of the subject. In Study I, hand movements were also shown on videoscreen. In Study IV, the experimenter was sitting in front of the subject speaking silently.

**Electric stimuli**

The median nerves were stimulated transcutaneously at the wrists (or at the palmar skin of the thumb and middle finger in study II) with 0.3-ms constant current pulses. The stimulus intensity exceeded the motor threshold (except in Study II) without being painful. The stimulus intensity was adjusted to produce subjectively equal sensations at both hands.

**Tactile stimuli**

The lower lip was stimulated once every 1.5 s with two balloon diaphragms driven by compressed air. The pressure of the 170-ms pulses, kept equal for all subjects, produced a sensation of brief touch.

## 4.3. Recording

In all studies, cortical magnetic signals were recorded with a whole-scalp 306-channel SQUID neuromagnetometer (Vectorview™, Neuromag Ltd; Helsinki) in a magnetically shielded room. Each of the 102 sensor elements of the device comprises two orthogonal planar gradiometers and one magnetometer. Before the experiment, the positions of four marker coils, placed on the scalp, were determined in relation to three anatomical landmark points (the nasion and both preauricular points) with an Isotrak 3D-digitizer. This procedure allowed alignment of the MEG and magnetic resonance image (MRI) coordinate systems. Anatomical T1-weighted MRIs of eight subjects' brains were obtained with a 1.5 T scanner (Siemens, Erlangen, Germany). In Study III, the muscle contractions were monitored with surface electromyogram (EMG) recording from three subjects.

The signals were bandpass filtered at 0.1–172 Hz and digitized at 600 Hz. Vertical and horizontal electro-oculograms (EOGs) were monitored to reject all MEG epochs coinciding with blinks and excessive eye movements; the artefact-rejection limits were set to 5000 fT/cm for MEG channels and to 150 μV for EOGs.

## 4.4. Data analysis

Sources of the evoked responses were modelled as single equivalent current dipoles (ECDs), best describing the most dominant cerebral currents during the strongest dipolar field patterns. ECDs were identified by a least-squares search using a subset of 16–18 sensors over the area of the maximum signal. The 3D locations, orientations, and the strengths of the ECDs were obtained in a spherical head model; the models were adjusted on the basis of individual MRIs.

The level of the ~20-Hz motor-cortex rhythm was analyzed by first filtering the spontaneous oscillatory signals through 14–30 Hz, then rectifying them and finally averaging them time-locked to the median nerve stimuli (Salmelin and Hari 1994). The mean level of the ~20-Hz (14–30 Hz) rebound in each condition was then quantified.

# 5. Experiments, results and brief discussions

## 5.1. The ~20-Hz rhythm is suppressed more during observation of live than video motor acts (Study I)

### 5.1.1. Experimental design

Ten healthy subjects were presented with live and videotaped finger movements (simple object manipulation) while the neuromagnetic signals were recorded. Median nerves were stimulated alternatingly (ISI of 1.5 s) to induce poststimulus ~20-Hz rebounds in the motor cortex. The session also included a *rest* condition, where subjects rested relaxed eyes open and an *act* condition, where subjects manipulated the small object themselves. One-minute segments from all four conditions were combined into blocks, and eight such blocks were presented to subjects. Figure 4 (right bottom) shows a snapshot of the hand manipulation movement presented in *video* and *live* conditions.

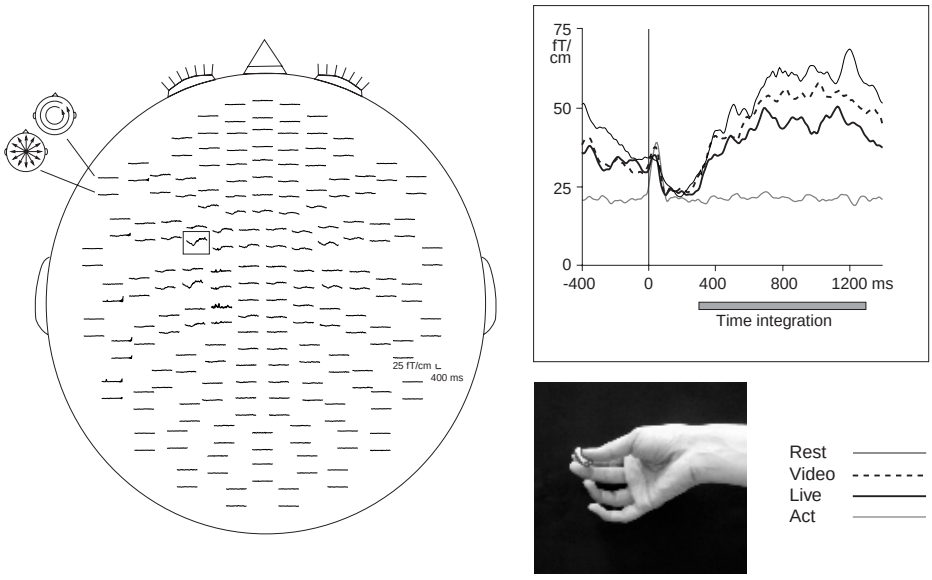


Figure 4. The level of the 14–30 Hz activity on 204 gradiometer channels as a function of time in rest condition in one subject (time period –400 to 1300 ms). The ~20-Hz rebounds in different conditions from the channel over the left motor cortex are shown enlarged on the right. The insert on the right bottom shows the hand manipulation movement presented in *video* and *live* conditions.

### 5.1.2. Results

Figure 4 shows the ~20-Hz level in one subject on 204 gradiometer channels during *rest* condition. After the right median nerve stimulus, the ~20-Hz level is first suppressed and then strongly enhanced; the rebound starts at about 300 ms and reaches its maximum at 700 ms. The strongest rebounds were seen above the contralateral Rolandic sensorimotor area. Figure 4 (right top) shows the indicated channel over the left motor cortex during all conditions.

In all subjects, the strongest rebounds were observed above the sensorimotor areas. Across all conditions, significant differences were observed in the levels of rebounds (ANOVA: $F(3,27) = 18.25$; $p = 0.004$ with Greenhouse–Geisser correction); post–hoc tests showed that the rebounds were stronger during *rest* than *video* ($p = 0.003$) and stronger during *rest* than *live* ($p = 0.001$).

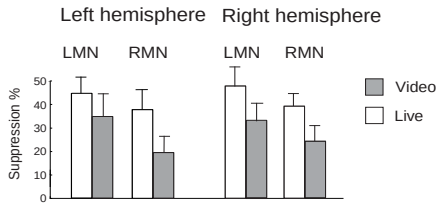


Figure 5. Mean (+SEM) suppressions of the ~20-Hz rebounds across all subjects as percentages of suppressions in *act* condition (*act* = 100 % suppression). LMN = left median nerve stimulus, RMN = right median nerve stimulus.

Figure 5 shows the mean suppressions of the ~20-Hz rebounds as percentages of suppression in the *act* condition when the rebounds were totally abolished in all subjects. The suppression was significantly stronger ($p = 0.004$) during the *live* (LH = 44% RH = 47% for LMN, LH = 37% RH = 38% for RMN) than *video* condition (LH = 32% RH = 35% for LMN, LH = 19% RH = 24% for RMN).

### 5.1.3. Discussion

In line with earlier MEG and TMS studies, these results show that the primary motor cortex is activated during observation of another person's actions. The effect was significantly smaller for videotaped than live movements, but also the videotaped movements significantly suppressed the ~20-Hz rhythm.

The live movements have apparently higher ecological validity than the videotaped movements, which could explain the stronger motor-cortex activation in the *live* condition. Moreover, the 2D videoscreen has probably less interesting visual properties than the live movements catching the attention of the subjects. Also the inherent unpredictability of live movements could affect the suppression of the ~20-Hz rhythm.

A recent PET study showed also different brain correlates for observation of hand grasping in 3D virtual reality, 2D video and live conditions (Perani *et al.* 2001). The monkey mirror neurons did not fire when the monkey was observing videotaped movements (Rizzolatti *et al.* 1996), suggesting differences in human and monkey mirror systems in differentiating live and natural movements.

The present results show that both live and videotaped movements are useful when studying the human MNS. Although the live movements activate the motor cortex more strongly, also the videotaped movements significantly suppress the ~20-Hz rhythm. Depending on the particular goals of the study, both video and live movements can be used as a stimuli.

## 5.2. The ~20-Hz rhythm reacts stronger to thumb than middle finger stimulation (Study II)

### 5.2.1. Experimental design

The reactivity of the ~20-Hz motor cortex rhythm was studied by stimulating thumb and middle finger electrically and by quantifying the poststimulus rebounds. Twelve healthy subjects participated in the study, nine of them right handed, two ambidextrous and one left-handed.

During the measurement, the subjects sat relaxed with their eyes open. The palmar sides of the thumb and middle finger of the right hand were stimulated alternatingly with an interstimulus interval of 2.0 s. An additional recording with an ISI of 0.5 s was performed in nine subjects. The stimulus intensities were adjusted to produce sensations of subjectively equal intensities in both fingers. Five minutes of oscillatory neuromagnetic activity was recorded. In an additional session with o.5 s ISI, 500 evoked responses were averaged on-line.

### 5.2.2. Results

Figure 6 (right) shows the level of the ~20-Hz rhythm in one subject measured by 204 gradiometers. Immediately after both stimuli, the ~20-Hz level is first suppressed and then strongly enhanced; this rebound starts at 400 ms and peaks at 1100 ms.

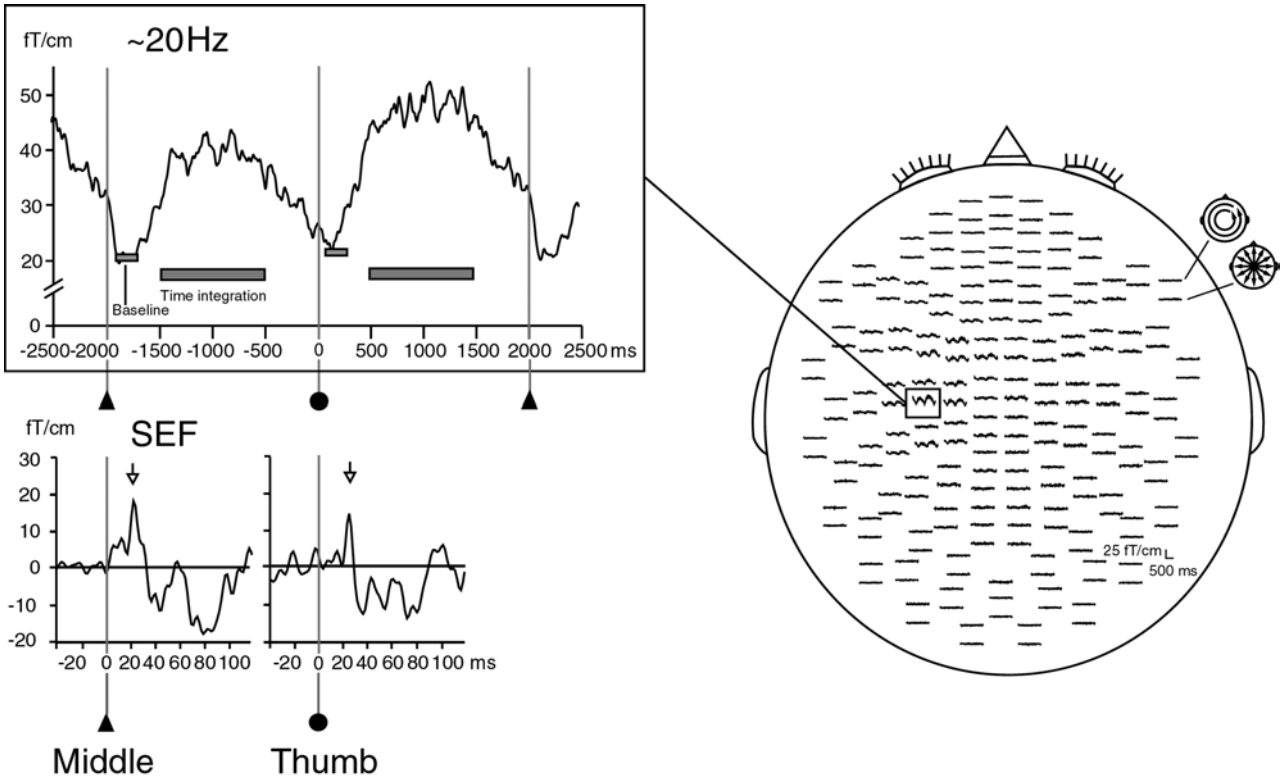


Figure 6. Right: The level of the 14–30 Hz activity of one subject, measured by 204 gradiometer channels as a function of time. The head is viewed from the top. The upper and lower traces of each signal pair refer to latitudinal and longitudinal field gradients measured by two orthogonal planar gradiometers. Left top: The level of the ~20-Hz rhythm from the indicated channel over the left sensorimotor cortex. Left bottom: The somatosensory evoked fields (SEF) from the same channel, the small arrows pointing to the 20-ms response. Stimuli to the thumb and middle finger are indicated below the figures.

The channel showing the most prominent rebounds is enlarged in Fig. 6 (left), showing the level of the ~20-Hz rhythm (left top) and the somatosensory N20m responses (left bottom) as a function of time. All subjects showed strongest reactivity of the ~20-Hz activity in channels above the left Rolandic region.

The rebounds (Fig. 7) were significantly higher after thumb than middle finger stimulation (5.3 ± 0.1 fT/cm vs 3.9 ± 0.7 fT/cm, $p = 0.005$) in the four channels with the used in quantification. Amplitudes of N20m (Fig. 7) were 14.9 ± 2.0 fT/cm to thumb stimuli, and 16.1 ± 2.6 fT/cm to middle finger stimuli ($p = 0.020$).

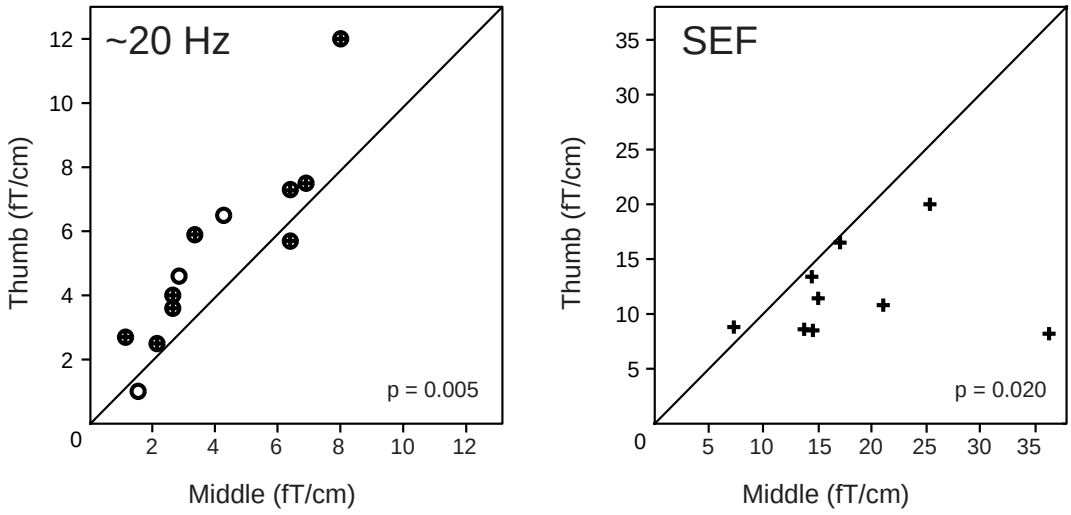


Figure 7. Left: The level of the ~20 Hz rhythm, after middle finger (horizontal) vs thumb (vertical) stimulation in 12 subjects. Right: N20m amplitudes for middle finger (horizontal) vs thumb (vertical) stimulation (additional recordings with ISI of 0.5 s, 9 subjects).

### 5.2.3. Discussion

The human thumb is uniquely evolved both morphologically and functionally, enabling precision grip and capability for wide range of movements. The unique role is reflected in the primary somatosensory and motor cortices where the representation areas are larger for thumb than the other fingers. However, there have been conflicting results of the size of the somatosensory evoked responses peaking around 20 ms for thumb and middle finger.

High-frequency oscillations (HFOs) above 300 Hz were stonger after thumb than middle finger stimulation (Hashimoto *et al.* 1996). HFOs have been proposed to have a role in intracortical inhibition (Hashimoto *et al.* 1996), and stronger HFOs after thumb stimulation might reflect specific somatosensory prosessing for thumb, providing information for the motor cortex for fine motor control. The HFOs inhibit the SI cortex, thereby decreasing N20m responses. The large human thumb (compared to other primates) probably requires more extensive functional representation in the motor cortex, which might be reflected as a stronger reactivity of the ~20-Hz rhythm after somatosensory stimulation. These functional interactions result in inverse thumb/middle finger ratio between the 20 ms responses and the ~20-Hz motor-cortex rhythm.

## 5.3. Observation of tool use activates primary motor cortex (Study III)

### 5.3.1. Experimental setup

The reactivity of the ~20-Hz rhythm from 10 healthy subjects was studied while they a) observed the experimenter to move small objects from plate to plate with chopsticks, b) observed the experimenter to execute similar movements but not touching or moving the objects, c) observed the experimenter to move objects with thumb-index finger grip from plate to plate, d) rested relaxed, e) manipulated the small object themselves.

### 5.3.2 Results

Figure 8 (left) shows the sources of the ~20-Hz activity superimposed on the surface rendition of the brain of Subject 3. In agreement with earlier observations, the current dipoles, used to model individual cycles of the ~20-Hz activity, are clustered just anterior to the central sulcus (Salmelin and Hari 1994; Hari *et al.* 1998). The Talairach coordinates for the median of all source locations were x = 35, y = -23, z = 48, thereby agreeing with the location of the primary motor cortex (Talairach and Tournoux 1998).

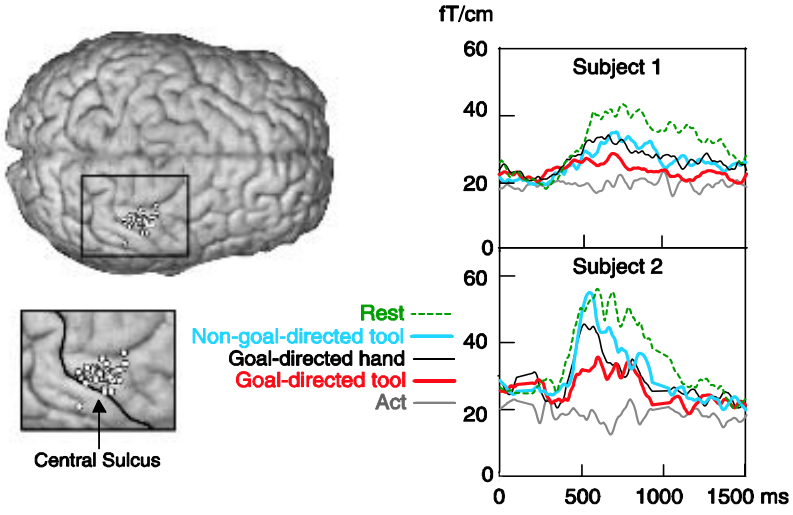


Figure 8. *Left:* Source locations of the ~20-Hz activity in one subject on a surface rendition of his MRI viewed from the top. The dots illustrate locations of the 50 equivalent current dipoles used to model the field patterns during single cycles of the ~20-Hz oscillations. *Right:* The level of the ~20-Hz rhythm as a function of time for Subjects 1 and 2 in one channel over the left sensorimotor cortex (RMN stimulation).

Figure 8 (right) shows for two subjects the temporal evolution of the ~20-Hz level at one channel over left sensorimotor cortex, contralateral to the RMN stimulation. During all except *act* conditions, the level of the ~20-Hz rhythm is strongly enhanced after the median nerve stimulus, starting at about 400 ms, and the rebound reaches its maximum level within 700 ms after the stimulus. Compared with the *rest* condition, the rebounds are clearly suppressed during the three observation conditions, and the suppression is stronger during observation of *goal-directed* than *non-goal-directed tool* use. During the *goal-directed hand* condition *("hand")*, which served here as a reference to allow comparison with an earlier study (Hari *et al.* 1998), the suppression was slightly smaller than during the *goal-directed tool use* condition.

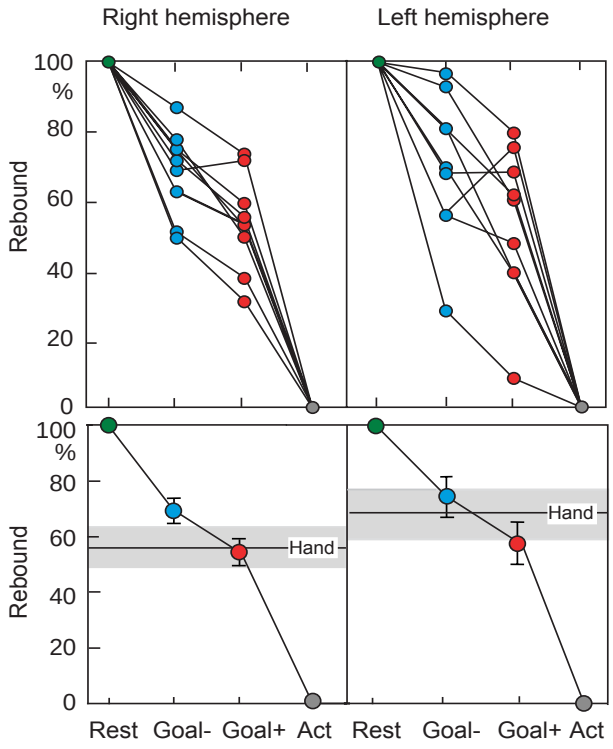


Figure 9. The normalized strengths of the ~20-Hz rebounds in hemispheres contralateral to median nerve stimulation in all conditions; the values were normalized individually as percentages of the rebound difference during *Rest* minus *Act*. Top: Rebound strengths in all 9 subjects, each individual's data connected with lines. Bottom: Mean (± SEM) rebound strengths across subjects, shown as dots and bars for tool conditions (*Goal+*, *Goal–*) and as a set of reference lines for the hand movement condition.

Figure 9 illustrates the values of the contralateral rebounds in all conditions, both as individual values (top, N = 9) and as mean ± SEM (bottom). The rebounds for the control ("*hand*") condition are presented as a grey reference belt (mean ± SEM). The suppression from the *rest* differed between conditions (ANOVA: *condition [goal+, goal–, hand]*, $F(2,16) = 5.4$, $p < 0.03$, Greenhouse-Geisser corrected; *hemisphere*, $F(1,8) = 0.4$, *hemisphere x condition* $F(2,16) = 1.0$,

both statistically non-significant, $p = 0.56$ and $p = 0.37$, respectively); post-hoc test *goal+* vs *goal–*, averaged across hemispheres, $p < 0.01$. In both hemispheres, the suppression is statistically significantly stronger during *goal+* than *goal–* (mean ± SEM difference 17 ± 6%, $p < 0.03$ in the left hemisphere, and 15 ± 3%, $p < 0.001$ in the right). In the *hand* movements condition the suppression of the rebound is 13 ± 5% ($p = 0.04$) stronger than during *goal–* tool use in the right hemisphere; in the left hemisphere the difference is 7 ± 6% (n.s., $p = 0.26$).

The rebound difference (*goal+ vs goal–*) in the left hemisphere was positively correlated with chopstick use during the last twelve months (median 5, range 2–20 times, $r = 0.83$, $p < 0.006$).

### 5.3.3. Discussion

The suppression of the ~20-Hz rhythm during observation of tool use indicates activation of the primary motor cortex. The suppression was significantly stronger when the subjects observed goal-directed than non-goal-directed tool use.

In monkeys, mere observation of tool use does not activate their F5 mirror neurons, but actual contact with the hand and object is required. These results broaden the view of human MNS, suggesting that also actions with tools are represented in this system. The positive correlation with motor cortex activation difference between goal-directed and non-goal-directed tool use and frequency of chopsticks use, suggests for the first time ever that experience can modify the MNS.

The stronger activation of the motor cortex during observation of goal-directed than non-goal-goal-directed tool use could be related to the observer's ability to understand and imitate these motor acts.

## 5.4. Activation of SI mouth cortex is modulated during speech viewing (Study IV)

### 5.4.1. Experimental design

We stimulated the lower lip (with tactile pulses) and median nerves (with electric pulses) in eight subjects to activate their SI mouth and hand representation ares while they either rested, listened to experimenter's speech, viewed her articulatory gestures or executed mouth movements themselves.

### 5.4.2. Results

The earliest deflections to bilateral lip stimuli peaked at 45 and 58 ms over the left and at 43 and 58 ms over the right anterior parietal area (Fig. 10). The earliest deflections to RMN stimuli peaked over the left (contralateral) anterior parietal area at 20 ms and 35 ms. The earliest deflections to LMN stimuli peaked at the same latencies over the contralateral anterior parietal area.

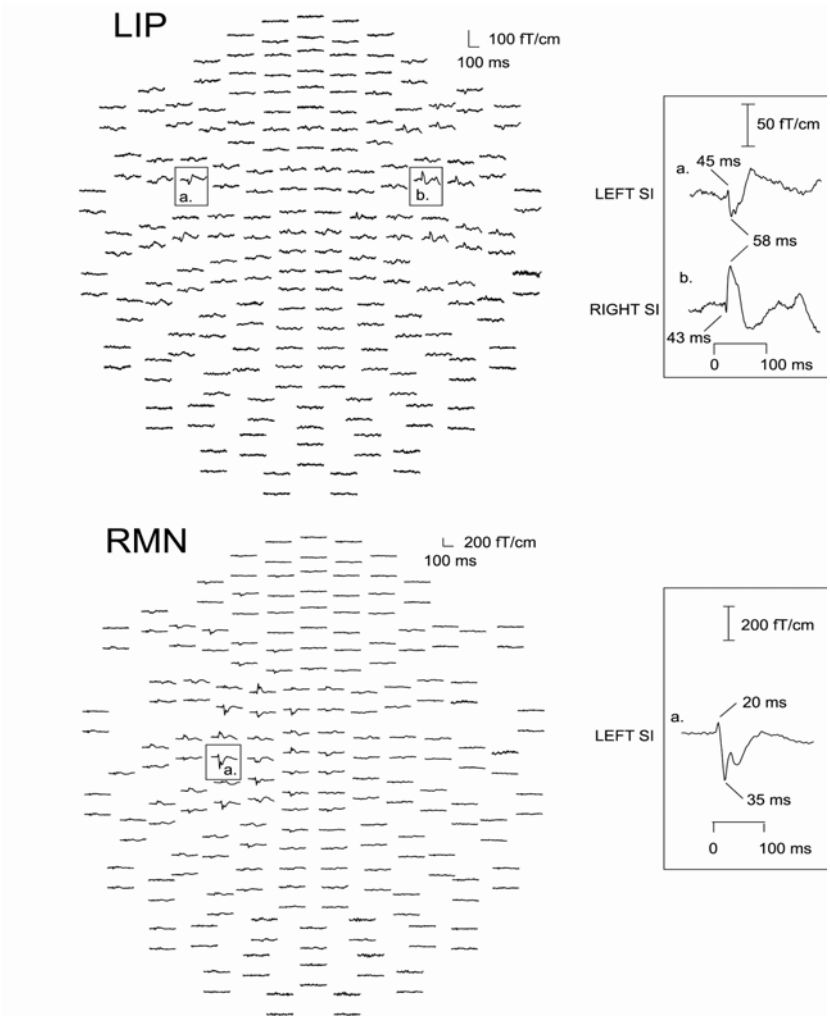


Figure 10. Whole-scalp neuromagnetic responses to the lip (upper part of the Figure, Subject 1) and the median-nerve stimuli (lower part of the Figure, Subject 5). The head is viewed from the top (nose up), and in each response pair, the upper trace illustrates the derivative of the magnetic field along the latitude and the lower trace along the longitude. Enlarged responses from the channels marked with squares are shown on the right side of the Figure.

Figure 11 shows the ECDs of one subject for the 58-ms responses to lip and the 35-ms responses to median-nerve stimuli superimposed on the axial and sagittal MRI slices. The sources

for both responses are located in the SI cortex, in the posterior wall of the central sulcus. ECDs for the lip stimuli are more lateral, anterior and inferior along the rolandic fissure than ECDs for the median-nerve stimuli, in agreement with the somatotopic organization of the SI cortex.

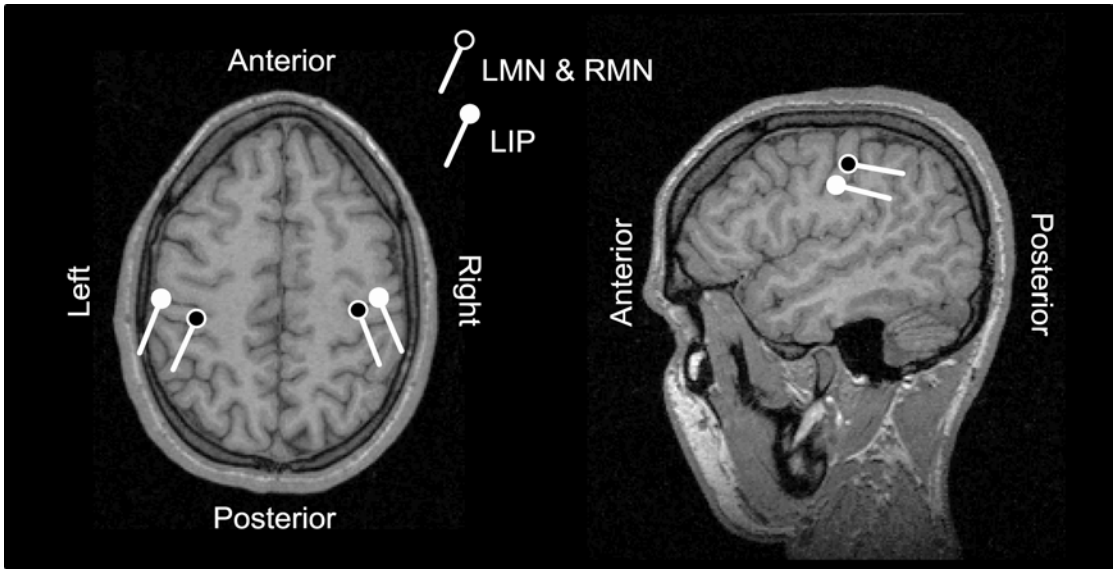


Figure 11. ECDs of Subject 1 to lip and median–nerve stimuli superimposed on the subject's own MR images.

Compared with the rest condition, subject's own mouth movements strongly suppressed the 58–ms lip responses in the mouth SI cortex of both hemispheres; this finding agrees with the well-known "sensory gating" (Schnitzler et al., 1995; Forss and Jousmäki, 1998). In contrast, the 35–ms responses to median nerve stimulation were slightly enlarged during mouth movements in the hand SI cortex of the left hemisphere and unchanged in the right hemisphere. The EMG signals recorded from mouth muscles of three subjects showed pronounced activity during mouth movement condition, but no activity was observed during other conditions.

In all subjects, own mouth movements decreased the strengths of mouth SI sources bilaterally. Viewing speech strengthened the left mouth-area sources consistently across subjects. In the right hemisphere, the SI sources were not systematically modulated during viewing speech. Listening to speech did not have systematic effects on the strengths of mouth SI sources in either hemisphere.

Figure 12 shows the mean percentual changes (relative to the rest condition) of the mouth and hand SI source strengths during speech observation and mouth movements. The strengths were measured at the peak latency of the early SI responses, at 54 ± 1 ms and 53 ± 1 ms for the lip stimuli, and at 34 ± 2 ms and 38 ± 1 ms for the median-nerve stimuli in the left and right hemispheres, respectively. Strengths of the left mouth SI sources increased by 16 ± 3% ($p < 0.01$) during viewing speech, without any significant effect in the right hemisphere. Listening to speech

did not affect the strengths of the mouth SI sources significantly in either hemisphere. Own mouth movements suppressed the strengths of mouth SI sources by 77 ± 7% ($p < 0.001$) in the left

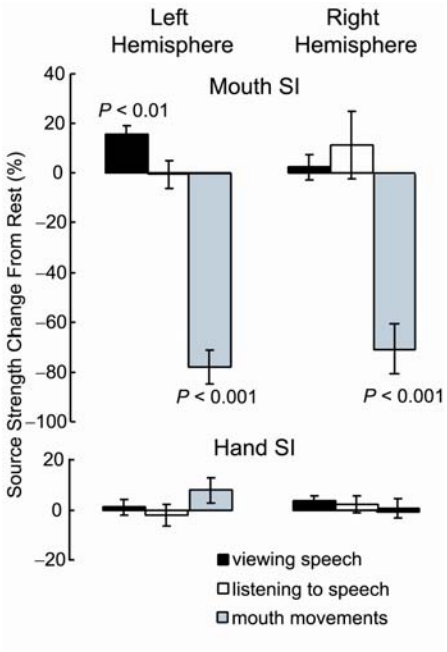


Figure 12. The mean (± SEM) percentual changes in source strengths during speech viewing, speech listening and mouth movements (relative to the rest condition) in the mouth and hand areas of the SI cortices. The strengths were measured at the latencies of 54 ± 1 ms and 53 ± 1 ms for the lip stimuli, and at 34 ± 2 ms and 38 ± 1 ms for the median-nerve stimuli in the left and right hemispheres, respectively.

hemisphere and by 70 ± 10% ($p < 0.001$) in the right hemisphere. Strengths of the hand SI sources were not modulated during own movements nor during speech viewing/listening.

### 5.4.3. Discussion

These results show that viewing other persons' articulatory mouth movements can enhance activity in the left SI mouth area. This effect was not seen in the corresponding region in the right hemisphere and not in hand area. Thus, viewing mouth movements activated the left SI in a somatotopic manner. The 35-ms responses to median nerve stimuli remained stable during speech viewing and listening. These findings suggest that a widely distributed neural system is involved in embodied simulation of other persons' acts and feelings. The present data suggest that also the SI is part of this circuitry, which is important for social interaction. Hence the SI cortex could subserve simulation of other person's movement-related sensations during observation of actions.

## 5.5. Schizophrenic patients show disease-specific changes in motor-cortex reactivity during observation and execution of action (Study V)

### 5.5.1. Experimental design

The neuromagnetic 20-Hz rhythm was studied from 11 twin pairs discordant for schizophrenia while they either rested, observed finger manipulation movements or executed manipulation movements themselves. Left and right median nerves were stimulated alternatingly to elicit 20-Hz rhythm rebounds.

### 5.5.2. Results

Figure 13 illustrates the ~20-Hz reactivity in all twin pairs. For both hemispheres and for both observation and acting conditions, the patients show weaker reactivity of the ~20-Hz rhythm than their healthy co-twins (binomial test for n = 11 pairs: rest-act p = 0.033 and rest-observe n.s. in left hemisphere; rest-act p = 0.006 and rest-observe p = 0.006 in right hemisphere).

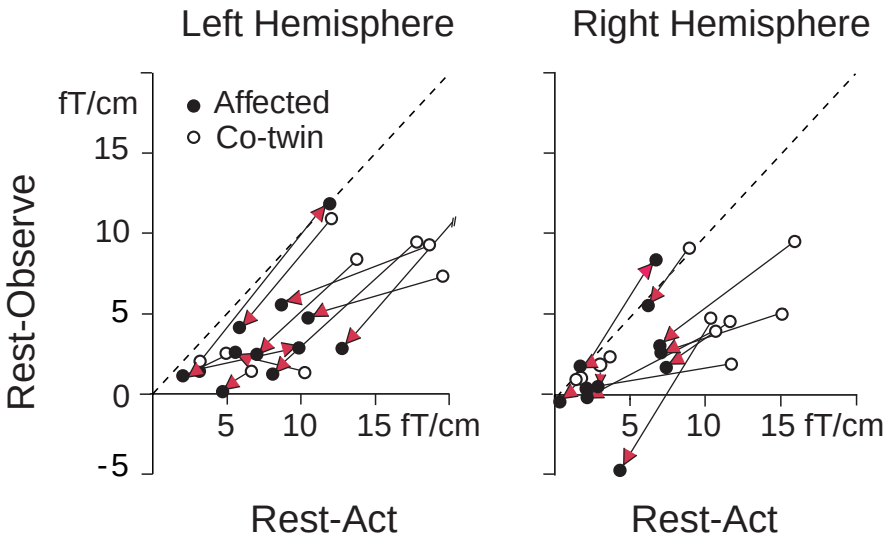


Figure 13. The ~20-Hz reactivity in all subjects, quantified as the difference between rest and observe conditions (along vertical axis) as a function of the difference between the rest and act conditions (along horizontal axis). Twin pairs are connected with lines, and the arrows point from the healthy twin (open circle) to the affected twin (filled circle).

The rest levels of the ~20-Hz rhythm did not differ between affected and healthy twins, nor was there any statistically significant difference between the groups in the strengths of cortical somatosensory evoked fields (N20m and P35m) arisising from the primary somatosensory cortex (t-

test, $p \geq 0.2$) The 20-Hz reactivity and the doses of neuroleptic medication expressed in chlorpromazine equivalents were not statistically significantly correlated, but had a positive trend (Pearson's $r = 0.43$, $p = 0.19$).

### 5.5.3. Discussion

The reactivity of the 20-Hz rhythm was systemically weaker in schizophrenic subjects, both during action observation and execution. The reactivity changes did not seem to reflect some general dysfunctioning because the somatosensory evoked fields and rest levels did not differ in affected and healthy subjects. The disease-specific weakened reactivity observed in the present study could be related to a general deficit in motor cognition, which may include mirror neurons but may not be specific to these cells.

# 6. General discussion

This thesis used MEG to study the activity of the MI and SI parts of the human MNS during observation of different actions in healthy and schizophrenic subjects.

In Study I we studied if viewing video acts would active M1. The ~20 Hz motor-cortex rhythm was suppressed more during observation of live than video ed and live hand movements would differ in their effectiveness to activate the human primary mot motor act, indicating that observation of live rather than videotaped movements activate MI more strongly.

In Study II, we studied whether the reactivity of the motor cortex would differ to thumb and middle finger stimuli. We found an inverse thumb/middle finger ratio between the 20-ms responses and the reactivity of the ~20 Hz motor-cortex rhythm, suggesting that the sensorimotor processing differs for thumb and middle finger in the human primary motor and somatosensory cortices.

To find out whether the motor-cortex part of the human MNS would be activated by observation of tool use, we studied observation of chopstick use in Study III. We found stronger activation of the motor cortex during observation of goal-directed than non-goal-goal-directed tool use, and this could be related to observer's ability understand and imitate these motor acts.To explore whether speech viewing and listening would affect cortical somatosensory processing the subjects listened to experimenter's speech, viewed articulatory gestures or executed mouth

movements themselves in Study IV. We found that viewing other persons articulatory mouth movements can enhance activity in the left SI mouth area.

In Study V, we investigeted whether schizophrenic subjects would show abnormalities in the motor-cortex part of their MNS during observation and execution of finger movements, compared with their healthy co-twins. The reactivity of the 20-Hz rhythm was systemically weaker in schizophrenic subjects, both during action observation and execution.

Mirror neurons were originally found in the ventral premotor cortex (area F5) of monkey. These neurons respond both when the monkey performs particular goal-directed action and when it observes another individual performing similar action (Pellegrino *et al.* 1992). The monkey mirror neurons activate only when actions are goal-directed and made with hand (or mouth). If the actions are just mimiced or made with tool, the monkey mirror neurons are not activated at all or only very weakly (Gallese *et al.* 1996). Recently, monkey mirror neurons have been shown to react to actions were the critical part (when the hand is touching the object) is hidden (Umilta *et al.* 2001) and also to sounds associated with hand actions (Kohler *et al.* 2002) These results suggest that the activity of the mirror neurons is correlated with action understanding. The sensory features of the actions (partially seen or heard) are pivotal to the activation of the mirror neurons only inasmuch as they activate the motor representation of the same actions within the observers' brain (Gallese *et al.* 2004).

The human mirror neuron system is activated in response to a wider range of actions than the monkey system. First, whereas the presence of an object (the target of the action) appears (Gallese *et al.* 1996) to be necessary to activate the mirror neuron system in the monkey, the observation of intransitive and mimed actions is able to activate the human system (Decety *et al.* 1997). Second, TMS experiments have shown that, in humans, motor evoked potentials (MEPs) recorded from the muscles of an observer, are facilitated when an individual observes intransitive, meaningless hand/arm gestures, as well as when an individual observes a transitive action (Fadiga *et al.* 1995a). In short, these data show that the human motor system codes both the goal of an observed action and the way in which the observed action is performed.

In contrast to monkey data, we found in Study III that (the motor-cortex part) of the human MNS is activated also during observation of tool use, and this activation is stronger when the tool use is goal-directed. Also we found correlation with tool use-experience and the activation of MI. The observed stronger activation of the motor cortex part of the human MNS during viewing of goal-directed than non-goal-directed movements could be related to experience-related understanding of actions, because the two sets of movements only differed in their purpose, not in their visual properties. The human MNS is likely much more evolved than the monkeys; humans

observe and use tools from early childhood, and probably such experiences expand the motor repertoire of the MNS. Also the areas where human MNS is located are greatly expanded compared with monkeys. Although some higher apes can use simple tools, only humans have the brain capacity and the hand functionality for efficient precision grasp and the use of complex tools (Marzke 1997; Susman 1998; Ambrose 2001). The activation of MI during observation videotaped motor acts (which is not seen in monkey F5 mirror neurons, Rizzolatti *et al.*, 1996), although weaker than during observation of live acts, probably reflects the sophistication of human MNS compared to monkeys.

If the executed and observed actions have shared neural representations, how can we distinguish between actions of self and others? This "problem of agency" might underlie some symptoms of schizophrenia, where patients often have dysfunction in distinguishing of actions of self and others, leading to delusions of control, thought insertion, and hallucinations (Frith 1987; Gray 1991; Frith 1992). We found in Study V systematically weaker reactivity of the ~20-Hz motor-cortex rhythm, both during action observation and execution, in schizophrenic subjects than in their healthy co-twins. This disease-specific weakened reactivity of the MI could be related to a general deficit in motor cognition, which may include mirror neurons but may not be specific to this cell group. In autistic subjects, the primary motor cortex reacts rather normally to action viewing (Avikainen *et al*., 1999) although activation of area BA 44 is significantly delayed and weakened (Nishitani *et al*., 2004). Further experiments should thus test more extensively the functionality of the motor and sensory "mirroring systems" in subjects with schizophrenia.

Somatosensory cortices might be involved in preserving the sense of self during action observation (Avikainen *et al.* 2002). It also has been suggested that somatosensory cortices participate in embodied simulation of somatosensory states of others (Adolphs *et al.* 2000).

In Study IV, viewing other person's articulatory mouth movements enhanced activity in the left SI mouth area. This effect was not seen in the corresponding region in the right hemisphere, nor in the SI hand area of either hemisphere. Thus, action viewing activated the left SI cortex in a somatotopic manner. These data suggest that embodied simulation other persons' motor acts involves a cortical circuitry that includes somatosensory areas.

Modulation of SI during speech viewing could be caused by feedforward modelling of sensory consequences ('efference copies') of an other person's simulated motor acts or it could reflect simulation of the feedback signals provided by somatosensory afferents from the articulatory organs. According to the first explanation, the SI activity modulation could be a consequence of action simulation in the MNS, whereas according to the latter one the SI cortex could simulate sensory signals independently of the MNS. These data suggest that the SI cortex is also involved in

sensory signals independently of the MNS. These data suggest that the SI cortex is also involved in this socially important circuitry. SI might be part in network which enables the observer to experience motor related sensations and to experience what the observed person is feeling.

Several interesting questions about MNS still remain unanswered. What is the role of MNS in evolution of language? Are motor areas essential for language perception as suggested by motor theory of speech (Liberman *et al.* 1967)? Interesting question is also how much transfer of cultural knowledge, such as tool use, depends upon MNS. Recent study indicates differences in learning strategies in human children and chimpanzees, so that children utilize imitation whereas chimpanzees reproduce the environmental results actions (emulation) (Call *et al.* 2004). Could humans use here MNS to imitate here and chimpanzees some other brain mechanism?

One could envision that dysfunction of MNS could lead to disorders in social communication. Antisocial personality disorder, autism spectrum disorders, Williams syndrome and schizophrenia are disorders which include substantial difficulties in social interaction. What is the role of MNS in these disorders? Study V and paper by Nishitani *et al*. (2004) suggest that in Asperger syndrome and schizophrenia there might a dysfunction of MNS, which may contribute some of the characteristic symptoms of these syndromes.

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# 8. References

Abbruzzese G, Marchese R, Buccolieri A, Gasparetto B and Trompetto C. Abnormalities of sensorimotor integration in focal dystonia: a transcranial magnetic stimulation study. *Brain* 2001, 124: 537–545.

Adolphs R, Damasio H, Tranel D, Cooper G and Damasio AR. A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *J Neurosci* 2000, 20: 2683–2690.

Ambrose SH. Paleolithic technology and human evolution. *Science* 2001, 291: 1748–1753.

Avikainen S, Forss N and Hari R. Modulated activation of the human SI and SII cortices during observation of hand actions. *Neuroimage* 2002, 15: 640–646.

Blume WT, Jones DC, Young GB, Girvin JP and McLachlan RS. Seizures involving secondary sensory and related areas. *Brain* 1992, 115 ( Pt 5): 1509–1520.

Burton H and Carlson M. Second somatic sensory cortical area (SII) in a prosimian primate, Galago crassicaudatus. *J Comp Neurol* 1986, 247: 200–220.

Call J, Carpenter M and Tomasello M. Copying results and copying actions in the process of social learning: chimpanzees ( Pan troglodytes) and human children ( Homo sapiens). *Anim Cogn* 2004.

Carr L, Iacoboni M, Dubeau MC, Mazziotta JC and Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A* 2003, 100: 5497–5502.

Chen R, Corwell B and Hallett M. Modulation of motor cortex excitability by median nerve and digit stimulation. *Exp Brain Res* 1999, 129: 77–86.

Decety J, Grezes J, Costes N, Perani D, Jeannerod M, Procyk E, Grassi F and Fazio F. Brain activity during observation of actions. Influence of action content and subject's strategy. *Brain* 1997, 120: 1763–1777.

Fadiga L, Fogassi L, Pavesi G and Rizzolatti G. Motor facilitation during action observation: a magnetic stimulation study. *J Neurophysiol* 1995a, 73: 2608–2611.

Fadiga L, Fogassi L, Pavesi G and Rizzolatti G. Motor facilitation during action observation: a magnetic stimulation study. *J Neurophysiol* 1995b, 73: 2608–2611.

Forss N, Hari R, Salmelin R, Ahonen A, Hamalainen M, Kajola M, Knuutila J and Simola J. Activation of the human posterior parietal cortex by median nerve stimulation. *Exp Brain Res* 1994, 99: 309–315.

Frith CD. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. *Psychol Med* 1987, 17: 631–648.

Frith CD. *The Cognitive Neuropsychology of Schizophrenia.*1992. Hove, UK: Lawrence Erlbaum Associates.

Gallese V, Fadiga L, Fogassi L and Rizzolatti G. Action recognition in the premotor cortex. *Brain* 1996, 119: 593–609.

Gallese V. The 'shared manifold' hypothesis – From mirror neurons to empathy. *J Cons Stud* 2001, 5–7: 33–50.

Gallese V, Keysers C and Rizzolatti G. A unifying view of the basis of social cognition. *Trends Cogn Sci* 2004, 8: 396–403.

Grafton ST, Arbib MA, Fadiga L and Rizzolatti G. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. *Exp Brain Res* 1996, 112: 103–111.

Gray JA, Feldon J. M., Rawlins, J. N. P., Hemsley D. R., Smith A. D. The neuropsychology of schizophrenia. *Behav Brain Sci*1991, 14: 1–84.

Guyton A and Hall J. *Textbook of Medical Physiology.*1996. WB Saunders Company.

Hari R, Karhu J, Hamalainen M, Knuutila J, Salonen O, Sams M and Vilkman V. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. *Eur J Neurosci* 1993, 5: 724–734.

Hari R, Salmelin R, Makela JP, Salenius S and Helle M. Magnetoencephalographic cortical rhythms. *Int J Psychophysiol* 1997, 26: 51–62.

Hari R, Forss N, Avikainen S, Kirveskari E, Salenius S and Rizzolatti G. Activation of human primary motor cortex during action observation: A neuromagnetic study. *Proc Nat acad SciU S A* 1998, 95: 15061–15065.

Hashimoto I, Mashiko T and Imada T. Somatic evoked high-frequency magnetic oscillations reflect activity of inhibitory interneurons in the human somatosensory cortex. *Electroencephalogr Clin Neurophysiol* 1996, 100: 189–203.

Hämäläinen M, Hari R, Ilmoniemi R, Knuutila J and Lounasmaa OV. Magnetoencephalography - Theory, Instrumentation, and Applications to Noninvasive Studies of the Working Human Brain. *RevModern Phys* 1993, 65: 413–497.

Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC and Rizzolatti G. Cortical mechanisms of human imitation. *Science* 1999, 286: 2526–2528.

Jasper H W. *Arch Psych ZeitschrNeurol* 1949, 183: 163–174.

Jeannerod M. The representing brain: neural correlates of motor intention and imagery. *Behav Brain Sci* 1994, 17: 187–245.

Jones EG and Powell TP. Connexions of the somatic sensory cortex of the rhesus monkey. I. Ipsilateral cortical connexions. *Brain* 1969, 92: 477–502.

Kandel E and Jessel TM. *Principles of Neural Science.*1991. Prentice-Hall International Inc.

Kohler E, Keysers C, Umilta MA, Fogassi L, Gallese V and Rizzolatti G. Hearing sounds, understanding actions: action representation in mirror neurons. *Science* 2002, 297: 846-848.

Liberman AM, Cooper FS, Shankweiler DP and Studdert-Kennedy M. Perception of the speech code. *Psychol Rev* 1967, 74: 431–461.

Llinas RR. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science* 1988, 242: 1654–1664.

Lopes da Silva F. Neural mechanisms underlying brain waves: from neural membranes to networks. *Electroencephalogr Clin Neurophysiol* 1991, 79: 81–93.

Marzke MW. Precision grips, hand morphology, and tools. *Am J Phys Anthropol* 1997, 102: 91–110.

Nishitani N and Hari R. Temporal dynamics of cortical representation for action. *Proc Natl Acad Sci U S A* 2000, 97: 913–918.

Nishitani N and Hari R. Viewing lip forms: Cortical dynamics. *Neuron* 2002, 36: 1211–1220.

Nishitani N, Avikainen S and Hari R. Abnormal imitation-related cortical activation sequences in Asperger's syndrome. *Ann Neurol* 2004, 55: 558–562.

Pellegrino Gd, Fadiga L, Fogassi L, Gallese V and Rizzolatti G. Understanding motor events: a neurophysiological study. *Exp Brain Res* 1992, 91: 176–180.

Penfield W and Jasper H. *Epilepsy and the Functional Anatomy of the Human Brain.*1954. Boston: Brown and Company.

Perani D, Fazio F, Borghese NA, Tettamanti M, Ferrari S, Decety J and Gilardi MC. Different brain correlates for watching real and virtual hand actions. *Neuroimage* 2001, 14: 749–758.

Perrett DI, Harries MH, Bevan R, Thomas S, Benson PJ, Mistlin AJ, Chitty AJ, Hietanen JK and Ortega JE. Frameworks of analysis for the neural representation of animate objects and actions. *J Exp Biol* 1989, 146: 87–113.

Rizzolatti G, Fadiga L, Gallese V and Fogassi L. Premotor cortex and the recognition of motor actions. *Cogn Brain Res* 1996a, 1996: 131–141.

Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D and Fazio F. Localization of grasp representation in humans by PET: Observation versus execution. *Brain Res* 1996b, 111: 246–252.

Rizzolatti G, Fogassi L and Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2001, 2: 661–670.

Rizzolatti G and Luppino G. The cortical motor system. *Neuron* 2001, 31: 889–901.

Rizzolatti G and Craighero L. The mirror-neuron system. *Annu Rev Neurosci* 2004, 27: 169–192.

Salenius S, Portin K, Kajola M, Salmelin R and Hari R. Cortical control of human motoneuron firing during isometric contraction. *J Neurophysiol* 1997a, 77: 3401–3405.

Salenius S, Schnitzler A, Salmelin R, Jousmaki V and Hari R. Modulation of human cortical rolandic rhythms during natural sensorimotor tasks. *Neuroimage* 1997b, 5: 221–228.

Salenius S, Schnitzler A, Salmelin R, Jousmäki V and Hari R. Modulation of Human Cortical Rolandic Rhythms during Natural Sensorimotor Tasks. *Neuroimage* 1997c, 5: 221–228.

Salmelin R and Hari R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. *Neuroscience* 1994, 60: 537–550.

Schnitzler A, Salenius S, Salmelin R, Jousmaki V and Hari R. Involvement of primary motor cortex in motor imagery: a neuromagnetic study. *Neuroimage* 1997, 6: 201–208.

Silen T, Forss N, Jensen O and Hari R. Abnormal reactivity of the approximately 20–Hz motor cortex rhythm in Unverricht Lundborg type progressive myoclonus epilepsy. *Neuroimage* 2000, 12: 707–712.

Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ and Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science* 2004, 303: 1157–1162.

Susman RL. Hand function and tool behavior in early hominids. *J Hum Evol* 1998, 35: 23–46.

Talairach J and Tournoux P. *Co-planar stereotaxic atlas of the human brain.*1998. New York: Thieme Medical Publishers, Inc.

Tiihonen J, Kajola M and Hari R. Magnetic mu rhythm in man. *Neuroscience* 1989, 32: 793–800.

Umilta MA, Kohler E, Gallese V, Fogassi L, Fadiga L, Keysers C and Rizzolatti G. I know what you are doing. a neurophysiological study. *Neuron* 2001, 31: 155–165.

Wicker B, Keysers C, Plailly J, Royet JP, Gallese V and Rizzolatti G. Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. *Neuron* 2003, 40: 655–664.