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CORTICAL MECHANISMS OF ACTION OBSERVATION, IMITATION AND SOCIAL PERCEPTION IN HEALTHY AND AUTISTIC SUBJECTS

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ACADEMIC DISSERTATION

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ABBREVIATIONS

ANOVA	analysis of variance
AS	Asperger's syndrome
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
HFA	high-functioning autism
IF	inferior frontal area
IPL	inferior parietal lobule
ISI	interstimulus interval
M1	primary motor cortex
MCE	minimum current estimate
MEG	magnetoencephalography
MEP	motor evoked potential
MN	median nerve
MNS	mirror-neuron system
MRI	magnetic resonance imaging
PET	positron emission tomography
PPC	posterior parietal cortex
PSP	postsynaptic potential
ROI	region of interest
SEF	somatosensory evoked field
SEM	standard error of mean
SEP	somatosensory evoked potential
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
TOM	theory of mind
TSE	temporal spectral evolution

LIST OF PUBLICATIONS

This thesis is based on the following six original publications, which will be referred to in the text by their Roman numerals (I–VI).

I Hari R, Forss N, **Avikainen S**, Kirveskari E, Salenius S, and Rizzolatti G: Activation of the human primary motor cortex during action observation: A neuromagnetic study. *Proc Natl Acad Sci USA* 1998, 95: 15061-15065.

II Avikainen S, Kulomäki T, and Hari R: Normal movement reading in Asperger subjects. *Neuroreport* 1999, 10: 3467-3470.

III 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.

IV Avikainen S, Liuhanen S, Schürmann M, and Hari R: Enhanced exstrastriate activation during observation of distorted finger postures. *J Cogn Neurosci* 2003, 15: 658-663.

V Avikainen S, Wohlschläager A, Liuhanen S, Hänninen R, and Hari R: Impaired mirror-image imitation in high-functioning autistic subjects. *Curr Biol* 2003, 13: 339-341.

VI Nishitani N**, Avikainen S** and Hari R: Abnormal imitation-related cortical activation sequences in Asperger's syndrome. *Ann Neurol* (under revision).

1. INTRODUCTION

Social interaction is an important part of human behaviour. Communication, both in terms of language and non-verbal interaction, forms the basis of our social behaviour. In non-verbal communication, information from gestures, gaze, facial expressions and movements is used to interpret other persons' intentions, goals, thoughts and feelings. For a long time, the knowledge about brain mechanisms underlying social cognition has merely been based on animal studies. The development of brain imaging techniques that allow studies of brain function in awake and acting individuals has opened new possibilities to explore the neural basis of human social cognition. In this study I have used magnetoencephalography (MEG) to explore human brain functions underlying action observation and imitation. MEG is a totally noninvasive functional brain imaging method, in which an excellent time resolution is combined with a good spatial resolution. The first whole-scalp MEG device, housing 122 sensors in a helmet-shaped array, was developed in Finland in the Low Temperature Laboratory of Helsinki University of Technology in 1992. The development of whole-scalp MEG systems has made it possible to study cortical activations simultaneously in different parts of the brain.

In the present work, brain functions of both healthy subjects and autistics individuals were investigated. Autism is a biological disorder, which severely affects social cognition. According to the diagnostic criteria, the symptoms include impairments in social interaction and communication as well as restricted, repetitive patterns of behavior. Although the more able autistic individuals, such as subjects with Asperger's syndrome, are of normal intelligence, they suffer from life-long abnormalities in social interaction. Many theories have been proposed to account for those deficits, but the biological basis of the social difficulties in autism is still poorly understood. The discovery of "mirror neurons" in the monkey frontal cortex has offered an important new tool to investigate the neural basis of social cognition. These neurons discharge both when the monkey performs hand actions and when he observes another individual to make similar actions. Mirror neurons form the basis of an action observation/execution matching system that has been suggested to play an important role in action understanding, imitation, and in the ability to detect and recognize mental states of others.

The present work aims to demonstrate the existence of the human action observation/execution matching system, to study its function both in normal and autistic subjects, and to examine mechanisms of social perception and imitation. The MEG studies focus on modulation of activation of the sensorimotor cortices during action observation and imitation. In addition, activation of the exstrastriate cortices to socially relevant hand stimuli is explored. Furthermore, behavioural mechanisms of imitation are examined in autistic subjects. 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 Anatomy and physiology of the cortical motor system

Body movements are controlled by a distributed motor system that involves the cerebral cortex, the brain stem, the basal ganglia, and the cerebellum. The primary motor and premotor cortices are located in the frontal lobes, anterior to the central sulcus. The main areas of the cortical motor system are the primary motor cortex, the premotor area, and the supplementary motor cortex (Figure 1). All these areas have their own topographical representations of different muscle groups and movements. The following introduction to the anatomy and physiology of the motor and somatosensory systems is mainly based on reviews by Ghez (1991), Kandel and Jessell (1991), Martin and Jessell (1991a), Martin and Jessell (1991b), Guyton and Hall (1996) and Rizzolatti and Luppino (2001).

2.1.1 The motor cortices

The primary motor cortex (M1) is located in the precentral gyrus and in the precentral wall of the central sulcus, forming the Brodmann's area (BA) 4. Similarly as the primary somatosensory cortex (SI), M1 is somatotopically arranged, with the face and mouth regions most laterally near the Sylvian fissure, the hand area in the middle, and the foot area most medially, mainly burried in the longitudinal fissure. Areas controlling hand movements and articulation have the largest representations. Ablation of a portion of M1 in monkeys causes weakness of the represented muscles. If the lesion is restricted to M1 and the caudate nucleus so that the premotor and supplementary motor areas are spared, postural and limb fixation movements can still be performed, but the ability to control fine movements is lost. The paralysis caused by a pure M1 ablation is hypotonic, since the primary motor cortex normally exerts a continuous tonic stimulation on the motor neurons of the spinal cord. In humans, the most common cause for M1 lesions is a stroke, which usually also damages other adjacent cortical and deeper motor structures, thereby resulting in spastic paralysis of the affected muscles due to disinhibition of the vestibular and reticular brain stem nuclei.

The premotor cortex is located anterior to M1, forming the ventrolateral part of Brodmann's area (BA) 6. It is also roughly somatotopically organized, and it is involved in controlling movements of different muscle groups during specific motor tasks. The supplementary motor area (SMA) forms the dorsomedial part of the BA 6 lying mainly in the longitudinal fissure. Electrical stimulation of SMA often causes bilateral muscle contractions, and SMA participates in organizing and planning of complex movements.

M1 receives somatotopically organized input from SI, as well as from the secondary somatosensory cortex (SII) and the posterior parietal cortex (PPC) (BA 5). Somatosensory information is conveyed to M1 also via the ventrobasal complex of thalamus. M1 has tight connections with the premotor and SMA areas, and via corpus callosum with the corresponding areas in the other hemisphere. The motor cortices receive afferent input from cerebellum and basal ganglia through thalamus (the ventrolateral and the ventroanterior nuclei).

2.1.2 The corticospinal tract

Signals from the motor cortex to the spinal cord, and further to the muscles, are transmitted mainly via the corticospinal tract. Most fibers of the corticospinal tract arise in the motor cortices, but the somatosensory regions and cingulate cortices are also represented (Galea and Darian-Smith 1994).

From the cortex, the corticospinal tract descends through the posterior limb of the internal capsule down to the brain stem and the medulla, where most of the fibers cross to the opposite side. The tract then continues downward in the cord as the lateral corticospinal tract, and it terminates mainly on the interneurons in the intermediate regions of the cord gray matter. Some of the fibers also synapse directly with the anterior motor neurons and some of them with the sensory relay neurons in the dorsal horn. The neurons synapsing with the spinal motoneurons participate mainly in the control of the distal limb muscles, especially in the hands, whereas the interneurons are parts of reflex arcs. Those corticospinal fibers that descend uncrossed on the ipsilateral side form the ventral corticospinal tracts and have a role in controlling bilateral postural movements.

Other pathways that contribute to the cortical movement control involve the basal ganglia, the cerebellum and various brain stem nuclei. For example, the

corticorubrospinal pathway serves as an accessory route for controlling of discrete movements in close association with the corticospinal tract.

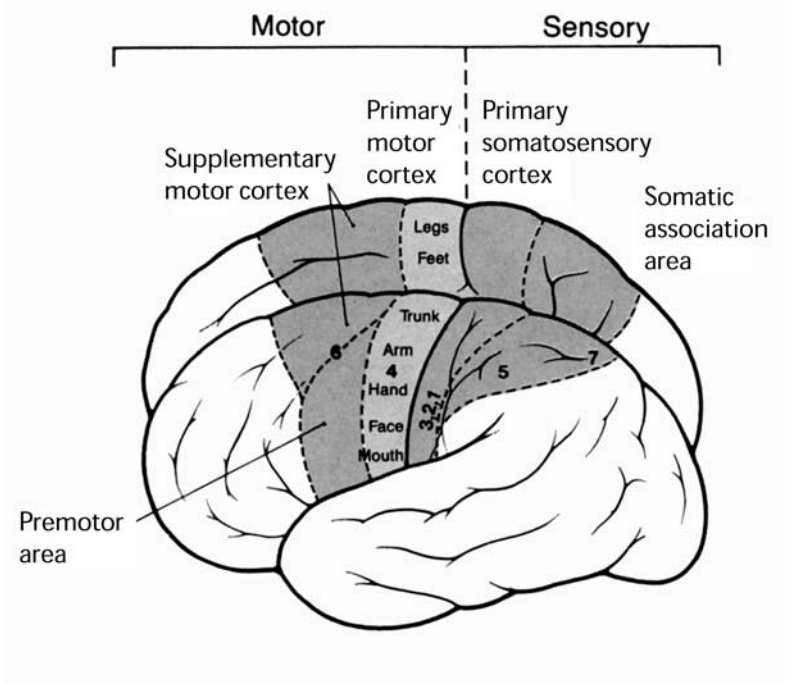

FIGURE 1 Organization of the motor and somatic sensory areas of the cerebral cortex. Modified from Guyton (1996).

2.2 Anatomy and physiology of the somatosensory system

2.2.1 Afferent somatosensory pathways

Somatosensation has four main submodalities: touch, proprioception, pain, and thermal sensation, and distinct receptor neurons transmit information further to the central nervous system (CNS). Usually a percept, such as recognizing an object in the hand, is based on integration of information from many somatosensory submodalities.

The sensory information from the peripheral receptors in skin, joints, muscles and subcutaneous tissue is transferred via afferent fibers to the spinal cord. The afferent and efferent fibers from the same body part travel together in the spinal nerves. Tactile and proprioceptive information is mediated via the dorsal column–medial lemniscal system, whereas other sensory modalities, such as pain, thermal, tickle and pressure sensations, are mediated via the anterolateral system.

The dorsal column–medial lemniscal system mediates mechanoreceptive sensation. The large myelinated fibers, having velocities around 30–110 m/s (Guyton and Hall 1996), enter the spinal cord from the dorsal roots of the spinal nerves and

ascend in the dorsal columns uninterruptedly until they synapse in the dorsal column nuclei (the cuneate and the gracile nuclei). Then the second-order neurons decussate to the opposite side and ascend to the contralateral thalamus through bilateral brain stem pathways called medial lemnisci. Additional fibers that carry sensory information from the head region, join these pathways in the brain stem. The fibers from the dorsal columns synapse on neurons in the ventral posterolateral nucleus of the thalamus, and the fibers from the trigeminal nuclei on neurons in ventral posteromedial nucleus. Together with the posterior thalamic nuclei, these nuclei are called as the ventrobasal complex from which the third-order neurons project further to SI and, to a lesser extent, to SII and PPC. One of the special features of the dorsal column–medial lemniscal system is its somatotopic organization that is maintained throughout the pathways from the dorsal columns to the somatosensory cortices.

After entering the dorsal horns, the small myelinated fibers (velocities up to 40 m/s) of the anterolateral pathway cross in the anterior commisure of the cord to the opposite side, ascending quite diffusely in the anterolateral portion of the lateral column. Then these fibers synapse on neurons in the reticular nuclei of the brain stem or in neurons in thalamic nuclei (ventrobasal complex and intralaminar nuclei).

2.2.2 Primary somatosensory cortex SI

The primary projection area for the somatosensory system is the SI cortex that is located in the anterior parietal cortex, in the posterior bank of the central sulcus and in the postcentral gyrus. SI comprises four cytoarcitectonic areas: 3a, 3b, 1, and 2. The thalamic neurons project mainly to areas 3a and 3b from which the neurons send fibers further backwards to areas 1 and 2. The four regions differ functionally: tactile information from skin is mainly processed in areas 3b and 1, whereas proprioceptive information from muscles and joints is tranferred to areas 3a and 2. Due to the dense connections between the different subareas, the sensory information can be effectively processed both in serial and parallel ways. All four areas are somatopically organized, with the face area lying most laterally and the foot area most medially. The sizes of the representation areas correlate with the density of peripheral innervation in different body parts (Penfield and Jasper 1954). SI is reciprocally connected to the ipsilateral motor cortex and to both ipsi- and contralateral SII and PPC cortices, as well as to the corresponding areas in the contralateral SI. Connections to the other hemisphere pass through corpus callosum.

Total removal of SI has been shown to produce severe deficits in position sense and in the discrimination of size, texture and shape, whereas the pain and thermal sensations are only altered but not abolished. Smaller lesions, located in the 3b hand area, produce deficits in texture, shape and size discrimination. Lesions in area 1 impair mainly texture discrimination, and lesions of area 2 alter size and shape discrimination (Randolph and Semmes 1974).

2.2.3 Secondary somatosensory cortex SII

The human SII cortex is situated in the parietal operculum, in the upper bank of the Sylvian fissure. Due to bilateral receptive fields, unilateral stimulation elicits activation in both hemispheres. SII shows a rough somatotopic arrangement: the face area lies anterior and the hand and foot areas in more posterior and deeper locations (Penfield and Jasper 1954; Haight 1972). Direct stimulation of the SII cortex in humans causes sensations of numbness and tingling in contra-, ipsi-, or bilateral body parts, and occasionally also feelings of 'desire to move', or even overt limb movements (Penfield and Jasper 1954; Richer *et al.* 1993). In monkeys, complete lesions of SII severely impaired learning of texture and shape discrimination and affected also the ability to detect size and roughness (Murray and Mishkin 1984). Neurons in SII project to ipsilateral M1, SMA (Jones and Powell 1969), and PPC (Burton 1986) and to contralateral SII. The importance of direct thalamic input to the SII activation is unclear and a debate of the order of information processing in the somatosensory network still continues. In macaque and marmoset monkeys, SII responses are abolished after SI ablation (Pons *et al.* 1987; Burton *et al.* 1990) and in patients with callosal transsection unilateral stimulation has been shown to activate only contralateral SI and SII cortices (Fabri *et al.* 1999). However, other animal studies (Burton and Robinson 1987; Murray *et al.* 1992; Turman *et al.* 1992) and studies with humans patients having lesions in the somatosensory areas (Caselli 1993; Forss *et al.* 1999) have supported parallel rather than serial activation pattern in the somatosensory cortices. Most probably, both types of activation occur in the human somatosensory cortical network.

2.2.4 Other somatosensory areas

Posterior parietal cortex is located in the parietal lobe, caudal to area 2, comprising areas BA 5 and 7. It receives input from SI and from pulvinar, and it

projects to SMA and to contralateral SI and SII. PPC is involved in higher-order somatosensory processing. Area 5 integrates tactile and proprioceptive information and input from the two hands, whereas area 7 receives both tactile and visual input, thereby allowing integration of somatosensory and visual information. PPC also has an important role in coding of visual and body-centered space: patients with lesions around PPC, especially in the right hemisphere, typically suffer from a neglect syndrome, an inability to attend to left-sided visual, tactile and auditory stimuli. In addition, areas on the mesial side of the frontal and parietal cortices participate in processing of tactile information (Penfield and Jasper 1954).

2.3 The mirror-neuron system

Mirror neurons were first identified and characterized in the monkey brain by Rizzolatti and his co-workers (di Pellegrino *et al.* 1992; Gallese *et al.* 1996; Rizzolatti *et al.* 1996a): a class of visuomotor neurons in the area F5 of the monkey ventral premotor cortex was shown to be activated both during execution and observation of hand actions. Later similar type of behaviour has also been found in other brain regions in monkeys and in the human brain, and the whole neuronal network involved in both execution and observation of actions has been called as a mirror-neuron (MNS) or action execution/observation matching system.

2.3.1 Area F5 of the monkey brain

The ventral premotor cortex of the monkey brain consists of two distinct areas, F4 and F5 (Matelli *et al.* 1985). Area F5 is situated in the rostral part of the inferior area 6, caudal to the inferior arm of the arcuate sulcus (Matelli *et al.* 1985). Microstimulation and single neuron studies have shown that F5 contains hand and mouth movement representations that are somatotopically organized: hand movements are represented dorsally and mouth movements ventrally (Rizzolatti *et al.* 1981; Kurata and Tanji 1986; Rizzolatti *et al.* 1988). F5 receives afferent input from the inferior parietal lobule (Petrides and Pandya 1984; Cavada and Goldman-Rakic 1989) and from the anterior intraparietal area (AIP) in the intraparietal sulcus (Matelli *et al.* 1986). F5 is reciprocally connected with the hand field of F1 and it sends efferent fibers to many subcortical motor areas (Matelli *et al.* 1986; Jeannerod *et al.* 1995). The monkey F5 has been suggested to be homologic with the human Broca's area (BA 44 and 45) (Mesulam 1990; Petrides and Pandya 1999; Rizzolatti and Luppino 2001).

The hand neurons in F5 have both motor and sensory properties. The motor properties include activation during certain type of object-related goal-directed hand movements, such as grasping, manipulating, tearing, and holding (Rizzolatti *et al.* 1988; Gallese *et al.* 1996; Rizzolatti *et al.* 1996a). The hand neurons are activated during both left and right hand movements and some of them discharge only in association with a certain type of movement like grasping, whereas some disharge during different types of movements. However, if a similar movement is made for other purposes, like pushing away, there is no discharge. Many of the neurons are selective even for certain type of hand grip, like precision grip, finger prehension, *e.t.c.* (Rizzolatti *et al.* 1988).

Some of the hand neurons in F5 have sensory properties that include activation when the monkey sees graspable objects ("canonical neurons") and when the monkey observes another monkey or human to perform hand actions ("mirror-neurons") (Rizzolatti *et al.* 1988; Gallese *et al.* 1996; Rizzolatti *et al.* 1996a; Murata *et al.* 1997). The canonial neurons are important for object-to-hand movement transformation (Jeannerod 1994; Rizzolatti *et al.* 1999).

2.3.2 Mirror neurons in monkeys

Some of the F5 hand neurons are activated both when the monkey performs hand actions and when he observes another monkey or human to perform similar actions (Gallese *et al.* 1996; Rizzolatti *et al.* 1996a) (Figure 2). These neurons are called mirror neurons. The observed actions that are capable of inducing a disharge of the mirror neurons include placing or taking objects from a table, grasping food and manipulating objects (Gallese *et al.* 1996; Rizzolatti *et al.* 1996a). There is a clear congruence between the effective observed and executed action (di Pellegrino *et al.* 1992). 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 merely defined by the goal of the action. The monkey mirror neurons do not discharge when the same action is made with a tool or when only an object or an agent is presented. The mirror neuron activation is not limited to hand actions. In a recent study by Ferrari *et al*. (2003), the F5 mirror neurons discharged also when the monkey observed mouth actions. Majority of these 'mouth mirror neurons' become active during observation and execution of ingestive actions, such as sucking and breaking food. Evidence for a more abstract representation of actions in the monkey brain has recently been obtained in two

studies. Mirror neurons where activated when the final part of the grasping hand action, the actual hand-object interaction, was hidden behind a screen (Umilta *et al.* 2001). Interestingly, no activation occurred if the monkey was aware that the object behind the screen had been removed. Furthermore, Kohler *et al.* (2002) recently demonstrated that, in addition to observation and execution of actions, some mirror neurons respond to sounds of actions. A part of these neurons responded to sounds with similar intensity as for observation of the same action.

Mirror-neuron-type behavior has also been found in other parts of the monkey brain. A set of neurons in the inferior parietal lobule, area PF, discharged during both execution and observation of goal-directed hand actions (Fogassi *et al.* 1998; Gallese *et al.* 2002). Furthermore, Perrett and his co-workers (Perrett *et al.* 1989; Perrett *et al.* 1990) have described neurons in the anterior part of the monkey superior temporal sulcus (STS), in area STSa, that discharge during observation of biological motion and some of them specifically during observation of goal-directed hand actions. However, these neurons do not seem to exhibit clear motor properties.

The discovery of mirror neurons has lead to many different speculations about their functional role. It has been suggested that the mirror neurons generate an internal representation of the action that can be used for different functions, including recognition and understanding motor events, motor learning, and imitation (Jeannerod 1994; Gallese *et al.* 1996; Rizzolatti *et al.* 1996a).

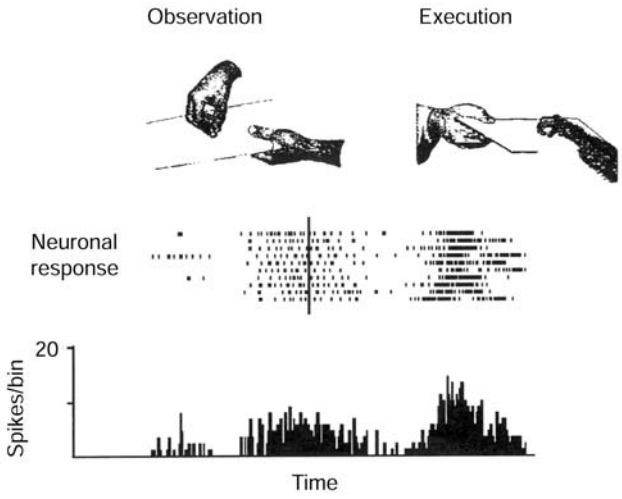

FIGURE 2 Visual and motor responses of a mirror neuron of area F5. Behavioural conditions are schematically represented in the upper row. In the lower part are series of consecutive rasters and the relative stimulus response histograms. Modified from Rizzolatti *et al.* (1996).

2.3.3 The mirror-neuron system in humans

After the discovery of the mirror neurons in monkeys, the next natural question was whether a similar action observation/execution matching system would exist in the human brain? During recent years several functional brain imaging studies with different techniques have provided evidence about existence, circuitry and function of the human mirror-neuron system. Before the studies of this thesis were started, it was known that motor evoked potentials (MEPs) elicited by a transcranial magnetic stimulation (TMS) and recorded from hand muscles, were significantly increased during observation of movements involving the same muscles (Fadiga *et al.* 1995). However, these data did not specify the anatomical level of the effect. Moreover, positron emission tomography (PET) activations were found in the inferior frontal gyrus (mainly in area 45), in the inferior parietal lobule, and in the STS region during observation of grasping hand movements (Grafton *et al.* 1996; Rizzolatti *et al.* 1996b). Thus, the activation detected during action observation did not totally overlap with that detected during action execution, meaning that no direct evidence was obtained of the existence of a human mirror-neuron system.

Taken together, in monkeys, neurons that show strict mirror-type behavior (activation during both execution and observation of an action) have so far been found from areas F5 and PF. The action representation system has been proposed to support many important functions such as action recognition and understanding, motor learning and imitation. Before the studies of this thesis, no direct evidence was available about the brain regions involved in the human counterpart of the monkey mirror neurons.

2.4 Social brain

In social communication, information from face expressions, eye gaze, and mouth, hand and body gestures is automatically used to interpret intentions, direction of attention and emotions of the other individuals. The perception and judgement of socially relevant stimuli involves several brain regions, including higher-order sensory cortices and the STS region, the amygdala, the ventral striatum and the orbitofrontal cortex (for a review, see Allison *et al.* 2000; Adolphs 2003). Additionally, regions in parietal, prefrontal and cingulate cortices have close relations to this system.

Most studies of social perception have focused on eye and face stimuli. In addition to gaze direction, orientation of the head, body posture and hand gestures (Langton and Bruce 2000) strongly influence social perception. People tend to look to

the same directions as others are looking or pointing. The direction of another person's gaze and pointing gestures trigger an automatic and obligatory shift of the observer's visual attention (Posner 1980; Friesen and Kingstone 1998; Langton and Bruce 2000). In monkeys, certain cells in the STS region discharge according to another monkey's direction of gaze (Perrett *et al.* 1985; 1992). Interestingly, the same cells also respond to head and body postures. Perret *et al.* (1992) suggested that the detection of direction of social attention is based on a hierarchical system that combines information from different body-language cues. They proposed that information from the eyes is at the highest level of hierarchy, overriding the information from the head and body, and that information from the head in turn overrides information from the body. However, behavioural experiments have shown that head orientation and hand gestures can influence the detection of attention direction even when they conflict with the eye information (Langton and Bruce 2000; Langton *et al.* 2000). Morover, in human infants and in non-human primates, head orientation appears to contribute more to the detection of attention direction than does eye gaze alone (Scaife and Bruner 1975; Itakura 1996; Corkum and Moore 1998).

Brain mechanisms of social cognition

Several studies of the visual system underline the role of the fusiform gyrus in processing structural and static properties of faces (Allison *et al.* 1994; Halgren *et al.* 2000; Haxby *et al.* 2000). In addition, there is evidence of a broader engagement of the fusiform area in social cognition, even in situations that do not require face processing (Schultz *et al.* 2003). The STS region is activated to several biological socially relevant stimuli. Monkey STS cells are activated to different forms of biological motion, such as head, mouth, hand and body movements (Hasselmo *et al.* 1989; Perrett *et al.* 1989; Oram and Perrett 1996). In humans, observation of gaze shifts (Wicker *et al.* 1998; Hoffman and Haxby 2000), non-linguistic mouth (Puce *et al.* 1998; 1999; Nishitani and Hari 2002), hand (Bonda *et al.* 1996; Grafton *et al.* 1996; Rizzolatti *et al.* 1996b; Grezes *et al.* 1999) and body movements (Bonda *et al.* 1996; Grossman *et al.* 2000; Grezes *et al.* 2001) activate STS region. STS projects to other areas that are involved in social cognition, such as the amygdala (Amaral and Insausti 1992) and the orbitofrontal cortex (Barbas 1988).

Amygdala has reciprocal connections both with the STS and the orbitofrontal cortex (Amaral and Insausti 1992) and it is activated to different social stimuli, such as monitoring of gaze (Kawashima *et al.* 1999), facial expressions, and related emotions

(Brothers *et al.* 1990; Morris *et al.* 1996; Yang *et al.* 2002) as well as body movement (Adolphs 1999). Amygdala has been suggested to attach emotional salience to socially relevant stimuli (Adolphs 1999; Oram and Richmond 1999; Puce *et al.* 1999; Mehta *et al.* 2000) and to influence memory, attention and decision making in the later stages of processing (Anderson and Phelps 2001; Adolphs 2003), for example in situations where subjects are making judgements of trustworthiness of other people (Adolphs *et al.* 1995; Adolphs *et al.* 1998; Winston *et al.* 2002). Orbitofrontal cortex is also activated by face and gaze stimuli (Thorpe *et al.* 1983; Wicker *et al.* 1998; Allison *et al.* 1999) and body movements (Grezes *et al.* 1999), and it is suggested to be important for social reinforcement and reasoning (Rolls 2000; Stuss *et al.* 2001; Stone *et al.* 2002). Interestingly, abnormal activation of both amygdala and orbitofrontal cortex has been found in criminal psychopats (Kiehl *et al.* 2001).

2.5 Autism spectrum disorders

During recent decades, the diagnosing, understanding and classification of the autism spectrum disorders has undergone enormous changes. Nowadays these neurodevelopmental disorders can be devided, according to the present DSM-IV and ICD-10 diagnostic criteria, into five subgroups: the autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's syndrome (AS), and pervasive developmental disorder-not otherwise specified (PDD-NOS). These subgroups differ mainly on the basis of accompanying language deficits, general cognitive delay and the degree of social and behavioural symptoms (Table 1). The following short introduction will focus on the autistic disorder and the Asperger's syndrome.

TABLE 1. DSM-IV/ICD-10 Diagnostic criteria for autism spectrum disorders. Modified from Lord *et al.* (2000).

	Autistic Disorder	Asperger's Syndrome	Rett's Disorder	Disintegrative Disorder	PDD-NOS
Age of onset	Delays or abnormal functioning before the age of 3 years, in at least one of araes I–III	No significant delay in language and cognitive development	Normal prenatal development, normal motor development for first 5 months, deceleration of head growth between 5–48 months	Normal development for at least the first 2 years, significant loss of previously acquired skills before age 10	Pervasive impairment in areas I–III, when criteria are not met for a specific disorder

I Qualitative impairments of communication	At least one of a–d. a) delay or lack of development of spoken language b) marked impairment in the ability to initiate or sustain conversation with others c) stereotypic and repetitive use of language d) lack of varied, spontaneous make-believe or imitative play	No significant delay in language skills	Severely impaired expressive and receptive language development and severe psychomotor retardation	Same as Autistic Disorder, along with loss of previously acquired expressive or receptive language	
II Qualitative impairment in social interaction	At least 2 of a–d: a) impairment in the use of non-verbal behaviours, *i.e* eye-to-eye gaze b) failure to develop peer relationships appropriate to developmental level c) lack of spontaneous seeking to share enjoyment and interests with others d) lack of social or emotional reciprocity	Same as Autistic Disorder	Loss of social engagement early in the course	Same as Autistic Disorder along with loss of previously acquired social skills	

III Restrictive, and stereotyped pattern of behaviour	At least one of a–d: a) preoccupation with one or more stereotyped or restricted patterns of interest b) inflexible adherence to non-functional routines or rituals c) stereotyped and repetitive motor mannerisms d) persistent preoccupation with parts of objects	Same as Autistic Disorder	Loss of previously acquired purposeful hand movements: poorly coordinated gait and trunk movements	Same as Autistic Disorder, along with loss of bowel or bladder control, play, motor skills previously acquired	
Exclusions	Disturbances not better accounted for by Rett's Disorder or PDD	Disturbances not better accounted for by another PDD or schizophrenia		Disturbances not better accounted for by another PDD or schizophrenia	

2.5.1 Autistic disorder

The autistic disorder, first described by Kanner in 1943, was not recognized as an independent clinical entity until in 1978, when it was included into the DSM-III criteria. The diagnostic criteria include qualitative impairment in social interaction and communication, as well as restricted, repetitive patterns of behavior (Table 1). At least some of the symptoms must be evident by the age of three, although the diagnosis can be made later. The prevalence of autistic disorder was earlier reported as being around 0.2–0.4 in 1000 children (for a review, see Fombonne 1999). However, recent data indicate that the prevalence may be much higher, around 0.7–6 per 1000 children (Wing 1993; Gillberg 1998; Kadesjö *et al.* 1999), depending on the diagnostic criteria and the population used. The increase in the prevalence rates can reflect improved recognition due to better diagnostic methods, broader criteria or an actual increase in the frequency of cases with autism. The prevalence does not vary by race (Yeargin-Allsopp *et al.* 2003). Up to 75% of autistic subjects show some degree of mental retardation, with typical spiky performance in testing: performance IQ tends to be better than verbal IQ (for a review, see Happe 1994b). The subjects labelled as high-functioning autistics

(HFAs) constitute only a minor fraction of the subjects (11–34%) (Gillberg 1998). Males are more affected than females, but the sex ratio varies according to the severity of the retardation, with 2–3:1 in the more retarded subjects and by 5:1 in the more able part of the disorder (Wing 1981b; Wing 1993; Gillberg 1995). The outcome in adulthood seems to mainly depend on the IQ and the level of useful language by the age of 5 years (Gillberg 1991). Majority of adult autistic subjects are not able to manage independently, and psychiatric comorbidities, such as depression and intermittent explosive disorder, are common (Gillberg and Billstedt 2000).

Approximately one third of the autistic subjects have epilepsy (Olsson *et al.* 1988). A minority of the autistic individuals show an interesting feature referred as "islets of ability", meaning superior ability compared with subject's other functioning in one or a few restricted areas that usually require attention to detail, memory, or computations, such as music, mathematics, puzzles, visuo-spatial tasks, route memory *e.t.c.* Such superior abilities are not taught and may appear totally spontaneously.

Autism seems to have a strong complex genetic predisposition (for a review, see Cook 2001). The sibling recurrence risk is around 4.5%, compared with population incidence of 0.1%–0.5% (Lord *et al.* 2000). Studies with twins have shown a very high concordance rate of up to 90% for the diagnosis among monozygotic twins compared with around 0–10 % among dizygotic twins, thereby suggesting contribution from more than one gene (Steffenburg *et al.* 1989; Bailey *et al.* 1995). Several chroromosome regions have been proposed to be involved, including choromosomes 1, 2, 5, 6, 7, 8, 13, 15, 16, 18, 19 and X . Due to the complexity of the predispositive genes and the heterogenety of the behavioural phenotype, so far no genes responsible for the disorder have been identified. However, finding of the gene (MECP2) responsible for Rett's syndrome (Amir *et al.* 1999) has encouraged the research in the field. Recent results have proposed a connection between neuroligins and predisposition to autism (Jamain *et al.* 2003). Neuroligins have an important role in formation of functional synapses.

Enlarged head circumference and brain size have been shown to be associated with autism (Bailey *et al.* 1993, 1998; Piven *et al.* 1995; Davidovitch *et al.* 1996; Lainhart *et al.* 1997). Neuropathological studies have reported quite heterogenous abnormalities in brainstem, cerebellum and limbic araes, including hippocampus, amygdala and anterior cingulate cortex. Brainstem alterations have been found in facial nucleus and superior and inferior olive (Rodier *et al.* 1996; Bailey *et al.* 1998; Kemper

and Bauman 1998). In cerebellum, loss of Purkinje cells is a common finding in subjects both with or without epilepsy (Bauman and Kemper 1985; Ritvo *et al.* 1986; Bailey *et al.* 1998; Kemper and Bauman 1998). Abnormally small and densely packed neurons have been reported in the hippocampus, amygdala, medial septal nucleus, and mamillary body (Kemper and Bauman 1998). Similarly, several structural magnetic resonance imaging (MRI) studies have identified relatively heterogenous and occasional abnormalities in a small number of subjects. Hypoplasia of the cerebellar vermis (Courchesne *et al.* 1988; Hashimoto *et al.* 1995), abnormalities in the amount of gray matter in the amygdala and associated brain structures (Abell *et al.* 1999), gray and white matter hyperplasia, especially in frontal regions in 2–3 year old children (Carper *et al.* 2002). Moreover, reduced volumes have been reported for amygdala, hippocampus, anterior cingulate cortex, and posterior corpus callosum (Egaas *et al.* 1995; Haznedar *et al.* 1997; Aylward *et al.* 1999). However, these findings have been quite inconsistent over different studies.

2.5.2 Asperger's syndrome

Asperger's syndrome, classified as one of the autism spectrum disorders, was first described by an Austrian physician Hans Asperger in 1944. However, the term Asperger's syndrome (AS) was not brought to a wider public until the early 1980s (Wing 1981a). The diagnostic criteria of the syndrome include normal language and cognitive development coupled with problems in social interaction, stereotyped patterns of behaviour, and poor motor skills (Table 1). The prevalence of AS has been estimated to be as high as 3–7/1000 school-age children (Ehlers and Gillberg 1993; Kadesjö *et al.* 1999). Since the early cognitive and language development appears to be normal, the diagnosis is usually made clearly later in AS than autism, typically in late childhood, or even in adulthood. Males are more often affected with the ratio around of 5–8 : 1 (Wing 1981b; Ehlers and Gillberg 1993; Kadesjö *et al.* 1999).

A high rate of family loading is typical for AS: first-degree relatives (especially fathers) often show similar symptoms, although they don't fulfill the diagnostic criteria, (Burgoine and Wing 1983; Gillberg and Gillberg 1989). Despite of the notion of AS being a predominantly genetic disorder, no specific chomosome regions for the syndrome have been identified so far. The prognosis tends to be better for AS than autistic subjects, even when compared with the high-functioning part of the autistic disorder (Rutter and Schopler 1987; Szatmari *et al.* 2000). However, comorbidities

include depression, bipolar disorder, tics, eating disorders, and obsessive-compulsive disorder (Gillberg and Billstedt 2000). Additionally, an enhanced risk has been reported for alcohol problems and for suicide (Wing 1981a; Hellgren *et al.* 1994; Wolff and McGuire 1995).

The overall IQ of AS subjects tends to be in normal range, with verbal IQ superior to performance IQ (Ehlers *et al.* 1997). In a study comparing high-functioning autistic and AS subjects, predictive features for AS were deficits in motor skills, visuo-motor integration, visuo-spatial perception, nonverbal concept formation, and visual memory, whereas HFA subjects showed more deficits in articulation, verbal output, auditory perception, vocabulary, and verbal memory (Klin *et al.* 1995). Prosopagnosia (inability to recognize familiar faces) may associate with AS (Kracke 1994). The symptoms of social impairment differ to some degree between AS and autism. For example, AS subjects are usually more aware of the presence of others and may even express great interest in making social contacts, but the style of their attempt is often inappropriate and akward (Wing 1981a). Moreover, their insensitivity to other persons' emotional expressions and implied communications, *i.e.* body-language, makes engagement with others difficult (Klin *et al.* 2000). In both autism and AS, peculiarities in the use of gaze in social interactions are typical. However, total gaze avoidance is unusual: the subjects rather show a lack of expected gaze, like in a situation where another person is talking (Tantam 1993) and a tendency to avoid looking at the central face (Pelphrey *et al.* 2002; Trepagnier *et al.* 2002). Although the diagnostic criteria include normal language development, the speech of AS subjects is often marked by poor prosody, egocentric conversational style, and tendency to talk incessantly (Klin *et al.* 2000). No consistent focal brain abnormalities have found in structural imaging, although a slightly reduced diameter of mesencephalon has been recently reported (Nieminen-von Wendt *et al.* 2002).

2.5.3 Theories of cognitive impairment in autism

Various theories have been proposed for the cognitive deficits in autism. Some focus mainly on the social deficits, like the theory-of-mind theory does, while others, such as the central coherence theory try to explain also the nonsocial features of the syndrome. The following paragraphs briefly describe the most widely studied theories of autism.

Theory of mind

One of the core social deficits underlying the social and communicative difficulties in autistic disorders, has been proposed to be the inability to understand the minds of others (Baron-Cohen *et al.* 1985; Leslie and Frith 1987). This "theory of mind" (TOM) or "mentalising" refers to an ability to attribute mental states (thoughts, beliefs, feelings) to self and to others in order to understand and predict other persons' behaviours on the basis of these states. Already 18 months old infants show true joint attention and an ability to understand pretence (Leslie and Frith 1987). Further developed TOM can be divided into three different levels. A first-order TOM (normally present in four year old children) is the ability to attribute mental states to others ("what Mary thinks") (Wimmer and Perner 1983) (Figure 3). A second-order TOM (normally present in children between five to seven years of age) refers to the ability to understand what another person might be thinking from a third person ("what Mary thinks John thinks"). A more advanced third-order level includes situations such as double bluff (*e.g* "he knows they think he will lie") (Happe 1994a). Children with autism have been shown to be impaired in a large range of different theory-of-mind tasks. The performance seems to be related somewhat to the age and verbal IQ level (Happe 1995). In a study by Baron-Cohen *et al.* (1985), 80% of four year old autistic children, whose intelligence was in the normal range, did not pass a first-order TOM task. In a further study (Baron-Cohen 1989), all tested autistic subjects (around 15 years of age) failed to pass a second-order TOM task, whereas non-autistic Down syndrome subjects with lower mental age were able to attribute the tested beliefs. Thus, some older autistic subjects seem to develop a theory of mind at the lower levels, but the development is clearly delayed (Baron-Cohen 1989).

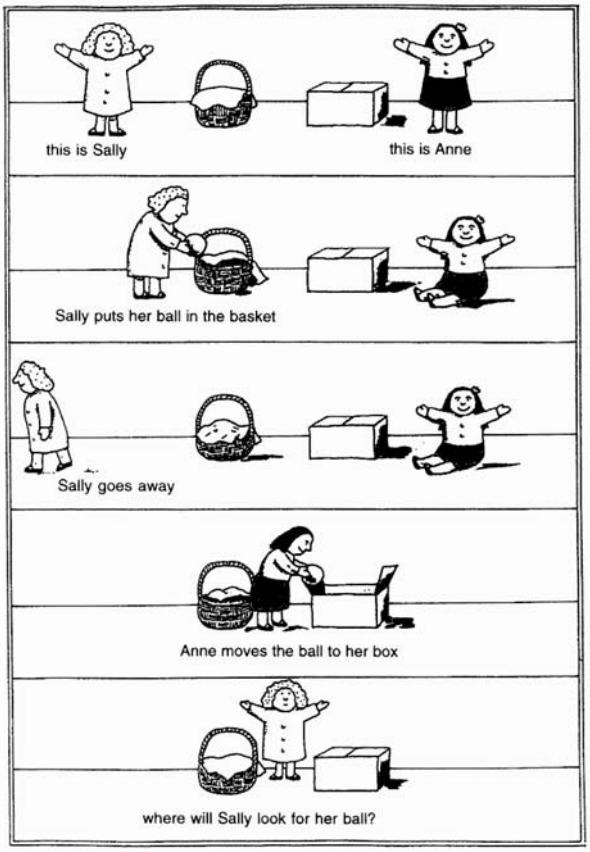

FIGURE 3 Example of a first-order "Sally-Anne" TOM task. The image is shown to a subject. At the end, the experimenter asks "Where will Sally look for her ball?" To answer correctly, the subject must realize that Sally falsely believes that the ball is still in the basket. Modified from Frith *et al.* (2000).

Baron-Cohen *et al.* (1994) found increased activation in the orbito-frontal cortex, while healthy subjects recognised mental state terms. In a PET study by Flectcher *et al.* (1995), the brain region most specifically associated with mentalising in healthy subjects was the left medial prefrontal cortex (BA 8/9). However, in AS subjects, with the same paradigm, significant activations were found in neighbouring brain areas (BA 9/10), suggesting that AS subjects used a different mechanism to solve the task (Happe *et al.* 1996). Furthermore, several studies have emphasized the role of the medial frontal lobe, the inferior parietal lobule, as well as the superior temporal gyrus in inferring mental states (Goel *et al.* 1995; Brunet *et al.* 2000; Castelli *et al.* 2000; Gallagher *et al.* 2000; Calder *et al.* 2002).

The TOM deficit theory has also faced critisism. In studies by Bowler *et al.* (1992) and Ozonoff *et al.* (1991), Asperger subjects were able to pass second-order TOM tasks, although they were socially impaired in every-day life. Furthermore, defects

in early joint attention (Sigman and Mundy 1989) and in primitive social skills (Klin *et al.* 1992) in young autistic subjects are not easily explained by the inability to mentalise. Deficits of TOM have also been reported in nonautistic subjects who suffer from learning disabilities, although their social skills in every-day life were within normal range (Frith and Happe 1994). Moreover, TOM theory fails to account for other nonsocial symptoms, such as restrictive and stereotyped patterns of behaviour (Frith *et al.* 1991).

Baron-Cohen *et al.* (1997a) have proposed that autistic subjects' ability to pass TOM tests is due to a ceiling effect. In a more difficult and advanced level test, in which subjects were making decisions about a person's mental states according to photographs of his/her eyes, AS subjects were impaired compared with controls (Baron-Cohen *et al.* 1997b).

Central coherence

Another proposal for the cause of cognitive deficits in autism is the "weak central coherence" theory (Frith and Happe 1994), which suggests that autistic subjects have a preference for processing local versus global information and that they are impaired in extracting meaning in context. Accordingly, healthy children recall meaningful sentences more easily than random word strings, whereas autistic childrens' performance is almost the same in both situations (Tager-Flusberg 1996). Moreover, autistic subjects usually focus on the actual words in a story and fail to extract the meaning (Happe and Frith 1996). Autistic subjects also perform well in hidden figures tests, which in turn are difficult to healthy people due to the normal tendency to see in a global way (Shah and Frith 1983). Weak central coherence could explain also many of the superior abilities found in autistic subjects. Frith and Happe (1994) suggests that this style of information processing could be independent from the TOM deficit, since subjects who are able to pass TOM tests still show marks of weak central coherence in their performance. Findings of signs of weak coherence in relatives of autistic subject (Smalley and Asarnow 1990) have raised an idea that the weak central coherence is a genetically transmitted feature of autism (Happe and Frith 1996).

Other theories

One theory about the social impairment in autism is the "affective theory" (Hobson 1986a; Hobson 1986b) that suggests that an innate inability to interact emotionally with others causes the observed social impairment. In line with this view,

autistic children were impaired in understanding emotional expressions (Hobson 1986a; 1986b). However, this theory suggests such impairments in the very early development that have not yet been extensively studied. Moreover, autistic subjects are able to show some degree of attachment and the early social smile may be present (Sigman and Ungerer 1984). Baron-Cohen *et al.* (1988) have argued that understanding emotions does not necessarily imply understanding beliefs.

Patients with frontal lobe lesions can show similar symptoms as autistic subjects (Damasio and Maurer 1978). These observations have lead to the executive function theory. Autistic subjects appear to be impaired in a range of executive function tests compared with otherwise handicapped controls (Pennington and Ozonoff 1996). However, executive function deficits are not specific to autism and the theory fails to explain many aspects of the nonsocial deficits, especially the superior skills (Happe and Frith 1996).

White matter theory

Similarities in the descriptions of subjects with nonverbal learning disabilities (Semrud-Clikeman and Hynd 1990; Klin *et al.* 1995) and AS have given rise to the "white matter theory" (Ellis and Gunter 1999). This hypothesis suggests that due to an unspecified cause, the development of the white matter has been disturbed leading in to deficits that are especially right-hemisphere dependent, such as impairment in face recognition, lack of prosody in speech, difficulties in drawing complex figures, pragmatic language difficulties, and poor social judgement. The theory also emphasizes difficulties in tasks requiring co-operation between the two hemispheres. Some functional imaging studies have shown abnormalities in the right hemisphere function in AS subjects (McKelvey *et al.* 1995), and in accompany with TOM deficit (Siegal *et al.* 1996; Winner *et al.* 1998). However, these findings are not compatible with all cases of AS, and sofar no histological evidence supports the white matter theory.

The role of amygdala

According to present knowledge, amygdala is one of the main regions involved in social cognition (Adolphs 2003). Adolphs *et al.* (1995) presented a patient who due to bilateral amygdala damages was not able to judge facial expressions of fear, anger, and the trustworthiness of individuals on the basis of photographs. Interestingly, high-functioning autistic subjects were also impaired in making judgements of the trustworthiness in an identical task (Adolphs *et al.* 2001). In a functional magnetic

resonance imaging (fMRI) study of (Baron-Cohen *et al.* 1999), healthy subjects showed activation in the superior temporal gyrus and the amygdala while judging, on the basis of eye expressions, what a person might think or feel. Autistic subjects activated the temporal lobe and frontal regions, but not the amygdala. Furthermore, patients with amygdala lesions have been found to be impaired in TOM tasks (Fine *et al.* 2001; Stone *et al.* 2003). Similarities between the symptoms of patients with amygdalar lesions and subjects with autism, as well as results of functional and structural imaging studies suggest that some pathology in the amygdala may be related to the social symptoms of autism.

Imitation and autism

Deficits in imitation have been suggested to be associated with the social impairment found in autism. According to Rogers and Pennington (1991), an early deficit of imitation might seriously affect the child's ability to develop social representations as it disrups the normal nonverbal communication between the mother and the baby. In later stages of development, the imitation deficit would then lead to impairments in emotion sharing, joint attention, pretend play, and TOM. Neonates' ability to imitate facial expressions (Meltzoff and Moore 1977) has lead to a hypothesis that imitation is the origin of emotional "contagion"; by sharing facial expressions with others the baby is able to experience the same emotions. Meltzoff and Gopnik (1993) suggest that deficits of this innate imitation system disturb the development of TOM. However, sofar there is no evidence of a basic impairment of emotional contagion in autistic children. Furthermore, subjects who due to other syndromes, such as blindness and paralysis, are not able to normally imitate during infancy, do not show a similar general social impairment as autistics do, although autistic symptoms are over-represented among blind children (Preisler *et al.* 1997), as well as in children having Mobius syndrome (congenital palsy of 6th and 7th cranial nerves) (Johansson *et al.* 2001). On the other hand, autism is common also among deaf children (Jure *et al.* 1991), who due to the lack of exposure to spoken language probably rely more on visual cues and imitation.

Numerous studies with very heterogenous experimental setups and participant groups have reported abnormalities of imitation skills in autistic subjects (for reviews, see Smith and Bryson 1994; Rogers 1999). Imitation of body movements and gestures appears to be more affected than imitation of actions with objects (DeMeyer *et al.* 1972; Heimann *et al.* 1992; Rogers *et al.* 1996). Impairments in imitation of abstract gestures

(Curcio and Piserchia 1978; Hammes and Langdell 1981), facial expressions of emotion (Loveland *et al.* 1994) and pantomimed actions (Hammes and Langdell 1981; Rogers *et al.* 1996) have also been reported. Autistic subjects are better in imitation of single actions than of action sequences (Rogers *et al.* 1996). Hobson and Lee (1999) found that only a few subjects with autism imitated the style with which the experimenter performed the action, although they otherwise were able to copy the same action. Moreover, autistic subjects did not copy the model's orientation when imitating self-oriented actions. Further, autistic subjects tend to make so called "reversal errors" when copying hand gestures. For example, when imitating an action, like holding hands palms away, they copy the hand view they have seen (palms toward themselves) without adopting the model's perspective (Ohta 1987; Perner 1996; Whiten and Brown 1999). Interestingly, imitation of behaviours of children with autism has been shown to increase their social behaviour (Field *et al.* 2001; Escalona *et al.* 2002).

Some imitation studies have failed to demonstrate differences between autistic and control groups (Morgan *et al.* 1989; Baron-Cohen *et al.* 1994; Charman *et al.* 1997). Verbal autistics appear to imitate gestures as well as control subjects do (Morgan *et al.* 1989). Accordingly, the ability to imitate familiar gestures has been suggested to be correlated with language comprehension (Sigman and Ungerer 1984). However, it has been argued that simplicity of the imitation tasks in these studies has resulted in ceiling effects.

2.6 Magnetoencephalography

The brain imaging studies of this thesis were carried out with magnetoencephalography (MEG) which is a totally non-invasive method that allows investigation of cortical dynamics on-line with a millisecond time-scale. MEG is based on detecting weak magnetic fields outside the head with superconducting sensors. The measured magnetic field pattern is used to calculate the most probable cerebral currents; these currents are mainly located within the fissural cortex. During last decades, the instrumentation has gradually progressed from single-channel devices to multi-channel systems that cover the whole scalp and allow signals to be measured simultaneously from different parts of the brain. The following methodological introduction is largely based on the reviews by Hari (1990) and Hämäläinen *et al.* (1993).

2.6.1 Origin of neuromagnetic signals

Cortical neurons are the main information-processing units of the brain. A neuron consists of a soma and a large number of dendrites that receive stimuli from other neurons via thousands of synapses; the axon transmits the signals further to other cells. When an action potential arrives along the axon to a synapse, transmitter molecules are relased into the synaptic cleft and bind to the receptors of a dendrite. Synaptic activation of neurons produces intracellular currents that are driven by movement of ions according to their chemical concentration gradients in the synaptic areas. These intracellular currents are often called in the MEG framework primary currents. In contrast to propagating action-potential-related currents, the synaptic intracellular and volume currents are passive. Volume currents flow in the surrounding medium and close the current loop, and therefore no charge is accumulated. In principle, the magnetic field is generated by both the primary and the volume currents. However, in a spherical structure, such as the brain, the primary currents are the main sources of the magnetic field detected outside the head.

Opening of ion channels through the dendrite's membrane changes the membrane potential: an event called the postsynaptic potential (PSP). Both action and synaptic currents generate magnetic fields. However, the magnetic field produced by a PSP is dipolar and decreases as $1/r^2$ with the distance r compared with the more rapidly decreasing $1/r^3$-dependent quadrupolar field of the action potential. Moreover, the longer duration of a PSP (tens of ms) allows more effective temporal summation of neighboring currents than with the 1-ms lasting action potentials. Thus, the MEG signals are likely produced by the synaptic current flow. To be able to measure magnetic signals outside the head, synchronous activation of tens of thousands of pyramidal cells is needed, and the size of a typically activated cortical area has been estimated to be around 1–2 cm^2 (Hari 1990).

The cortical neurons consist of both pyramidal and stellate cells. The stellate cells have symmetrically organized dendritic trees, whereas apical dendrites of the pyramidal cells lie in parallel to each other and perpendicular to the cortical surface. Because only currents that have a component tangential to the surface of a spherically symmetric conductor produce a magnetic field detectable outside the sphere, electrical currents in the pyramidal neurons of the fissural cortex are assumed to be the primary generators of neuromagnetic fields. Approximately 2/3 of the human cortex is buried within the

fissural cortex, including the primary cortical projection areas, making most of the cortical sources accessible to MEG. Because currents in the convexial cortex often are at least slightly tilted from the radial direction, they can also contribute to the MEG signals, especially because they are closer to the sensors than currents in the fissural cortex.

2.6.2 Instrumentation

Since brain's magnetic signals are extremely weak (5–500 x 10^{-14} T), special Superconducting Quantum Interference Device (SQUID) detectors are needed in neuromagnetic measurements. With these devices, the magnetic signal is first detected with a pickup coil that converts the magnetic flux into an electric current. The current flows then further into a signal coil that is coupled to the SQUID. For superconductivity, the SQUIDs are immersed in –269 ºC liquid helium. The device's sensitivity to external noise greatly depends on the configuration of the flux transformers. A magnetometer consists of only one pick-up loop and is sensitivite both to brain signals and enviromental noise. In addition to the pickup coil, first-order gradiometers have an additional compensation coil that is wound in opposite direction. They are effective in measuring signals from nearby sources, whereas fields from distant noise sources are cancelled, because they produce equal but opposite currents in the two coils. In first-order axial gradiometers, the two coils are connected in series and, as with magnetometers, the maximum signals are detected on both sides of a local (current dipole) source. In planar first-order gradiometers the two opposite coils are coupled as a figure-of-eight-shaped structure on the same plane, and the maximum signal is picked up just above the source. Compared with axial gradiometers, planar gradiometers are slightly less sensitive to deep sources, whereas their sensitivity to local sources is better. The measurements of Studies I–III of the present thesis were conducted with a Neuromag-122™ (Ahonen *et al.* 1993) whole-scalp neuromagnetometer that has 122 first-order planar gradiometers, organized in pairs, in 61 locations. Each gradiometer pair measures two orthogonal tangential derivates of the magnetic field. This device, developed by Neuromag Ltd. in our laboratory in 1992, was the first neuromagnetic device that covers the whole scalp. Measurements for Studies IV and VI were carried out with a whole-scalp 306-channel neuromagnetometer

(Vectorview™, Neuromag Ltd; Helsinki) that applies two orthogonally oriented planar gradiometers and one magnetometer at each of the 102 positions (Figure 4).

Since the flux-transfomers' ability to reject external magnetic disturbances is limited, the measurements have to be carried out inside a magnetically shielded room. The walls of a typical shielded room consist of several layers of μ-metal and aluminum that cancel both low- and high-frequency magnetic noise. In our present magnetically shielded room, passive shielding is combined with active shielding, in which compensation coils produce a magnetic field opposite to the external noise.

FIGURE 4 The 306-channel whole-scalp neuromagnetometer Vectorview™ (Neuromag Ltd; Helsinki). Subjects is sitting with her head supported against the bottom surface of the sensor helmet.

2.6.3 Source modelling

The greatest challenge for source modelling in neuromagnetism is the inverse problem: estimation of the cerebral current sources that underlie the measured magnetic fields detected outside the head. No unique solution exists to this problem.

For a feasible solution, one needs a model of the source current and a model of the volume conductor, the head.

The most common conductor model is a homogeneous sphere model. This model is suitable for modelling of most cortical regions, including the sensorimotor and occipital cortex. In those locations, where the shape of the brain most strongly deviates

from a sphere, like in the most frontal and basal regions, a realistic head model can provide more accurate information.

The simplest model of a cortical current source is a current dipole. The equivalent current dipole (ECD) model can be used if the activated cortical area is small enough to appear as a point like source when detected from outside the head. An ECD has orientation, strength, and three spatial coordinates. The ECD best explaining the measured field can be calculated by a least-squares search. The validity of the dipole model can be assessed with the goodness-of-fit (*g*) value that indicates how much the field pattern of an ECD accounts for the measured field variance (Kaukoranta *et al.* 1986). If several brain areas are simultaneosly active, a multidipole model can be applied. In case of spatially and/or temporally separatible sources, single dipoles can first be identified one-by-one using a 1-dipole model. Thereafter all dipoles can be included into a time-varying multidipole model, in which the strengths of the ECDs are allowed to change as a function of time, while the dipole locations and orientations are kept fixed.

Distributed source models, with no or only minor assumption of the number of the activated sources, have been recently developed. Minimum Current Estimate (MCE; Uutela *et al.* 1999), which is based on minimum L1-norm estimates, models the signals with a current distribution where the total sum of the current amplitudes is as small as possible, while it still explains almost all the measured signals. For visualization, the estimates are projected radially on the surface of a head (boundary element) model and color-coded according to the activation strength. Compared with the dipole model, the MCE method calculates time courses of source volumes rather than of pointlike sources. The dipole model can be more accurate than MCE in modelling individual nonsimultaneous sources, but with temporally overlapping sources the methods perform equally well (Stenbacka *et al.* 2002).

2.6.4 Other functional neuroimaging techniques

During recent years functional imaging has rapidly progressed and grown in neuroscience. Many techniques, including MEG, electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET), allow studying of brain functions online non-invasively in awake behaving subject.

EEG measures the electric component of the electromagnetic field (for a review, see Niedermeyer and Lopes da Silva 1998). In EEG, electric potentials that are generated by neuronal currents are measured with electrodes attached to the scalp. Both EEG and MEG have an excellent temporal resolution in (sub)millisecond scale. While the brain's magnetic fields are not affected by the skull and other tissues covering the brain, the current flow to the scalp is distorted due to different conductivities of these tissues. Since both radial and tangential currents contribute to the EEG signal, the source analysis is more difficult than with MEG. Magnetic field diminishes rapidly as a function of distance. The advantage of EEG is a better sensitivity to radial and deep sources. In addition, the instrumentation is less expensive and movable, thereby allowing telemetric and long-term recordings. EEG can also more easily be used to study children, epileptic, and confused patients. Certainly, in some situations the best way is to combine these two methods.

The most widely used functional brain imaging technique is at present fMRI. It is based on measuring of changes in the local haemodynamics and in the level of haemoglobin oxygenation in the activated brain area. The blood-oxygen-level-dependent (BOLD) signal results from different magnetic properties of the haemoglobin and deoxyhaemoglobin. The spatial resolution of fMRI is 1–3 mm, but since the method is based on changes in the blood flow and brain metabolism that follow local neuronal activity quite slowly, the temporal resolution is limited to hundres of milliseconds (Rosen *et al.* 1998).

In PET recordings, changes in blood flow, blood volume and metabolic activity of different tissues are measured by injecting radioactive isotope markers into the subject's bloodstream (Ter-Pogossian *et al.* 1975). Break up of the radioactive substances creates positrons. When the positrons are captured by electrons two photons are emitted. These photons are detected by the PET cameras. PET can also be used to study distribution of receptors for different neurotransmitters. The spatial resolution of PET is around 5 mm, whereas the temporal resolution is not better than tens of seconds.

Nowadays different functional brain imaging techniques are combined in many advanced research centers to obtain the most realistic and accurate picture of the brain function in awake and behaving humans.

2.7 Spontaneous brain rhythms

Neurons in thalamus and cerebral cortex of human and animal brain generate rhytmic intrinsic oscillations. Such spontaneous activity exhibits characteristic frequency ranges and is assumed to be mediated mainly by the thalamocortical neurons with some contribution also from the intracortical networks (Lopes da Silva 1991). The thalamic relay neurons have two distinct physiological states: a transmission mode and an oscillatory mode, depending on the neuron's membrane potential. During the transmission mode, the thalamic neurons are in a more depolarized state and the incoming exitatory signals produce single action potentials, allowing transmission of different sensory stimuli to the cortex. During the oscillatory mode, the neurons are hyperpolarized by inhibitory input and a short depolarization causes a burst of action potentials (Martin 1991). The changes between transmission and oscillatory modes are probably regulated by inputs from the reticular thalamic nucleus and from deeper nuclei in the forebrain and brain stem.

In spite of intensive studies, the possible functional role of cortical macroscopic oscillations is largely unknown. The hypotheses include idling, preparation of the system to react more rapidly to external stimuli (Kuhlman 1978, Hari and Salmelin 1997), gating, and changing information transfer properties of the active cortex (Lopes da Silva 1991). It has also been suggested that the cortical rhythms might have a role in co-ordination of neural activity between the central and peripheral nervous systems (Vallbo and Wessberg 1993; Conway *et al.* 1995; Salenius *et al.* 1996; Hari and Salmelin 1997).

The best known electric oscillations in the human brain are the alpha and mu rhythms, which both show specific reactivity and can easily be detected with MEG.

The occipital alpha rhythm, first described by Berger (1929), refers to spontaneous around 8–13 Hz sinusoidal-like activity appearing in the posterior parts of the brain. EEG and MEG alpha rhythms dominate posterior spontaneous signals of awake relaxed adults who are resting with their eyes closed (Adrian 1944; Chapman *et al.* 1984; Salmelin and Hari 1994; Niedermeyer and Lopes da Silva 1998). Both EEG and MEG alpha rhythms can be blocked by opening the eyes and by external visual stimulation. The parieto-occipital sulcus is the main source for the human MEG alpha activity (Williamson and Kaufman 1989; Lu *et al.* 1992; Salmelin and Hari 1994;

Salenius *et al.* 1995), since in the calcarine fissure opposite directions of the source currents lead to partial cancellation (Hari and Salmelin 1997).

The mu rhythm

In Studies I and II reactivity of the rolandic mu rhythm was used to probe the functional state of the sensorimotor cortices. The rolandic comb-shaped mu rhythm was first described by Gastaut (1952) with EEG. It is blocked by movements of limbs, especially those of contralateral limbs and by somatosensory stimulation (Chatrian *et al.* 1959; Pfurtscheller and Aranibar 1979; Salmelin and Hari 1994). The human magnetic mu rhythm exhibits two dominant frequency components around 10 Hz and 20 Hz (Tiihonen *et al.* 1989b). Sources of the 20-Hz component are localized anterior from the central sulcus over the precentral motor cortex, whereas the 10-Hz component originates more posteriorly in the somatosensory region (Salmelin and Hari 1994).

Both components of the mu rhythm react with a rebound after a short movement or a somatosensory stimulus, but the rebound of the 20-Hz activity is about 0.3 s faster and clearly stronger (Salmelin and Hari 1994). The 20-Hz rebound follows a somatotopic representation of the moved body part, whereas all sources of the 10 Hz component cluster near the somatosensory hand area (Salmelin *et al.* 1995). The slightly different timing, strength and location of the rebounds suggest that these two frequency components are associated with different functional networks. The 20-Hz component seems to merely reflect functions of the motor system, whereas the 10-Hz component is more clearly related to the somatosensory system.

The level of the 20-Hz activity is bilaterally enhanced within 500 ms after a median nerve (MN) stimulation (Salmelin and Hari 1994; Salenius *et al.* 1997). This rebound is abolished during object manipulation (Salmelin and Hari 1994; Salenius *et al.* 1997) and it is also diminished during motor imagery of such movements (Schnitzler *et al.* 1995a). The rebound has been suggested to be associated with increased inhibition in the motor cortex (Salmelin and Hari 1994), whereas suppression of the rebound likely reflects increased excitability of the motor cortex, either due to disinhibition or due to increased excitatory input.

2.8 Somatosensory evoked responses

Somatosensory evoked responses can be recorded to electric and mechanical stimuli to study the function and reactivity of the somatosensory system in healthy

subjects and in different patient groups. Furthermore, somatosensory evoked responses are widely used in clinical practice to diagnose and follow different pathological conditions that affect the somatosensory system.

Somatosensory evoked potentials

Somatosensory evoked potentials (SEPs) can be recorded both non-invasively from the scalp and, in special situations, intraoperatively directly from the cortex. Short-latency SEPs recorded from the scalp to electrical median nerve stimuli usually show a surface negative deflection (N20) over the parietal cortex 18–23 ms after the stimulus onset and a positive deflection (P30) at 30 ms. Waveforms with the same latency, but of opposite polarity can be recorded over the frontal areas (Allison *et al.* 1991). The neuronal sources underlying SEPs are still under debate. However, several studies support the model by Allison *et al.* (1989) with one tangential generator in area 3b of SI and one radial generator in area 1 (Wood *et al.* 1988; Baumgartner *et al.* 1991; Hari 1991).

Somatosensory evoked fields

Somatosensory-evoked fields (SEFs) measured with MEG show a very similar temporal behavior as do SEPs, but the source areas can be determined more accurately (for a review, see Hari and Forss 1999).

The earliest deflection to electrical median nerve stimulation peaks around 18–20 ms (N20m) over the contralateral anterior parietal cortex (Tiihonen *et al.* 1989a). The ECD of N20m points anteriorly at the hand area of the SI cortex as the response probably arises from the fissural area 3b (Wood *et al.* 1985; Tiihonen *et al.* 1989a; Hari 1991). For lower-limb stimulation, the first cortical deflection is seen later, at around 40 ms. N20m is followed by a deflection with opposite polarity peaking around 30–35 ms (P35m), with ECD pointing posteriorly in the SI cortex. The source of the P35m has been shown to be more superior and medial to the source of N20m in several studies. The generator areas for the magnetic SI responses follow similar somatotopical order as is found in electrical cortical stimulation studies (Penfield and Jasper 1954) and intracranial SEP recordings (McCarthy *et al.* 1993).

Activation of the secondary somatosensory (SII) cortices to sensory stimulation was first shown noninvasively in MEG recordings (Hari *et al.* 1983, 1984). The SII SEFs for median nerve stimuli peak bilaterally over the temporoparietal regions at around 80–140 ms after stimulus onset and for lower limb stimulation 10–30 ms later.

The ECDs of the responses are located in the upper banks of the Sylvian fissures in SII cortices. The contralateral SII response is typically slightly earlier and stronger than the ipsilateral response (Hari *et al.* 1983, 1984, 1993; Frot and Mauguiere 1999).

Neuronal activation due to bilateral input from the two hands stongly overlaps in the SII cortex: when the left and the right median nerves were stimulated in pairs with a 300 ms interstimulus interval (ISI) within a pair, the second response was clearly delayed (Simoes and Hari 1999). Furthermore, intervening tactile stimuli presented to either contra- or ipsilateral hand suppressed the SII responses to right index finger stimuli (Simoes *et al.* 2001). SII cortices seem to have an important role in integration of input from both body halves and in the maintenance of unified body scheme; for example SII activity decreases during perception of a distorted body image (Flor *et al.* 1998; Hari *et al.* 1998).

The mesial cortex of the paracentral lobule has been shown to be activated around 110–115 ms to attended electrical median nerve stimuli (Forss *et al.* 1996). In MEG recordings, PPC activation has been shown to both electrical and airpuff stimuli 70–110 ms after the stimulus onset (Forss *et al.* 1994a, b).

Both SEPs and SEFs are modulated during isometric contraction of muscles near the stimulated nerve (Cheron and Borenstein 1987; Cohen and Starr 1987; Huttunen and Homberg 1991; Kakigi *et al.* 1995; Schnitzler *et al.* 1995b; Forss and Jousmäki 1998; Lin *et al.* 2000). This phenomenon, known as somatomotor "gating," has been explained by different mechanisms, including interaction between input from cutaneous mechanoreceptors and muscle spindles in SI (Kakigi *et al.* 1995), effect of cortical movement-related activation (Starr and Cohen 1985) and tuning of neurons towards relevant tactile signals from the region of muscle contraction (Huttunen *et al.* 1996; Forss and Jousmäki 1998). Modulation of somatosensory responses during simultaneous tactile stimulation has been frequently reported (Kakigi and Jones 1985; Cohen and Starr 1987; Schnitzler *et al.* 1995b; Huttunen *et al.* 1996). Furthermore, both in monkeys and in humans, attention to sensory stimuli increases activation in the somatosensory areas (Burton *et al.* 1997; Steinmetz *et al.* 2000), more strongly in the SII than SI cortices (Poranen and Hyvärinen 1982; Garcia-Larrea *et al.* 1991; Hari 1991; Hsiao *et al.* 1993; Mima *et al.* 1998; Lam *et al.* 1999). Both short-and long-latency SEFs are also modified by simultaneous visual stimuli and the long-latency responses by auditory stimuli (Lam *et al.* 1999; Lütkenhoner *et al.* 2002).

3. AIMS OF THE STUDY

The aim of this study was to investigate the possible existense and function of the human mirror-neuron system by using magnetoencephalography in healthy and autistic subjects and to examine mechanisms of imitation and social perception. The specific goals of Studies **I**–**VI** were:

I To establish the existence of the human action observation/execution matching system and to find out whether observation of manipulative hand movements influences activity of the human primary motor cortex.

II To find out whether subjects with Asperger's syndrome would show disorders in the motor cortex part of the mirror-neuron system.

III To investigate whether the somatosensory cortical network would influence the human mirror-neuron system.

IV To study perception of socially valid body-language cues in visual cortical areas.

V To characterize mechanisms of imitation in adult Asperger syndrome and high-functioning autistic subjects.

VI To assess functioning of the mirror-neuron system in subjects with Asperger's Syndrome and in healthy control subjects during orofacial imitation.

4. METHODS

4.1 Subjects

In Studies I, III, IV, and V, altogether 32 healthy adult volunteers (16 females, 16 males, age range 18–37 years) were studied. Some of the subjects participated in several experiments. In Studies II, V and VI, 15 autistic subjects (four females, 11 males, age range 19–46 years) were investigated; 12 of the subjects had been clinically diagnosed according to the ICD-10 criteria as having Asperger's syndrome and three as having autism. All subjects gave their informed consent after full explanation of the experiment. Moreover, the experimental protocols had prior approval by the Ethical committee of the Hospital District of Helsinki and Uusimaa.

4.2 Magnetoencephalographic recordings (Studies I–IV and VI)

4.2.1 Stimuli and tasks

In Studies I–III, left and right median nerves (LMN, RMN) were alternately stimulated at wrists with 0.2-ms constant-current pulses with an internal stimulus interval (ISI) of 1.5 s. The stimulus intensities varied from 7 to 13 mA and exceeded the motor threshold. During stimulation, the subjects were either (i) resting with the eyes open with no task, (ii) manipulating a small object (a plastic cylinder, height 2 cm, diameter 1 cm) with their right hand, or (iii) observing when another person was similarly manipulating the same object with her right hand on the subject's right side. During the rest and observation conditions, the subjects were instructed to keep their hands steady and relaxed. In the rest and manipulation conditions, the subjects were instructed to look straight ahead and to avoid both saccades and looking at their own hands; no exact fixation point was given. One of the experimenters stayed in the measurement room near the subject (but not visible to her/him) during the whole recording to make sure that the instructions were followed. The manipulation and observation conditions were performed in a random order, and the rest condition was recorded at the beginning and at end of the session.

In Study IV, we presented visual stimuli that consisted of 48 different static color images of 36 natural and of 12 distorted finger postures, all designed by Poser™ 4.0 programme. The stimuli included images of both left and right hands viewed from two different angles: one view similar to subject's own hands and the other resembling

another person sitting in front of the subject. The distorted finger postures were designed by bending (by computer) the distal phalanxes of different fingers into clearly unnatural positions. The 15 deg x 17 deg stimuli were presented in a random order once every 3.2 s and were displayed for 2 s. All stimuli were similar in content complexity and luminance and were displayd with equal probabilities (1/48) during the measurement. The subjects had two tasks: In the *Observation* condition, they were asked to lift the right index finger, when the presented image was identical to the previous one. In the *Imitation* condition, they were asked to imitate the previous natural finger posture whenever the subsequent hand image was replaced with an imperative stimulus (an image of a small ball).

In Study VI, still pictures of a face of a young female were projected on a screen 90 cm in front of the subject. Three different pictures (lip protrusion, contracting of both sides of the mouth, and lip opening) were presented in a random order for 551 ms with an ISI of 3.6–4.4 s. All stimuli were presented with the same luminance, contrast, and size (15 cm x 20 cm). The subjects were asked to imitate the lip forms as soon and accurately as possible.

4.2.2 Recordings

All recordings were carried out in a magnetically shielded room where the subjects sat relaxed with their head supported against the bottom surface of the helmet-shaped neuromagnetometer. The subjects were instructed to avoid head movements and eye blinks during data collection. In Studies I–III, cortical signals were recorded with a 122-channel whole-scalp neurogradiometer Neuromag-122™ (Neuromag Ltd; Helsinki), and in Studies IV and VI with a 306-channel whole-scalp Vectorview™, device (Neuromag Ltd; Helsinki).

Signals from four indicator coils, attached to the scalp, were used to define the exact head position within the sensor helmet. The coil locations with respect to three anatomical landmarks (nasion, and left and right preauricular points) were found with a 3-D digitizer thereby allowing further alignment of the MEG and MRI coordinate systems. In addition, head MRIs of 24 subjects were acquired in the Department of Radiology of the Helsinki University Central Hospital with a 1.5-T Siemens Magnetom™ device.

Both vertical and horizontal electro-oculograms (EOGs) were recorded during all MEG measurements for detecting eye blinks and extreme eye movements. In Study VI,

bipolar electromyograms (EMGs) were recorded from the orbicular muscle of mouth in five AS subjects and in all control subjects; moreover in in Study I, EMGs were recorded from the right first interosseus, thenar, and forearm extensor muscles from five subjects.

The recording passband of the MEG signals was 0.03–190 Hz and the sampling rate 597 Hz in Studies I–III, 0.02–200 Hz and 600 Hz in Study IV, and 0.1–600 Hz and 600 Hz in Study VI. The ongoing spontaneous activity was recorded continuosly and stored on an optical disk for off-line analysis (Studies I–II, IV, and VI). About 90 artefact-free single responses were averaged on-line separately for each MN stimulus (Studies I–III). In Studies IV and VI, a minimum of 60 single responses was averaged for the natural and distorted finger postures and a minimum of 80 responses for the lip forms.

4.2.3 Data analysis

Analysis of spontaneous activity (Studies I and II) started by visual inspection and by calculation of amplitude spectra of signals recorded during the resting condition (eyes open and eyes closed with no stimuli) to find the individual frequency maxima. Then the reactivity of the ~20-Hz rolandic activity was quantified by using the temporal-spectral-evolution (TSE) method (Salmelin and Hari 1994) to reveal time-locked changes in the level of the rhythmic activity. First the signals were bandpass filtered through about 14–30 Hz (Studies I and II) and also through 7–15 Hz (Study I). Then the filtered signals were rectified and finally averaged time-locked to the median nerve stimuli.

In Studies I–IV and VI we used the sphere model because the main areas of interest were the sensorimotor cortex and posterior regions, in which the sphere is a good model for the brain.

Sources of SEFs, evoked responses and oscillatory signals were modeled as single current dipoles (Studies I, III and VI). The magnetic field patterns were first visually examined in 2-ms steps to identify all local and stable dipolar field patterns to obtain an initial estimate of the number of activated sources during the analysis period. Then the ECD, best describing the most dominant source during the strongest signals of each dipolar field pattern, was identified by a least-squares search using a subset of 16 to 30 channels over the source area. Thus, the 3-D locations, orientations, and strengths of the ECDs were obtained in a spherical head model, based on the subject's individual MR

images. The validity of the single-dipole model was evaluated by computing the gooodness of fit (Hämäläinen *et al.* 1993). Thereafter the analysis was extended to cover the entire time period and all channels were included in computing a time-varying multidipole model. In Study III, the multi-dipole model, found during the resting condition, was used to compare activation strengths as a function of time in all three (rest, manipulation, observation) conditions. Finally, the waveforms predicted by the model were compared with the original measured signals.

In Study IV, the data were analyzed with MCE based on L1-norm (Uutela *et al.* 1999). Two large regions of interest (ROIs) of the extrastriate cortex of the occipital lobe in both hemispheres were first selected. Differences between cortical activation strengths in response to natural and distorted finger posture stimuli were computed within the two ROIs across a time window that showed the most marked and consistent differences across subjects. The exact onset time of the difference between the natural and distorted finger stimuli was evaluated by computing cumulative amplitudes of mean responses in left and right occipital areas as a function of time. Then the subtraction curves were computed between the cumulative amplitudes for each subject. Next, the difference curves were averaged across conditions and areas, and *t* tests at each point along the time axis served to probe the deviance of the mean difference from zero. The results of the *t* tests were plotted as a function of time to indicate the onset of the consistent statistically significant difference between natural and distorted stimuli.

Statistical analysis of amplitudes and latencies was done with *t* tests and nonparametric tests (Studies I, II, and III, VI) and with chi-squared test (Study VI) and ANOVA (Studies II, IV, and V).

4.3 Behavioral imitation experiment (Study V)

In this experiment, the subjects were asked to imitate experimenter's hand movements. The performance of each subject was videotaped for further analysis. The subjects sat face-to-face to the experimenter, and a pen and a blue and a green cup were placed on the table in front of them (Figure 5). First there was a short instruction and rehearsal period: the subjects were instructed to imitate on-line, as simultaneously as possible, the experimenter's hand movements that consisted of putting a pen with the left/right hand into a green/blue cup using one of two possible grips. In the movement sequence there were three different aspects in which the subjects had to pay attention

to: the hand (left or right), the grip (two possibilities), and the end point (green or blue cup). In the *Crossed* condition, the subjects were instructed to use the crossed hand for imitation (*e.g*. the subject's right hand corresponding to the experimenter's right hand; anatomical correspondence). In the *Mirror-image* condition, the subjects were instructed to imitate as if looking in a mirror (*e.g.* the subject's left hand corresponding to the experimenter's right hand; spatial correspondence). Afterwards two independent experimenters observed the videotapes and rated each trial.

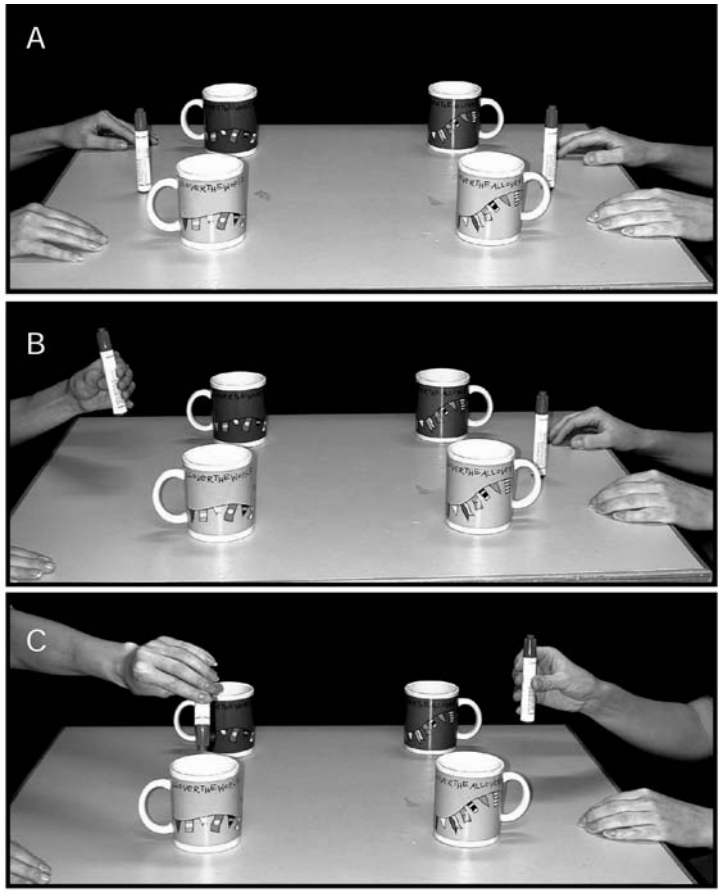

FIGURE 5 Example of the Mirror-Image imitation. Subject imitates the experimenter's movements as simultaneously as possible. Adapted from Study V.

5. EXPERIMENTS

5.1 The ~20-Hz rebound is suppressed during hand action observation (Study I)

Reactivity of the rolandic ~20-Hz activity was used to probe the functional state of the primary motor cortex during three conditions: rest, object manipulation, and observation of the same action made by an other person (Figure 6).

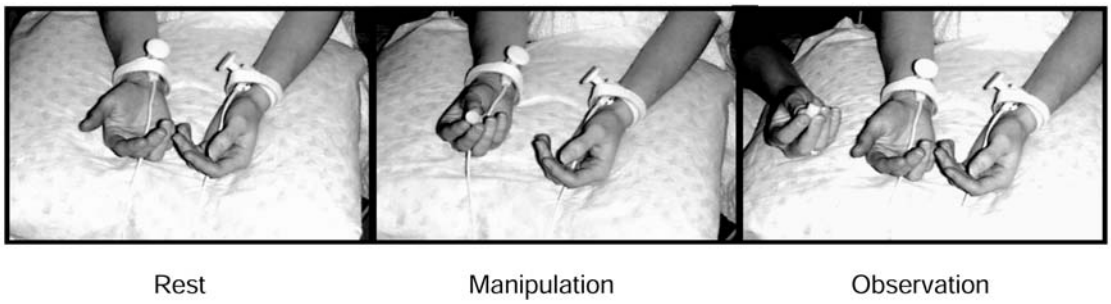

FIGURE 6 The three experimental conditions: rest, manipulation and observation. The left and right median nerves were stimulated alternatingly at wrists. Adapted from Studies I and III.

5.1.1 Results

Eight healthy adult subjects (4 females, 4 males) participated in the study. Figure 7 illustrates the results of one subject. During rest condition the level of the ~20-Hz activity in the rolandic region enhanced transiently after right median nerve (RMN) stimulation and reached its maximum about 500 ms after the stimulus. The inset in Figure 7 shows that the rebound was totally abolished during object manipulation and it was also strongly diminished and shortened during observation of same action. Figure 8 shows that the sources of the 20-Hz activity were clustered just anterior to the central sulcus in the posterior part of the precentral cortex. The task effects on the rebound were quantified by integrating the TSE curves over the hand regions of both hemispheres from 500 to 1500 ms after MN stimuli. During manipulation, the ~20-Hz rebounds were significantly suppressed ($p < 0.001$) in both hemispheres for both LMN and RMN stimuli.

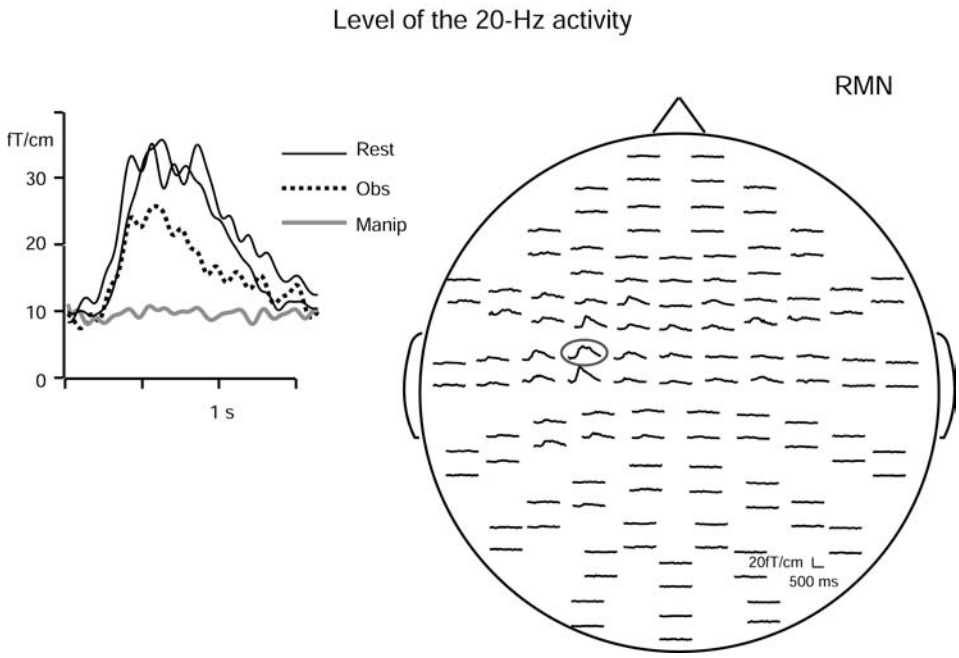

FIGURE 7 Level of the ~20-Hz activiy as a function of time in one subject to RMN stimuli. Right: The responses in all 122 detectors; the head is viewed from the top, and in each response pair, the upper trace illustrates the field derivate along the latitude and lower trace along the longitude. Left: Signals from the left rolandic region enlarged in all three conditions. Adapted from Study I.

The decreases during action observation were about 40% ($p < 0.005$) of the suppressions during manipulation and did not differ significantly between the LMN and RMN stimuli, nor between the hemispheres.

The rebound of the 7–15 Hz activity was also dampened during action observation, but the suppressions were statistically significant only in the left hemisphere for LMN stimuli. Control experiments indicated that the observed suppressions of the rebound during action observation cannot be explained by attentional changes or concurrent muscle activity.

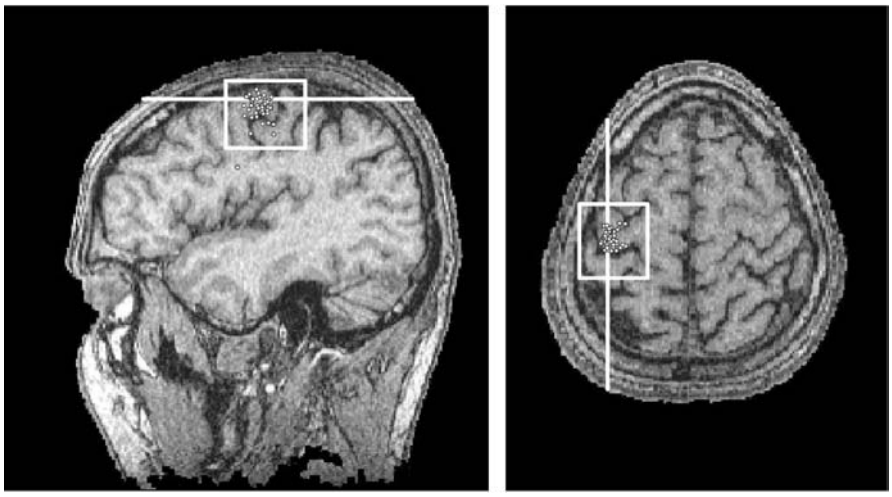

FIGURE 8 Source locations of the ~20-Hz activiy in the left hemisphere of one subject. The dots illustrate single equivalent current dipoles that were used in modelling the field pattern of a 20 Hz oscillatory cycle. The clusters concentrate to the precentral motor cortex. Adapted from Study I.

5.1.2 Discussion of Study I

These results show that the activity of the precentral motor cortex is significantly modified during observation of manipulative hand movements. The effect is similar to that seen in the motor cortex during execution of the same action, thereby strongly supporting the existence of an action execution/observation matching system in the human brain and providing the first evidence of the involvement of the primary motor cortex in it.

Since the study focused on changes in the level of ~20-Hz rolandic activity, concurrent activation of other mirror-neuron-system-related brain areas could not be assessed.

Although our subjects were instructed only to observe the manipulation, it was not possible totally rule out that they also used motor imagery during action observation. However, the possible motor imagery component appears negligible since the electromyograms did not show any increase of sustained muscle activity during action observation although small increase of electromyographic activity has been detected during active motor imagery (Schnitzler *et al.* 1997).

The presence of the ~20-Hz rebound effect during both action observation and motor imagery suggests that it can be employed for studying the motor-cortex part of

the action representation system with different stimulus setups and in different patient groups.

5.2 The ~20-Hz rebound is suppressed in Asperger subjects (Study II)

Autistic subjects' social deficits could be related to a dysfunctional mirror-neuron system. To investigate whether AS subjects would show disorders in the motor-cortex part of the mirror-neuron system, we compared reactivity of the ~20-Hz rebound in Asperger and healthy subjects using the same task as in Study I.

5.2.1 Results

In the Asperger group, four subjects met the ICD-10 criteria for Asperger's syndrome and one for autistic disorder (three males, two females). All subjects were deficient in attributing mental states according to the "strange stories" theory-of-mind test by Happe (1994a). However, the degree of the deficit varied among subjects. As expected, the subject with autistic disorder had greatest difficulties in his performance and the two female subjects performed the test better than the males.

Figure 9 shows the level of the ~20-Hz rolandic activity of one AS and one control subject during rest, object manipulation, and action observation. In both subjects, the ~20-Hz rebound was totally abolished during object manipulation and it was also significantly diminished during action observation. Thus in both AS and healthy subjects the primary motor cortex was activated during both execution and observation of hand movements.

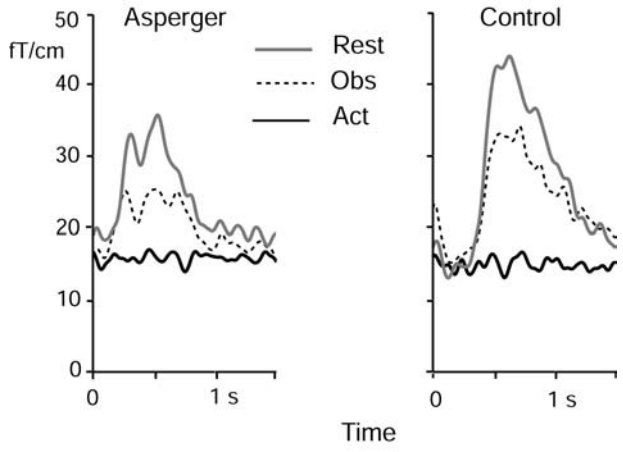

FIGURE 9 The ~20-Hz level as a function of time for one AS and control subject from one rolandic channel in the left hemisphere during all three conditions. Adapted from Study II.

Figure 10 shows the individual differences (rest minus action observation) in the ~20-Hz activity level with different stimulus and hemisphere combinations. The level of the ~20-Hz rebound decreased systematically during action observation in both groups ($p < 0.03$, binomial test), as is reflected by the consistently positive values in Figure 10 in all except Asperger subject 4 (RMN stimulation in the left hemisphere).

The mean decreases of the ~20-Hz activity during action observation varied from 23% to 41% ($p < 0.01$) of the suppressions during manipulation in AS group and from 31% to 46% ($p < 0.01$) in the control group. There were no significant differences between the LMN and RMN stimulations nor between the hemispheres, nor did the two groups differ significantly from each other during manipulation and action observation (univariate repeated measures ANOVA).

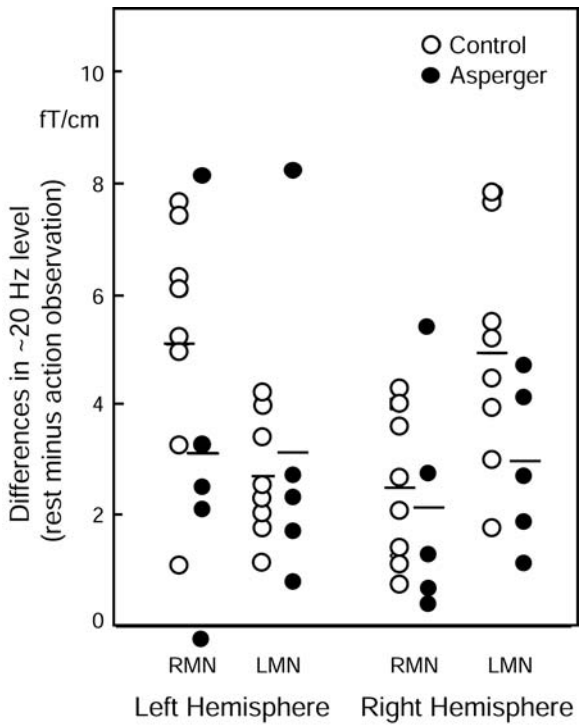

FIGURE 10 The decrease in the ~20-Hz rebound (from 500 ms to 1500 ms after median nerve stimulation, rest mnus action observation) in AS and control groups for different stimulus and hemisphere combinations. Each symbol represents one observer. Mean values are shown as horizontal lines. Adapted from Study II.

5.2.2 Discussion of Study II

These results show that observation of manipulative hand actions activates the primary motor cortex of Asperger and normal subjects approximately to the same extent.

Subjects with Asperger's syndrome often pass theory-of-mind tasks (Ozonoff *et al.* 1991; Bowler 1992), although they have social problems in everyday life. However, the "strange stories" used in the study are more difficult to understand and to explain than the standard TOM tests and suit well for testing able AS and autistic subjects (Baron-Cohen *et al.* 1997a).

In spite of the observed deficits in the theory-of-mind ability, the AS group showed activation of the primary motor cortex during action observation indicating that the theory-of-mind deficit seems not to be related to coding of observed motor actions at the motor cortex level. Interestingly, the suppression of the ~20-Hz activity during action observation was automatic and distinct throughout the AS group, although some subjects had difficulties in following the observation task.

5.3 Activity of the SI and SII cortices is modulated during action observation (Study III)

Median nerve stimuli were used to probe the functional states of the primary and secondary somatosensory cortices SI and SII while the subjects observed and performed unilateral hand actions.

5.3.1 Results

During the rest condition, the earliest deflections of the SEFs peaked over the contralateral anterior parietal cortex about 20 ms and 36 ms after the stimulus and the longer-latency responses bilaterally over the temporoparietal regions at 84–91 ms. The locations of the ECDs of the early and longer-latency responses agreed with activation of the contralateral SI and bilateral SII cortices. In one subject, contralateral SII responses were not detectable to neither LMN nor to RMN stimuli, and in another subject the RMN stimulation did not elicit ipsilateral SII responses. In all other seven subjects, sources of the 30–43 ms SI responses and of the contralateral (72–120 ms) and ipsilateral (75–120 ms) SII responses were found in all conditions. The mean latencies

of the SI and SII responses did not differ statistically significantly between the conditions.

In the further analysis, a multi dipole model, found during the rest condition, was used to compare activation strengths of SI and SII sources in all three (rest, manipulation, observation) conditions. Figure 11 shows the mean (+ SEM) changes of SI and SII source strengths during manipulation and action observation compared with the rest condition. Both manipulation and observation had parallel effects on the responses to LMN stimuli: the 35-ms SI signals were significantly enhanced and the contra- and ipsilateral SII signals were suppressed. Similar modulation was seen in the responses to RMN stimuli during action observation. Only responses to RMN stimuli during manipulation behaved in an opposite manner: the SI responses were suppressed ($p < 0.001$, 2-tailed t test for paired differences) and the ipsilateral SII responses increased ($p = 0.008$, binomial test).

The control experiments showed that attention to visually presented stimuli influenced the SII responses, but the effect was significantly weaker than during observation of hand actions thereby indicating that changes in the SII activations during hand action observation can be explained only in part by changes in visual attention.

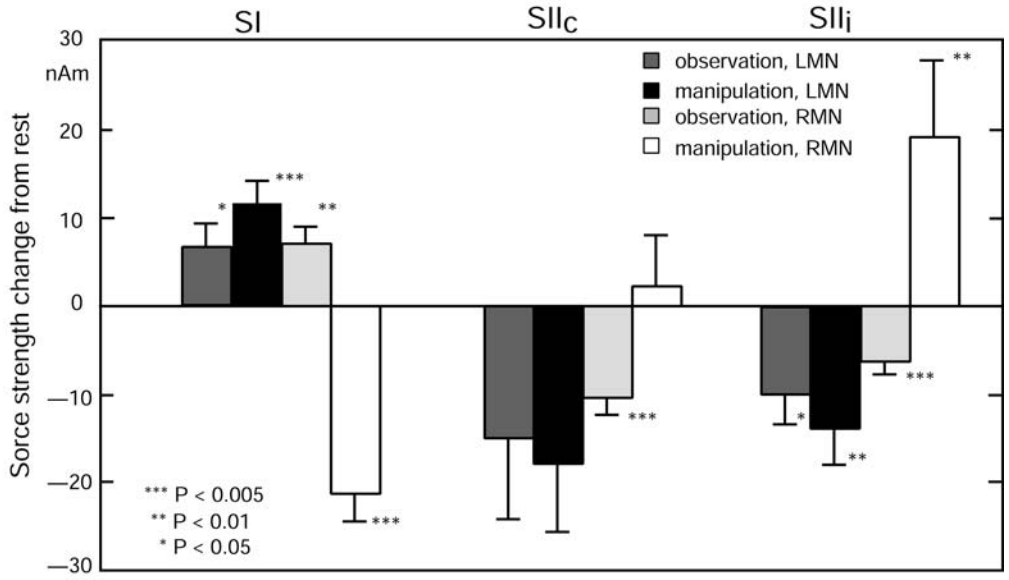

FIGURE 11 The mean (+ SEM) changes of source strengths from rest in the primary somatosensory (SI), the contralateral secondary somatosensory (SIIc) and the ipsilateral secondary somatosensory (SIIi) cortices. Statistical significances are indicated. Adapted from Study III.

5.3.2 Discussion of Study III

The main results of this study were enhancement of the early SI activity and bilateral suppression of the SII activity during both execution and observation of manipulative hand actions. Only when the hand was both stimulated and moving, the responses behaved in an opposite way, in line with previous studies of somatosensory "gating" during hand motor acts (Schnitzler *et al.* 1995b; Huttunen *et al.* 1996; Forss and Jousmäki 1998).

By definition, action execution and observation have parallel effects on the MNS. Because observation and execution of hand actions had parallel effects on the SI and SII cortices, the human SI and SII cortices can be considered as parts of the human MNS, or at least as brain structures closely related to the MNS function.

5.4 Activation is enhanced in visual exstrastriate areas during observation of distorted finger postures (Study IV)

In studying brain mechanisms underlying perception of socially valid body-language cues, we compared activation of the exstrastriate visual areas when subjects observed natural *vs.* distorted finger postures.

5.4.1 Results

Most of our subjects spontaneously reported that the images of the distorted fingers were unpleasant. Figure 12 (B) illustrates examples of stimuli and Figure 12 (A) activation strengths as a function of time for the left and right occipital ROIs in one subject. At 250–700 ms, activation is stronger for distorted than natural postures as is indicated by the shaded areas between the activation curves. The insert C in Figure 12 shows that in the whole group of subjects the difference between responses to distorted *vs.* natural postures reached statistical significance ($p < 0.05$) about 260 ms after stimulus onset.

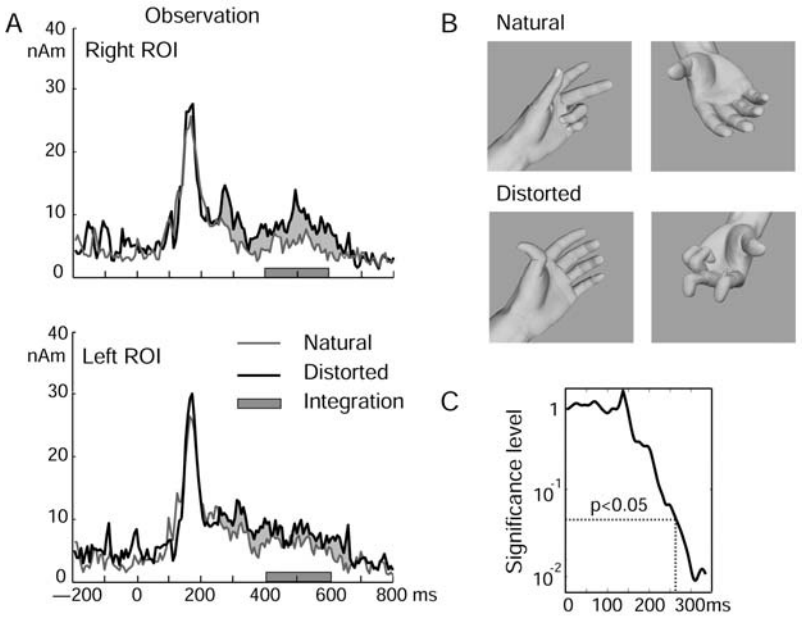

FIGURE 12 A: The mean amplitude of left and right ROIs as a function of time in one subject during observation condition. The horizontal bars indicate the time window used for quantification of the responses. B: Examples of the stimuli. C: Significance levels for differerences between cumulative amplitudes of the responses to distorted vs. natural postures (paired *t* test) plotted as a function of time. Adapted from Study IV.

Figure 13 shows the individual source strengths (mean at 400–600 ms) in the left and right ROIs for distorted finger postures as a function of the corresponding source strengths for natural postures. In both *Observation* and *Imitation* conditions, the symbols tend to be above the diagonal, implying stronger activation for the distorted than natural postures. The activations were on average 19% stronger for the distorted than natural postures (ANOVA, p = 0.02), regardless of condition.

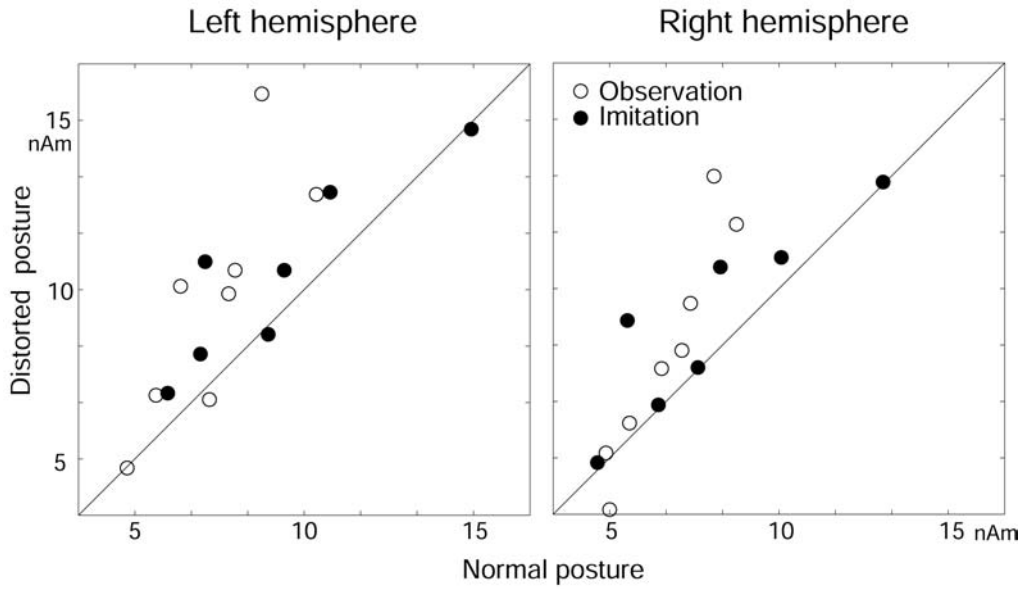

FIGURE 13 The mean source strengths at 400–600 ms for responses to distorted postures plotted as a function of the source strengths to natural postures for all subjects. Adapted from Study IV.

5.4.2 Discussion of Study IV

Our results show that the extrastriate cortices react more strongly to observation of distorted than natural finger postures. The effect started around 260 ms and was most consistent across subjects 400–600 ms after stimulus onset.

Voluntary attention affects processing throughout the visual pathways (for a review, see Treue 2001). However, it is unlikely that the stronger responses to distorted than natural finger postures would just reflect stronger voluntary attention paid on the distorted fingers. The natural and distorted postures were presented in a random order and the processing loads were in the *Observation* condition equal to both types of stimuli, (the subject performed an one-back recognition task for all stimuli) and in the *Imitation* condition, the load was even stronger for the natural postures (as only those postures had to be imitated).

The rather late (250–300 ms) onset of the difference between the distorted and natural postures and the similarity of physical salience in the hand stimuli suggests top-down modulation from other brain regions; the earliest stages in visual processing are merely bound to physical features of the stimuli that are rapidly fed forward (Roelfsema and Singer 1998; Tomita *et al.* 1999; Lamme and Roelfsema 2000; Tanaka 2001).

One plausible explanation for the enhanced extrastriate activation is related to the emotional valence of the unpleasant distorted postures. It is obvious that rather sophisticated visual processing is required before the emotional features (valence) of the stimuli become evident and before an "emotional capture" can occur. Amygdalar activation could be expected, in analogy to activations observed after threatening and fear-provoking stimuli (Breiter *et al.* 1996; Cahill *et al.* 1996; Whalen *et al.* 1998; Tabert *et al.* 2001). Interestingly, amygdalar activation by visual stimuli is associated with bilateraly enhanced activation of extrastriate cortices (Morris *et al.* 1996; Paradiso *et al.* 1999).

5.5 Mirror-image imitation is impaired in Asperger and high-functioning autistic subjects (Study V)

Mechanisms of imitation in Asperger and high-functioning autistic subjects were examined using an error analysis in a behavioural imitation task.

5.5.1 Results

Figure 14 illustrates the mean rates of error for cup, hand, and grip in *Crossed* and *Mirror-image* conditions and in both subject groups. In both autistic and control group, the end-point (cup) was imitated most correctly (mean ± SEM errors 5% ± 2.4%), whereas the largest number of errors (29% ± 3.6%) occurred with the hand grip (ANOVA $F(2,28) = 22.1$, $p < 0.001$). In the *Crossed* condition, the performance of the two groups did not differ, indicating that the autistic subjects had understood the given instructions and were capable to perform the tasks.

Normally people prefer imitation as in a mirror. Accordingly, the control subjects made significantly fewer errors in the *Mirror-image* than in the *Crossed* condition ($p < 0.001$ for the total number of errors, *t* test). However, the autistic subjects did not improve their performance in the *Mirror-image* condition and made significantly more errors than the control subjects ($p < 0.005$). The difference between the groups was significant for the grip ($p < 0.01$) and for the hand ($p < 0.01$). The same trend was seen in a linear trend analysis of variance on group by condition, which approached statistical significance (ANOVA, $p < 0.07$).

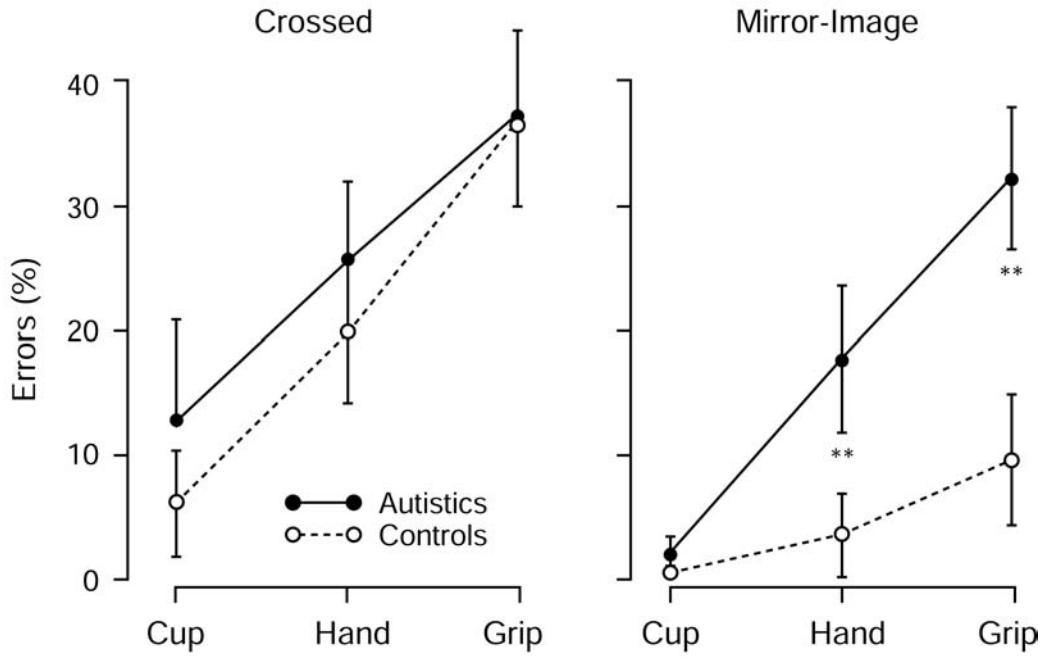

FIGURE 14 The mean error rates for both subject groups as percentage of all sequences in the Crossed and Mirror-Image conditions. Statistical significance ($p < 0.01$) is indicated with asterisks. Adapted from Study V.

5.5.2 Discussion of Study V

The results demonstrate that adult Asperger and high-functioning autistic subjects are deficient in on-line imitation of goal-directed hand movements when the imitation occurs in a mirror-image fashion, a situation which healthy subjects find the most natural one. The performance of the autistic group was not facilitated from viewing other persons' mirror-image movements, indicated by the similar error rates in the two conditions.

Spontaneous imitation of peers starts already in early childhood. Young children imitate as in a mirror (Wapner and Cirillo 1968) and only later learn to transpose the relationships between the observed person and themselves. Autistic subjects' lack of spontaneous seeking of social reciprocity and relations with others might have impaired the normal development of their imitative skills.

The autistic subjects were able to asses the behavioural goal (the cup) in a normal manner. Because the end point of the movement sequence is at the top of the hierarchy of goals guiding imitation (Gattis *et al.* 2002), it would most likely be the last step to be disturbed in subjects with an imitative deficit.

These results provide a new insight into the difficulties that autistic subjects face in viewing and understanding actions of others.

5.6 Imitation-related cortical activation sequences are abnormal in Asperger's syndrome (Study VI)

Cortical activation was compared between Asperger and healthy subjects while they imitated still pictures of lip forms.

5.6.1 Results

The motor performance of AS and control subjects differed; the mouth EMGs lasted significantly longer in the AS than the control group ($p < 0.001$), indicating prolonged imitation in the AS subjects. However, the onset latencies of the mouth EMGs did not differ between the two groups.

Five main activation areas were identified in both groups: the occipital cortex (Brodmann's area (BA) 18; Occ), the region of the STS (BA 22), the inferior parietal lobule (IPL) (BA 40), the infero-posterior frontal area (IF or Broca's area)(BA 44/45), and the M1 (BA 4) (Figure 15 B). In the control group all these areas were consistently activated, in agreement with earlier results with Japanese subjects (Nishitani and Hari 2002). In the AS subjects, the left IF area was activated in 6/8 subjects, and the right IF only in 3/8; this hemispheric difference was statistically significant (chi-squared test; $p < 0.01$).

Figure 15 A illustrates responses of one control and one AS subject from all the main activation areas in the left hemisphere. The activation progresses from the occipital area (118–121 ms), to STS, to IPL, to IF, and at last to M1. The duration of the whole activation sequence was about 230 ms in the control subjects and about 245 ms in the AS subjects. The latencies at Occ, STS, and IPL did not differ between the two groups. However, from IPL to IF, the interval was statistically significantly longer (about 60 ms in the left hemisphere, $p < 0.01$) for the AS than the control subjects. The peak latencies of all areas of the right hemisphere showed a pattern similar to those in the left hemisphere. Although there was a tendency toward a longer latency between the IF and M1 areas in AS subjects, the latencies did not significantly differ between the two groups.

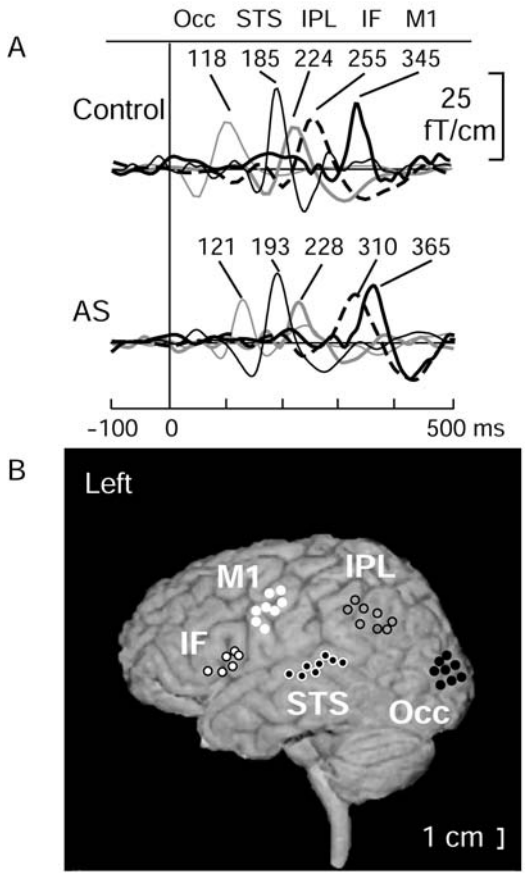

FIGURE 15 A: MEG signals of one control and AS subject from five main areas on the left hemisphere; occipital (Occ), superior temporal sulcus (STS), inferior parietal lobule (IPL), inferior frontal area (IF), primary motor cortex (M1). B: The main source locations of all AS subjects superimposed on Talairach standard brain. Each symbol represents one AS subject in each brain area. Adapted from Study VI.

The source strengths did not differ between the two groups in Occ, STS, nor IPL areas. However, the activations of both IF and M1 areas were significantly stronger in the control subjects than in the AS subjects: The median values of the IF activation were 100% stronger in controls than in AS subjects in the left hemisphere ($p < 0.05$) and 175% stronger in the right ($p < 0.01$); the corresponding values for the M1 activations were 75% ($p < 0.01$) in the left and 100% ($p < 0.05$) in the right hemisphere.

Figure 16 shows individual source strengths plotted as a function of the response latency at the IF and M1 areas. The responses tended to be both delayed and smaller in the AS than the control subjects, forming two separate clusters. The two groups were compared by calculating source strength/latency values (in units of nAm/s); the median values of the groups differed at $p < 0.01$ in the left hemisphere and $p < 0.02$ in the right hemisphere for both IF and M1 areas.

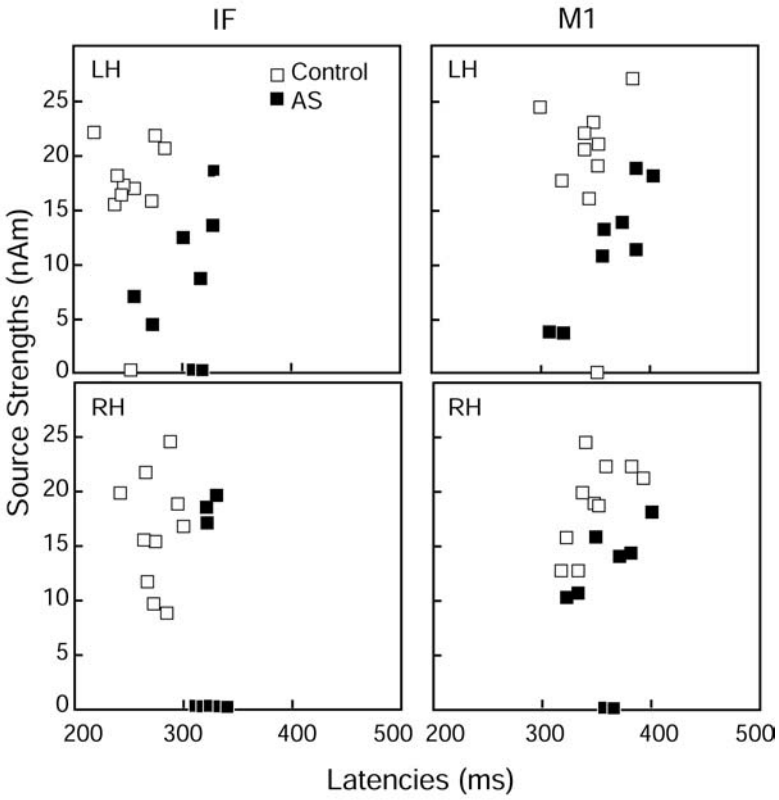

FIGURE 16 The relationship between the source strength and latency at IF and M1 areas in both hemispheres for all subjects. If a source was absent in a subject, the source strength was regarded as zero and plotted on the median latency value of each group. Adapted from Study VI.

5.6.2 Discussion of Study VI

Compared with the control group, AS subjects showed slight but statistically significant abnormalities in the cortical activation during imitation. However, the same cortical regions were activated both in AS and control subjects and there were no significant differences between the groups in the perceptual part of the activation cascade (Occipital and STS activation). Activation of the inferior frontal cortex (Broca's area in the left hemisphere and its counterpart in the right hemisphere) was in both hemispheres delayed and weaker compared with the control subjects. Furhermore, significantly less frequent activation was seen in the right than the left IF area and activation of the M1 was weaker. The duration of the mouth muscle EMG activity was significantly longer in AS subjects. However, the EMG onset latencies did not differ between the two groups and the MEG response latencies were similar at the initial stages of the activation chain (in the occipital areas, STS region, and IPL), suggesting

that the observed IF and M1 abnormalities unlikely reflect some behavioral differences between the groups.

Broca's region has both motor and linguistic functions. Subjects with Asperger's syndrome have normal language development and thus it is improbable that the observed abnormal IF activation in AS subjects would be related to language-related dysfunction of Broca's region.

The present study suggests dysfunction of the frontal parts of the mirror-neuron system (IF and M1 areas) in AS subjects.

6. GENERAL DISCUSSION

The studies of this thesis focus on mechanisms of action observation, imitation and social perception in healthy and autistic subjects. The results are further discussed in the context of cortical mechanisms for action representation and social perception.

6.1 The human mirror-neuron system

6.1.1 Is there a human mirror-neuron system?

The discovery of the mirror neurons in the monkey brain inevitably lead to the question of the existence of a human mirror-neuron system. First indirect evidence of the existence of the human MNS came from the TMS study by Fadiga *et al.* (1995) and from PET experiments by Rizzolatti and co-workers (Grafton *et al.* 1996; Rizzolatti *et al.* 1996b). Study I provided support for the human MNS and the first evidence of the involment of the primary motor cortex in it. These results were further supported by a a double-pulse TMS study by Strafella and Paus (2000). Thereafter evidence of the existence of a human mirror-neuron system has been obtained in several studies (Iacoboni *et al.* 1999; Nishitani and Hari 2000; Nishitani and Hari 2002).

The monkey mirror neurons discharge during execution and observation of different type of goal-directed hand and mouth actions. However, there is no discharge or at least the discharge is much weaker if the same movements are just mimiced without an object or if they are made with a tool (Rizzolatti *et al.* 1996a). The experimental setup used in the Studies I–III was constructed according to the knowledge from the monkey data, without prior knowledge of the sensitivity of the human MNS to different stimuli; manipulation of a small object was performed in live in the measurement room in front of the subject. This approach has later been proved to be an effective choice. More recently, the human MNS has been shown to react more strongly to movements performed in live than movements shown on a video (Järvelainen *et al.* 2001). However, in contrast to the monkey data, movements with tools seem to activate the human MNS and this activation also depends on whether or not objects are involved (Järveläinen *et al.* 2003). In addition to hand actions, mouth and foot actions, as well as still pictures of actions can activate the human MNS (Buccino *et al.* 2001; Nishitani and Hari 2002).

6.1.2 Where in the brain?

A cortical area that is active during both execution and observation of an action can be considered to have mirror properties (Rizzolatti *et al.* 2001). In the monkey brain, this type of activity has sofar been found in the F5 and PF areas. The knowledge of the extent of the monkey MNS is rather limited, since the data is merely based on single-neuron recordings that do not allow simultaneous recordings from different parts of the brain.

According to the functional imaging data the human MNS appears to be more widespread. A fMRI study by Iacoboni *et al.* (1999) showed activation in the left inferior frontal cortex (BA 44) and the right anterior parietal region during observation and imitation of finger movements; additional activation was observed also in the right parietal operculum during imitation. The activations were strongest during the imitation task. Increased activation of the parietal operculum during imitation is in line with the modulation of the SII activity during execution and observation actions in Study III. However, in Iacoboni *et al.* (1999), the parietal operculum was activated only during imitation, not during action observation. The discrepancy between the results probably results from the different sensitivities of the two techniques and the approach used in Study III (median nerve stimuli). The involment of different areas in the human MNS and the temporal pattern of activation was further studied with MEG by Nishitani and Hari (2000). During observation, execution, and imitation of grasping hand movements activation spread from the left inferior frontal frontal cortex (BA 44) to the left M1, and then further to the right M1. Activations of Broca's area and left M1 were strongest during imitation. In the fMRI study by Buccino *et al.* (2001), observation of different mouth, hand, and foot actions elicited somatotopically organized activation in the premotor areas and roughly also in the posterior parietal lobe. The parietal activation was only related to object-directed actions. Using a similar setup as in Study VI, activation was recently observed to progress in healthy subjects from the STS, to the inferior parietal lobule, and to the inferior frontal lobe, and finally, to the primary motor cortex, during both observation and imitation of static images of lip forms (Nishitani and Hari 2002). Interestingly, in a recent study by Ferrari *et al.* (2003) also monkey mirror neurons were activated by communicative mouth gestures.

Taken together, recent brain imaging studies show that the human MNS is a wide-spread cortical system that involves at least Broca's region, the primary motor cortex, and the parietal lobe. In addition, the STS region, showing activation during both

observation and imitation of hand and mouth actions, is closely connected to the MNS function. However, since STS has not been shown to be activated during just execution of an action, it can not at present be regarded as one of the actual mirror-neuron areas.The mirror-neuron-like behavior found in the SI and SII cortices suggests that the human somatosensory network can be considered as part of the human MNS, or at least as brain structures closely contributing to the MNS function. MNS activation is strongest during imitation, which links both execution and observation of the action. The temporal order of MNS activation has been shown by the MEG studies to progress from the STS region, to the inferior parietal area, then to the inferior frontal lobe and at last to the primary motor cortex (Nishitani and Hari 2002, Study VI). In the future, more studies are needed to clarify the specific role of the different cortical areas in the action representation system.

6.1.3 Problem of agency

Mirror neurons represent different actions by discharging during execution and observation of the action (Rizzolatti *et al.* 1996a). These representations have been suggested to be crucial for the knowledge of the external world (Rizzolatti *et al.* 2001). The shared representations of the executed and observed actions lead to the question that how can one distinguish who is the agent: Is it me or another person who is moving?

The information of the agent is tightly linked to the body image. Interestingly, the ability to access one's own body scheme seems crucial for making proper judgements about motor acts of other individuals, as is implied by findings that some patients with anosognosia deny other patients' paralysis (Ramachandran and Rogers-Ramachandran 1996). Percept of body image has been suggested to involve parietal and prefrontal cortices (Damasio 1996; Berlucchi and Aglioti 1997). Accordingly, activity of the SII region in the parietal operculum is modified during percepts of distorted body image (Hari *et al.* 1998). As the somatosensory cortices also have mirror properties (Study III), it seems natural that the information of the agent during MNS activation would be interrelated with somatosensory activity. In line with this view, agency judgements have been found to be associated with activity in the somatosensory cortices (Ruby and Decety 2001).

Internal simulation of movements, in order to understand the observed action, is possible only if both the motor act and its sensory consequences can be predicted. The

role of somatosensory network in the MNS could involve this efference copy signal. In line with this view, both the SI and SII cortices are activated during expectation of tickling (Carlsson *et al.* 2000).

6.1.4 Functional role of the MNS

MNS function is based, according to the direct-matching hypothesis (Rizzolatti *et al.* 2001), on mapping of the visual representation of an action onto the observer's own motor representation of the same action. This matching function has been suggested to be in involved in different behaviors, such as action understanding, imitation, attributing mental states, and even in some aspects of language. In action understanding, the motor knowledge of the observer is used for understanding and recognizing actions of others (Rizzolatti *et al.* 2001). In line with this assumption, in a PET study by Grezes *et al.* (1998) the premotor areas were stronger activated during observation of meaningful arm actions, when the subjects had to undertand the purpose of the actions than when they just had to imitate the actions.

The term imitation can be used to describe many kind of functions in biology, sociology and psychology. When simple defined as copying by an observer of an action performed by a model, the underlying neural mechanism has been proposed to be based on the MNS (Iacoboni *et al.* 1999; Nishitani and Hari 2000; Rizzolatti *et al.* 2001; Nishitani and Hari 2002; Wohlschläger and Bekkering 2002). The function of the MNS may involve different imitative phenomena, such as 'response facilitation' (an automatic tendency to reproduce observed movements) including release phenomena in birds and yawning, laughing and neonatal imitation in humans (Meltzoff and Moore 1977), further to higher order imitation and imitative learning (Rizzolatti *et al.* 2001; Wohlschläger and Bekkering 2002).

The possible role of the MNS in other complex cognitive functions, such as language (Rizzolatti and Arbib 1998) and mind-reading (Gallese and Goldman 1998), has also been discussed. In line with the motor theory of speech perception (Liberman and Mattingly 1985; Liberman and Whalen 2000), suggesting that successful linguistic communication is not dependent on sound, but rather on a neural link between the sender and the receiver that allows production of phonetic gestures, Rizzolatti and Arbib (1998) proposed that the action execution/observation matching system could have served as the neural prequisite for the development of interindividual communication and finally speech. Interestingly, in a recent study by Petitto *et al.*

(2001), babies with profoundly deaf parents were shown to convey a kind of silent linguistic babling with their hand movements.

Gallese and Goldman (1998) have proposed that the ability to detect and recognize mental states of others could have evolved from the MNS. According to one of the dominant mind-reading theories, the simulation theory (Davies and Stone 1995), other person's mental states are detected by matching their states with resonant states of one's own. Shared representations of different actions could serve as the basis of getting the observer into the same 'mental shoes' as the target (Gallese and Goldman 1998). According to the simulation theory, all mental states requiring TOM, irrespective of whether they are are attributed to others or to oneself, should involve same neuronal system. However, in a fMRI study by Vogeley *et al.* (2001), modeling ones own mental-states activated at least in part dintinct brain regions than modeling the mental-states of others, opposed to the basic idea of simulation.

Although the relation of the MNS to different cognitive functions is still merely speculative, the discovery of the mirror neurons has offered a new tool to investigate brain function in our social enviroment. Future goals in this field include mapping of all brain areas involved in the mirror-neuron system and obtaining more information about their precise role in it. Futhermore, more information is needed about different stimulus types and modalities that are able to evoke mirror-neuron type activation, about the connection of the mirror-neuron system with different cognitive capacities, and about the possible role of a dysfunctional mirror-neuron system in different patient groups.

6.2 Autism

The autism spectrum disorders are a group of neurodevelopmental disorders that have a great variability in their clinical presentation but alltogether share some core symptoms, such as social impairment, deficits in communication, and restrictive pattern of behaviour. Autism has been a great challenge for neuroscience during the last decade. Although a lot has been learned since the time when it was thought to be a psychogenic syndrome caused by "refrigerator mothers", the rapidly growing body of literature reports very heterogenous findings and theories about the basis of autism. Abnormalities have been observed in many brain regions. However, not all subjects with autism show any abnormalities *e.g.* in structural or functional brain imaging, and none of the found abnormalities characterizes all subjects. In spite of the intensive

research, we still don't know whether autism is a single syndrome varying in severity or whether the autism spectrum of disorders have multiple etiologies that nonetheless lead into similar core symptoms.

Autism is a rather common syndrome affecting about 0.7% of the general population of children and adolescents (Gillberg and Wing 1999). Since it is a lifelong disorder with severe deficits in social interaction and communication and since many of the subjects have psychiatric and neurologic comorbidities, there is a great need for long-term institutional, medical, educational and psycho-social care. The costs for the individuals, the families and the society are significant. Even subjects at the able end of the disorder often have problems in coping independently due to the social deficits that make their every-day life difficult. Sofar the treatment in autism merely includes rehabilitation and symptomatic medication, no curative treatment exists. Although these means can of course relieve comorbid symptoms and help the subjects and families to manage in every-day life, there is evidence (Gillberg and Billstedt 2000) that the core features of autism do not change much over time. On the other hand, most of the intensive rehabilitation has only been performed during the last decade, and randomised follow-up studies of these interventios are merely lacking. Most effective results have sofar been obtained from early and highly intensive intervention programmes (Howlin *et al.* 1995).

6.2.1 Autism and mirror neurons

None of the cognitive theories of autism (such TOM, weak central coherence and executive function deficit) has proven to be exclusive and none has been able to explain the whole range of symptoms found in autism. Most theories focus on social symptoms, since in spite of the wide clinical variation all subjects with autism spectrum disorders suffer from social deficits. However, the neural basis of the deficit is largely unknown.

The discovery of mirror neurons has lead to hypothesis of their role in social cognition (Gallese and Goldman 1998; Rizzolatti *et al.* 2001; Williams *et al.* 2001). Especially, when evidence of the human counterpart of the monkey mirror neurons was found, a question of the possible dysfunction of the MNS in conditions associated with social impairments, such as autism, was raised. Dysfunction of the MNS could lead in impairments in imitation, action understanding and further in difficulties in using and understanding body-language, mentalising, joint attention and even some aspects of

language (Williams *et al.* 2001). Total dysfunction, partial dysfunction, a dysfunction in certain parts of the MNS, or a developmental delay could all be in question.

In Studies II, V, and VI the hypothesis of possible connection between MNS and autism was tested. Study II showed rather normal activation of the primary motor cortex in a group of AS subjects both during observation and execution of manipulative hand actions, in spite of the deficit in their TOM abilities. The results exluded the possibility of a total dysfunction of the MNS in Asperger subjects. Furthermore, no evidence was found of the connection between a TOM deficit and MNS dysfunction. However, the number of subjects was small (N = 5) and although no statistically significant differences were observed, a slight tendency was evident toward a weaker activation of the M1 in AS subjects.

In Study V, the AS and HFA subjects' imitation abilities were examined by using a behavioural task. Recent evidence suggests that human imitation is based on the mirror-neuron system (Iacoboni *et al.* 1999; Nishitani and Hari 2000; Wohlschläger and Bekkering 2002). Normally people tend to imitate as in looking at a mirror (Bekkering *et al.* 2000; Iacoboni *et al.* 2001) and observation of movements in a mirror-image view speeds up performance also in non-imitative tasks (Brass *et al.* 2000; Brass *et al.* 2001). However, Study V showed that AS and HFA subjects are impaired in goal-directed imitation, when the imitation occurs in a mirror-image fashion. As certain aspects of imitation, such as imitation requiring self-other visual transformations, are most susceptible for MNS function (Williams *et al.* 2001), a developmental delay or a dysfunction of the MNS could explain the observed results.

In Study VI, the hypothesis of a MNS dysfunction in autism was tested further by recording cortical activations while AS subjects imitated orofacial gestures. The results showed abnormal activation in the IF and M1 areas. As the the human mirror-neuron areas (the inferior parietal region, the Broca's region and the M1) are activated in sequence, dysfunction of both frontal and parietal part of the MNS could explain the delayed and weaker activation of the IF and M1 areas. Broca's region, the homologue of monkey F5 area, is activated during observation, execution and imitation of hand and mouth movements (Iacoboni *et al.* 1999; Nishitani and Hari 2000; Nishitani and Hari 2002) and considered as an essential part of the human MNS. Dysfunction of the IF part of the MNS could affect social abilities via connections to the orbitofrontal cortex and to the anterior ventral medial frontal region that are considered to contribute to theory of mind.

The STS region is closely connected to the MNS function and it has an important role in perception of many kind of socially relevant visual stimuli (for a review, see Allison *et al.* 2000; Puce and Perrett 2003). Interestigly, the STS region is also activated in tasks requiring mentalising (McGuire *et al.* 1996; Gallagher *et al.* 2000). In line with these results, autistic children, have been shown to be impaired in visual recognition of biological motion (Blake *et al.* 2003). In a PET study by Castelli *et al.* (2000), activations of the STS and medial prefrontal cortex were weaker in autistic than in control subjects during a mentalising task, whereas the activity of the exstrastriate cortices did not differ from the controls. However, in Study VI activation of the occipital and STS areas did not differ between AS and control subjects. This discrepancy probably reflects different activation cascades within the STS region; perception of an mouth and hand actions in order to imitate might be intact in the STS level in AS subjects, whereas processing of more abstract and complex social stimuli (such as cartoons and stories of TOM) could be affected. Accordingly, perception of goal-directed hand actions was found to activate the caudal STS and the intraparietal sulcus, whereas perception of expressive whole-body motion activated the rostrocaudal STS, as well as the limbic structures, including the amygdala (Bonda *et al.* 1996).

Subjects in Studies II, V, and VI were adults and had AS (except one subject in Study II and two subjects in Study V who were autistic) representing the able end of the autism spectrum disorders. This subject group was chosen, since MEG recordings require some co-operation from the subjects, especially when tasks involve active participation. Additionally, the subjects have to keep their heads steady during the measurement to avoid movement artefacts and to enable identification of accurate source locations. Futhermore, in the AS group the amount of other factors that could affect the results, such as medication, comorbidities and language problems, is at minimum. Adult subjects were studied, because the knowledge of MEG responses in children and adolescents is still rather limited. However, in adults with the most "mildest" form of the disorder, the size of the effect could be smaller than in more severely affected subjects. On the other hand, although most AS and high-functioning autistic subjects, are of normal intelligence, they suffer from social difficulties, which according to the MNS hypothesis are just the symptoms that are linked with the MNS function.

Altogether, the results from Studies II and VI suggest that MNS dysfunction can account for a part of the imitation and social impairments in subjects with Asperger's

syndrome. Since we only studied able adult subjects, it would be interesting in the future to examine MNS function in more affected and younger subjects. Furthermore, modulatory influences from the prefrontal theory-of-mind regions on the MNS should be evaluated.

In autism research, lack of replication of studies, small and heterogenous experimental groups and poor control of other confounding variables have for long been a problem, therefore future studies should attempt to investigate more homogeneous subgroups within the autism spectrum disorders. Effective communication between reseachers on this field will help to integrate and update the diagnostic criteria for the different subgroups. The studies should also aim at integrating information from different fields of the research, such as genetics, functional imaging and neuropsychology. Hopefully, in the near future we are able to understand much better the biological mechanisms underlying the mystery of autism.

6.3 Social perception in the exstrastriate cortices

The brain basis of social communication is complex: The stimuli are highly variable, and the responses strongly depend on the context, emotional state, and motivation of the subject. In social perception face and finger stimuli have an important role. Recognition of both stimuli is overlearned during development and distorted images evoke disgust, fear, and other negative emotions. Thus, these stimuli could be processed along similar pathways, via visual and limbic cortices (Brothers *et al.* 1990; Morris *et al.* 1996; Pessoa *et al.* 2002; Yang *et al.* 2002; Geday *et al.* 2003). Studies on the time course of face processing have shown that some coarse categorization can occur already around 100 ms (Liu *et al.* 2002), whereas more detailed processing, such as identity, requires around 170 ms in the exstrastriate cortices (Sams *et al.* 1997; Halgren *et al.* 2000; Liu *et al.* 2002). Activation of amygdala by neutral faces has been observed already around 120 ms (Halgren *et al.* 1994), and by emotional faces around 180 ms (Streit *et al.* 2003). The results of Study IV agree with with top-down modulation from amygdala to extrastriatal areas, starting 250–300 ms after stimulus onset. The distorted postures did not differ from the natural postures in physical salience, therefore rather sophisticated visual processing is required before the emotional features of the stimuli become evident.

Social perception involves a distributed interacting neural network including visual, temporal and limbic structures and higher frontal regions, such as the orbitofrontal and the prefrontal cortices. All stages of processing (initial feed-forward, later top-down modulation

from higher regions) form a dynamic and complex circuitry that ables us to interact with others in our social enviroment.

7. SUMMARY

MEG enables measuring of temporal dynamics of cortical functions non-invasively at a millisecond scale. In the present thesis, MEG was used to study modulation of cortical motor and somatosensory functions, spontaneous brain activity, and the time courses of activation in cortical networks supporting imitation and social perception.

In Studies I and II, the reactivity of the rolandic ~20-Hz activity was used to probe the functional state of the primary motor cortex in both healthy and autistic subjects. In Study I, the level of the ~20-Hz activity was significantly modified during both object manipulation and observation of the same action, indicating activation of the primary motor cortex in both conditions. This study supported the existence of a human mirror-neuron system and provided the first evidence of the involvement of the primary motor cortex in it. Although the autistic subjects studied in Study II were deficient in their theory-of-mind ability, the reactivity of their ~20-Hz activity was similar as in healthy subjects, suggesting that the deficit of theory of mind in autism is not related to markable dysfunction of the motor-cortex part of the action execution/observation matching system.

In Study III, the activity of the SI and SII cortices was similarly modified during both performing and observing of manipulative hand actions (with the exception of areas directly involved in monitoring the hand that is both stimulated and moving). The results suggest that the somatosensory cortical network can be considered to have mirror properties, and the findings support the idea of a widespread mirror system in humans.

The cortical mechanisms of perception of hand postures were investigated in the Study IV. Activity of the exstrastriate occipital areas was bilaterally enhanced, starting around 260 ms after the stimulus onset, when subjects observed unnatural distorted finger postures. The enhancement of the exstrastriate activity probably reflects top-down modulation of the visual cortices from the amygdala, due to emotional valence of the distorted hand postures.

The behavioral experiment of Study V showed that Asperger and high-functioning autistic subjects have a special deficit of imitation, lacking the natural preference for

imitating in a mirror-image fashion. The results support the hypothesis of possible MNS dysfunction in autism.

In Study VI cortical dynamics of healthy and Asperger's syndrome subjects was studied while subjects imitated still pictures of orofacial gestures. Activation of the inferior frontal lobe was both delayed and weaker and activation of the primary motor cortex weaker in AS than in healthy subjects. The results imply abnormal premotor and motor activation in AS subjects during imitation and suggest a connection between MNS dysfunction and the social and imitation deficits found in autism.

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