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**IMAGING LANGUAGE FUNCTION WITH MEG
AND FMRI**

Doctoral Dissertation

Mia Liljeström



**Aalto University
School of Science and Technology
Low Temperature Laboratory
Brain Research Unit**

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Mia Liljeström

Doctoral dissertation for the degree of Doctor of Science in Technology to be presented with due permission of the Faculty of Information and Natural Sciences for public examination and debate in Auditorium F239a at the Aalto University School of Science and Technology (Espoo, Finland) on the 28th of May 2010 at 12 noon.

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School of Science and Technology
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Brain Research Unit**

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Abstract <p>This Thesis considers the cortical mechanisms underlying language function, as measured by magnetoencephalography (MEG) and functional Magnetic Resonance Imaging (fMRI). In MEG, interpretation of the data critically depends on the ability to estimate the underlying neural activity and localize it to a certain part of the brain. In this Thesis, the accuracy of this procedure is explored in localization of cortical rhythms and for different head conductor models. A comparison of different source modeling techniques shows that rhythmic activity can be identified reliably with a variety of tools, such as equivalent current dipoles (ECDs), minimum norm approaches (MCE_{FD}, minimum current estimates in the frequency domain), and beamformers (DICS, dynamic imaging of coherent sources). The results show that DICS is more sensitive to weak sources than the two other methods, both in measured and in simulated data. Computer simulations also demonstrate that for source localization performed under normal noisy conditions, a simple spherically symmetric head conductor model is in most cases a sufficient model for the conductivity geometry of the head.</p> <p>This Thesis specifically considers the cortical processing of action and object naming. We investigate whether different cortical regions are activated when actions or objects are named from the same images, and how the content of the image affects the brain correlates of naming. The MEG and fMRI results presented in this Thesis indicate that verbs and nouns are processed within the same cortical network, and demonstrate that image category (action/object) has a stronger influence than naming category (verb/noun) on the activation pattern within this network.</p> <p>In addition, we consider the relationship between MEG evoked responses and fMRI BOLD (blood-oxygen-level-dependent) signals in language tasks. We demonstrate differences between these two measures in both picture naming and reading, and show that such differences do not depend on experimental procedures such as different participants, languages, or task. In particular, we demonstrate an opposite stimulus effect for symbols and letter strings in the left occipito-temporal cortex in MEG vs. fMRI in reading, although the simultaneously measured electroencephalogram (EEG) was similar. We argue that the observed differences within this region reflect different neural generation mechanisms of the MEG evoked response and fMRI BOLD signals.</p>		
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Denna avhandling använder funktionella avbildningstekniker, såsom magnetoenkefalografi (MEG) och funktionell magnetavbildning (fMRI, functional magnetic resonance imaging), för att kartlägga hur språkliga funktioner bearbetas i hjärnan. Avhandlingen strävar efter att ge en mångfacetterad bild av både metoder och kognitiva frågor inom funktionell avbildning. Ett centralt problem inom MEG är att identifiera de områden i hjärnan som gett upphov till det uppmätta magnetfältet. Denna avhandling utvärderar olika metoder för identifiering av kortikala rytmer. Resultaten visar att kortikala rytmer kan lokaliseras tillförlitligt med hjälp av ett flertal olika metoder, såsom ekvivalenta dipolmodeller (ECD), minsta norm metoder (MCE _{FD}) och spatialfilter (DICS). Jämförelsen visar att DICS kan identifiera områden med svaga kortikala rytmer som de övriga metoderna inte förmår identifiera. Vidare demonstrerar en granskning av olika modeller för att beskriva huvudets konduktivitetsprofil att en enkel sfärisk modell oftast är tillräcklig då man löser det inversa problemet.				
Avhandlingen granskar särskilt bearbetning av verb och substantiv i hjärnan, samt hur olika typer av bilder som illustrerar en utförd handling eller ett enskilt föremål påverkar aktiviteten i hjärnan vid benämningen av en bild. Resultaten från både MEG och fMRI påvisar att verb och substantiv bearbetas i ett gemensamt nätverk av områden i hjärnan. Inom detta nätverk har dock bildens innehåll (en handling/ett föremål) en större betydelse för aktiviteten än vilken kategori av ord (verb/substantiv) som skall benämñas.				
Därtill undersöks förhållandet mellan BOLD (blood-oxygen-level-dependent) signalen i fMRI och framkallade responser i MEG. Resultaten påvisar skillnader mellan dessa metoder vid benämning av bilder och läsning som inte går att förklara med olikheter i experimentella tillvägagångssätt, t.ex. uppgift, språk, eller försökspersoner. Avhandlingen demonstrerar att MEG och fMRI kan uppvisa rakt motsatta effekter för symboler och bokstavskombinationer i vänstra temporal-occipitala hjärnbarken vid läsning, trots att det samtidigt uppmätta elektroenkefalogrammet (EEG) inte påvisade skillnader. Resultaten tyder på att BOLD-signalen i fMRI och de framkallade responserna i MEG i detta fall härför sig till skilda neurala mekanismer.				
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Academic dissertation

Imaging language function with MEG and fMRI

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List of publications

This Thesis consists of an overview and the following publications:

- P1** **Liljeström M**, Kujala J, Jensen O, Salmelin R, 2005. Neuromagnetic localization of rhythmic activity in the human brain: a comparison of three methods. *Neuroimage* 25:734–745.
- P2** Tarkiainen A, **Liljeström M**, Seppä M, Salmelin R, 2003. The 3D topography of MEG source localization accuracy: effects of conductor model and noise. *Clinical Neurophysiology* 114:1977–1992.
- P3** **Liljeström M**, Tarkiainen A, Parviainen T, Kujala J, Numminen J, Hiltunen J, Laine M, Salmelin R, 2008. Perceiving and naming actions and objects. *Neuroimage* 41:1132–1141.
- P4** **Liljeström M**, Hultén A, Parkkonen L, Salmelin R, 2009. Comparing MEG and fMRI views of action and object naming. *Human Brain Mapping* 30:1845–1856.
- P5** Vartiainen J, **Liljeström M**, Koskinen M, Renvall H, Salmelin R, 2010. MEG and fMRI reveal different activation patterns in reading. *TKK Report; TKK-KYL-022*.

Contributions of the author

The publications included in this Thesis are all the result of a group effort. I was the principal author in publications P1, P3, and P4, and actively participated in the writing of the manuscripts in publications P2 and P5. I performed the main data analysis in publications P1, P3, and P4 and participated in the data analysis in publication P5. I prepared the head conductor models in publication P2, and performed preliminary noiseless simulations. I was responsible for carrying out the fMRI and MEG recordings in publications P1, P3, and P4, and actively participated in the fMRI, MEG and EEG recordings of publication P5.

Abbreviations

BEM	Boundary element model
BOLD	Blood-oxygen-level-dependent
DICS	Dynamic imaging of coherent sources
dSPM	Dynamic statistical parametric mapping
EEG	Electroencephalography
ECD	Equivalent current dipole
EOG	Electro-oculogram
EPI	Echo planar imaging
erDICS	Event-related dynamic imaging of coherent sources
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
GLM	General linear model
iEEG	Intracranial EEG
IFG	Inferior frontal gyrus
LFP	Local field potentials
MEG	Magnetoencephalography
MCE	Minimum current estimate
MCE _{FD}	Frequency-domain MCE
MNE	Minimum norm estimate
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MUA	Multi-unit spiking activity
NMR	Nuclear magnetic resonance
pSPM	Power statistical parametric map
RF	Radio frequency
ROI	Region-of-interest
SAM	Synthetic aperture magnetometry
SNR	Signal-to-noise ratio
STG	Superior temporal gyrus
SUA	Single-unit spiking activity
SQUID	Superconducting quantum interference device
TE	Echo time
TR	Repetition time
V1	Primary visual cortex
VWFA	Visual word-form area

Preface and acknowledgements

This work was carried out in the Brain Research Unit and in the Advanced Magnetic Imaging Center of the Low Temperature Laboratory at Aalto University School of Science and Technology (formerly Helsinki University of Technology).

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Vuokko has kept me going also during those days that caffeine and love for science have not been enough to drive my motivation.

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Mia Liljeström

1 Introduction

One of the most intriguing and complex of human cognitive skills is our ability to understand and produce language. Early studies investigating the neural basis of language function were restricted to very rare circumstances, such as intracortical recordings in patients undergoing surgery, or to comparing neuropsychological symptoms and region of brain lesion. During these past two decades, advances in non-invasive brain imaging methods have given us the opportunity to venture into the healthy human brain. As damage to the brain may alter the way a task is processed, this has been a clear advantage.

What we can measure significantly constrains our understanding of the underlying neural processes. In neuroimaging, a range of techniques have been developed, each of which has its own strengths and weaknesses. In this Thesis, we have used three different techniques to study language function, namely functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and, to a lesser extent, electroencephalography (EEG). fMRI relies on local blood flow changes, reflecting the overall change in blood oxygenation between two experimental conditions with millimeter precision, typically integrated over a long time of ongoing processing. fMRI thus measures neural activity only indirectly (the so called blood-oxygen-level-dependent, or BOLD, signal). In contrast, MEG and EEG provide direct measures of synchronized neural activation with millisecond resolution, by measuring the magnetic field produced by neuronal currents, or the electric potential at the surface of the head, respectively. Lately, fMRI has been the fastest growing neuroimaging technique, due to its excellent spatial resolution and the availability at many research centers. Yet, the poor time resolution is a real limitation. The excellent temporal resolution in MEG and EEG, on the other hand, provides the means to study the timing of neural activity. However, in the latter methods the location of the underlying neural activity cannot be inferred with certainty.

At best, by applying different techniques that complement each other to studying language, we can address complex issues that may be beyond the scope of a single technique. Together, these techniques may provide us with detailed information both on the location and the timing of cortical processing. Due to the different nature of the signals, it is possible that MEG and fMRI are sensitive to different components of the overall neural activity, particularly in tasks that reach beyond early sensory processing or basic motor performance.

Analysis of brain-damaged patients with specific deficits has played an important role in deducing the roles of cortical regions involved in language function. The observation that some patients display a disproportionate difficulty in processing verbs, while others have a deficit in processing nouns, served as a framework for the experimental setup in our picture naming studies. Our experiments addressed the differences and similarities in naming verbs (actions) and nouns (objects) in healthy subjects using fMRI and MEG.

1.1 Aims and outline of the Thesis

This Thesis considers the cortical mechanisms underlying language function using three neuroimaging techniques, MEG, EEG, and fMRI. In particular, the three main goals were to investigate: (i) source localization accuracy in MEG (Studies P1, P2) (ii) cortical processing of action and object naming (P3, P4), and (iii) the correspondence between MEG evoked responses and fMRI BOLD signals in language tasks (P4, P5).

An ongoing question in MEG and EEG research is the functional significance of cortical oscillatory activation in specific frequency bands. Methodological advances in source modeling have offered new possibilities for localizing the generators of cortical rhythmic activity in MEG. Study P1 aimed at comparing the performance of three different inverse solutions for localizing rhythmic activity.

The source localization accuracy in MEG depends on several factors, such as the signal-to-noise ratio and the accuracy of the conductor model used to describe the conductivity geometry of the head. The goals of Study P2 were to investigate the effect of different head conductor models on source localization accuracy, and to study how the presence of noise affects the source localization performance.

Studies P3 and P4 investigated fMRI and MEG activations in picture naming. The participants named objects and actions from images that illustrate a simple event. In addition, objects were named from images depicting an object, without an associated action. These two experiments aimed at investigating whether different cortical regions are activated when actions or objects are named from the same images, and how the content of the image affects the brain correlates of naming.

Different functional brain imaging methods may give at least partly complementary information. Studies P4 and P5 investigated the similarities and differences between MEG and fMRI measures in two complex cognitive tasks, picture naming and reading. These studies focused on the correspondence (or lack of it) between MEG evoked responses and the fMRI BOLD activation. The aim was to study how well the results from the two different methods converge when the experimental design and the subjects are exactly the same.

In the following chapters, I will outline these experiments and the relevant background information. The basic principles of MEG and EEG are described in Chapter 2, whereas Chapter 3 discusses experiments P1 and P2. Chapter 4 gives an introduction to the basic principles of fMRI and reviews the literature on the neural basis of the BOLD signal. Chapter 5 considers the neural mechanisms of language production, as measured by picture naming, and language comprehension, through processing written words. In addition, the current literature on verb and noun processing in the brain is reviewed and experiments P3 and P4 are discussed. Chapter 6 considers the combined use of MEG and fMRI and the results from Studies P4 and P5. In Chapter 7 the main findings and some future directions are discussed.

2 Magnetoencephalography and electroencephalography

Magnetoencephalography (MEG) is a completely noninvasive method which detects the weak magnetic fields created by synchronous electrical activation of thousands of neurons. The measurement is conducted outside the head using extremely sensitive SQUID (superconducting quantum interference device) sensors (Zimmermann et al., 1970). The first MEG measurements using SQUID sensors were reported in 1972 by David Cohen (Cohen, 1972), who measured the spontaneous rhythmic activity of a healthy subject and an epileptic patient. Nowadays, measurements are performed using whole-head systems which can detect the magnetic field at multiple locations outside the head simultaneously with millisecond temporal resolution. The locations of the underlying cortical activity can be estimated from the measured magnetic fields.

MEG and electroencephalography (EEG) are two complementary techniques. Whereas MEG measures the magnetic field produced by neural activity, EEG measures the scalp electric potentials produced by the same neural activity.

2.1 MEG and EEG signal generation

Neural currents

Neurons are the functional units of the nervous system. They generate and conduct electrical changes in the form of nerve impulses. Neurons consist of a cell body, or soma, numerous dendrites, which receive afferent signals, and an axon which transfers signals to other cells. The neuron is enclosed by a cell membrane, which separates the tissue into intracellular and extracellular compartments with different ion concentrations, maintaining a resting potential across the membrane. In human neurons the resting membrane potential is approximately -70 mV .

The functional role of a neuron is mainly defined by its connections. There are typically thousands of synapses connecting to a single neuron. When an electrical signal arrives at the synapse, the presynaptic neuron releases neurotransmitters, which diffuse to the postsynaptic cell membrane, causing a postsynaptic potential. Excitatory connections cause a depolarization, whereas inhibitory connections cause a hyperpolarization of the cell membrane. The effects of the postsynaptic potentials are integrated both spatially and temporally and, if the membrane potential reaches a certain threshold at the initial segment of the axon, an action potential is fired.

The electric currents produced by neuronal activity produce weak electromagnetic fields, which are measurable outside the head. The postsynaptic potentials are of much lower voltage than action potentials, but they last longer and involve a larger surface area, making the temporal summation of postsynaptic currents flowing in neighboring dendrites highly effective. The current distribution of the postsynaptic potential can be represented by a current dipole oriented along the dendrite, whereas the current pattern of a propagating action potential can be

described as two oppositely directed dipoles traveling along the axon (Hämäläinen et al., 1993). In an infinite homogeneous conductor, the dipolar electromagnetic field of the postsynaptic potential is attenuated in proportion to $1/r^2$, whereas the quadrupolar field of the action potential is attenuated in proportion to $1/r^3$. The electromagnetic field of the postsynaptic potential can thus be detected farther away from the source.

Measurable electromagnetic signals are believed to be generated by the postsynaptic potentials of pyramidal cells (Murakami and Okada, 2006). Pyramidal cells are large neurons with dendrites reaching out in parallel to each other. Activation of several excitatory synapses causes a net current perpendicular to the cortical surface. Hence cortical activity within sulci produces currents which are oriented tangentially with respect to the surface of the head, whereas activation within the gyri produces current sources that have a radial orientation. This has implications for MEG and EEG sensitivity profiles, MEG being more sensitive to activation in sulci, whereas EEG detects activation in both sulci and gyri (Hämäläinen et al., 1993). A measurable signal is estimated to be generated when (tens of) thousands of neurons are synchronously activated (Murakami and Okada, 2006).

Evoked responses vs. rhythmic activity

The most frequently used neurophysiological measures are so called evoked responses which are time- and phase-locked to stimuli or tasks. To resolve the evoked responses against the ongoing background activation stimulus-locked averaging across multiple trials is usually required. The first measured MEG evoked responses were recorded in 1975 in response to simple sensory stimulation (Brenner et al., 1975). From early studies focusing on fairly simple sensory responses, experimental designs employing evoked responses are now being applied also to highly complex cognitive tasks (e.g. Salmelin et al., 1994; Helenius et al., 1998).

Another approach is to study the ongoing background, or rhythmic activity. Rhythmic activity, i.e. synchronized oscillatory activation of neural populations, produces electromagnetic fields at a number of different frequencies. These rhythmic oscillations are the most prominent feature of the background MEG or EEG. The first recordings of rhythmic activity were made by Berger with EEG, who recorded the 10 Hz alpha rhythm over posterior parts of the brain (Berger, 1929). The mu rhythm, detected over the primary sensory and motor cortices, was first measured in the 1950s (Gastaut, 1952; Chatrian et al., 1959). Importantly, the cortical rhythms display clear stimulus- and task-specific reactivity, and a variety of different tasks have been shown to induce changes in the ongoing cortical rhythms. For example, the posterior alpha rhythm is strongest when the subject has his eyes closed, and is dampened by opening the eyes, whereas limb movements or tactile stimulations suppress the mu rhythm (Salmelin and Hari, 1994b; Salmelin et al., 1995). Task-related changes in gamma band activity (30–100 Hz) have been recorded from multiple brain regions, and have been proposed to have a role in various cognitive functions, such as early visual processing (Adjamian et al., 2004), visual search (Tallon-Baudry et al., 1997), and attentional selection (Fries et al., 2001), whereas theta band activity (4–8 Hz) has been suggested to play a role in memory processing (Osipova et al., 2006). In Study P1, we investigated source localization of cortical rhythmic activity.

2.2 Source localization in MEG

The inverse problem in MEG and EEG is the estimation of the underlying current distribution from the known magnetic field or electric potential. In this Thesis the current generators were not localized using EEG, therefore this section considers mainly MEG source localization, although many of these considerations apply to EEG as well.

The forward problem

To solve the inverse problem, we must first solve the forward problem, i.e. calculate the magnetic field outside the head, given a primary current distribution within the brain. If the primary current sources and the distribution of the electromagnetic parameters are known, the magnetic fields can be calculated from Maxwell's equations. Neuromagnetic signals are generally relatively slow (below 1000 Hz). Consequently, a quasi-static approximation of Maxwell's equations can be made. In a quasi-static approximation, the magnetic field $\mathbf{B}(\mathbf{r})$ at the point \mathbf{r} can be calculated with the Ampère–Laplace law

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \frac{\mathbf{J}(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} dv', \quad (2.1)$$

where $\mathbf{J}(\mathbf{r}')$ is the current density at the source point \mathbf{r}' . The permeability of the tissue is approximately the same as for free space, i.e. $\mu = \mu_0$.

The total current density $\mathbf{J}(\mathbf{r}')$ can be divided into two components, the primary current $\mathbf{J}_p(\mathbf{r}')$, and the volume current $\mathbf{J}_v(\mathbf{r}') = \sigma(\mathbf{r}')\mathbf{E}(\mathbf{r}')$. Here, σ is the conductivity of a macroscopic conductor and \mathbf{E} is the electric field. The primary currents inside or in the vicinity of a cell are caused by neural activity, while the volume currents are passively flowing ohmic currents that result from the effect of the electric field on the charge carriers in the conducting medium. Consequently, the source of brain activity is found by locating the primary current. In the quasi-static approximation, the electric field is determined by the negative gradient of the scalar potential V as $\mathbf{E} = -\nabla V$. Thus, the current density can be expressed as

$$\mathbf{J} = \mathbf{J}_p + \sigma\mathbf{E} = \mathbf{J}_p - \sigma\nabla V. \quad (2.2)$$

From the quasi-static approximation we get $\nabla \cdot \mathbf{J} = 0$. Now, taking the divergence from Equation (2.2) we find that

$$\nabla \cdot (\sigma\nabla V) = \nabla \cdot \mathbf{J}_p. \quad (2.3)$$

For a current density that approaches zero sufficiently fast when \mathbf{r}' approaches infinity the magnetic field can be obtained from (Hämäläinen et al., 1993)

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \frac{(\mathbf{J}_p + V\nabla' \sigma) \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} dv'. \quad (2.4)$$

Here, the first term is due to the primary current and the second is due to the volume current, where σE is replaced by an equivalent current $V\nabla' \sigma$. For solving Equations 2.3 and 2.4 an appropriate conductor model must be chosen. Equation 2.3 is then solved for V with proper boundary assumptions. Once V is known \mathbf{B} can be calculated using Equation 2.4.

Spherically symmetric conductor models

Typically, the head is modeled by a spherically symmetric conductor, which provides an analytical solution to the forward problem. In a spherically symmetric conductor, the volume currents do not contribute to the radial component, $\mathbf{B}_r = \mathbf{B}(\mathbf{r}) \cdot \mathbf{e}_r$, of the magnetic field (Hämäläinen et al., 1993), and \mathbf{B}_r can be calculated from Equation 2.1 by replacing \mathbf{J} by the primary current \mathbf{J}_p ,

$$\mathbf{B}_r(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \frac{\mathbf{J}_p(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \mathbf{e}_r dv'. \quad (2.5)$$

It can be shown (Hämäläinen et al., 1993) that the whole field \mathbf{B} can be derived from its radial component. By integrating the radial component of the magnetic field the magnetic scalar potential U is obtained,

$$U(\mathbf{r}) = \frac{1}{\mu_0} \int_{t=1}^{\infty} \mathbf{B}_r(t\mathbf{r}) dt. \quad (2.6)$$

The resulting magnetic field can then be calculated from $\mathbf{B} = -\mu_0 \nabla U$.

For symmetry reasons, radial currents do not produce a magnetic field outside a spherical conductor. Due to the sphere-like symmetry of the head, radial sources produce extremely weak magnetic fields outside the head. The sensitivity of MEG is therefore highest to sources within the sulci, which are oriented tangentially with respect to the local head curvature.

Realistically shaped conductor models

A more accurate solution to the forward problem can be obtained using a realistically shaped conductor model. The conductor is assumed to consist of homogeneous compartments with realistically-shaped boundaries. In a boundary element model (BEM) the surface is formed of triangles (Hämäläinen and Sarvas, 1989), typically

using anatomical information from MRIs. In a piecewise homogeneous conductor, $\nabla\sigma$ is nonzero only at the boundaries and the magnetic field can be written as a summation over all boundaries (Geselowitz, 1970)

$$\mathbf{B}(\mathbf{r}) = \mathbf{B}_0(\mathbf{r}) + \frac{\mu_0}{4\pi} \sum_{i,j} (\sigma_i - \sigma_j) \int_{S_{ij}} V(\mathbf{r}') \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \times d\mathbf{S}', \quad (2.6)$$

where \mathbf{B}_0 is the magnetic field due to the primary current, and σ_i is the conductivity of compartment i . S_{ij} is the boundary between the compartments i and j . If the potential $V(\mathbf{r}')$ on all surfaces and the primary current distribution is known (Hämäläinen et al., 1993), the magnetic field can be calculated. Typically, the potential is assumed to be constant on each triangle.

Single-compartment models include only the surface of the brain, whereas three-compartment models include the surface of the brain, the skull and the scalp (Figure 2.1). In practice, single-compartment realistic models of the brain are often used for calculating the magnetic field, since the currents on the skull and scalp contribute much less to the recorded field. In Study P2, we investigate the effect of different head conductor models on the accuracy of MEG source modeling.

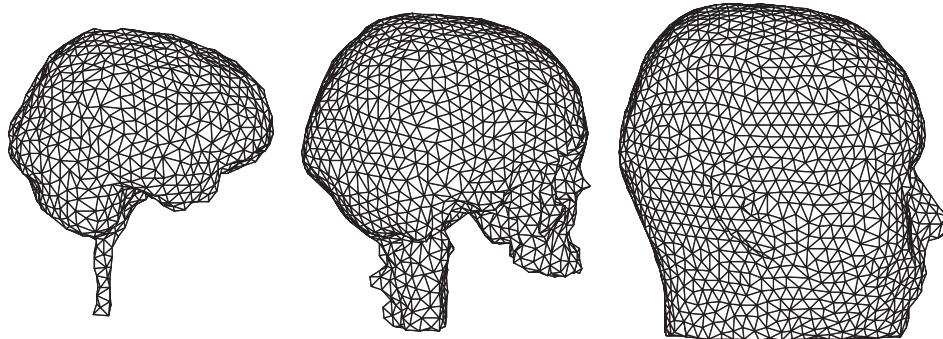


Figure 2.1. The three-layer BEM model. The triangle meshes describe the surface of the brain, skull, and scalp compartments. From Study P2.

The inverse solution

The inverse problem in MEG is to estimate the primary currents that explain the measured distribution of the magnetic field. The solution to the inverse problem is non-unique, and highly ill-posed in the sense that small measurement inaccuracies may cause large errors in the solution. For solving the inverse problem unambiguously, suitable assumptions must be made about the underlying sources to restrict the number of possible source configurations (for reviews, see e.g. (Hämäläinen et al., 1993; Baillet et al., 2001)).

Dipole modeling

The most commonly used approach for solving the inverse problem in MEG is to assume that an active cortical area can be modeled as an equivalent current dipole

(ECD). The ECD can be described as a concentration of the primary current \mathbf{J}_p to a point \mathbf{r}_Q ,

$$\mathbf{J}_p(\mathbf{r}) = \mathbf{Q} \delta(\mathbf{r} - \mathbf{r}_Q), \quad (2.7)$$

where \mathbf{Q} is the equivalent current dipole, and $\delta(\mathbf{r})$ is the Dirac delta function. The current dipole is a reasonable assumption if the active area is small relative to the distance to the sensors (Hämäläinen et al., 1993). A current dipole can also be used to represent the center of a more distributed source area. The location, orientation and amplitude of the dipole can be determined from the distribution of the MEG measurements with a least-squares search. A multidipole model can be constructed for example, by incorporating several ECDs, identified separately at different time points, in the model. The source strengths as a function of time can be found by allowing the amplitudes of the ECDs in this multidipole model to vary, while keeping the positions and orientations fixed. This approach was used in Studies P4 and P5.

For localizing rhythmic activity, the ECDs can be identified sequentially from band-pass filtered MEG data. Using this approach, the non-averaged MEG data are first filtered and single ECDs are computed at successive time samples with a least-squares fit to a chosen subset of sensors. The obtained ECDs cluster in areas producing oscillatory activity, representing a distribution of the mostly likely source areas. This approach was used in Study P1. We used goodness of fit (Kaukoranta et al., 1986) and confidence volume as acceptance criteria for the ECDs.

Minimum norm solutions

An alternative approach is to assume a distributed source model. In minimum norm solutions explicit a priori information about the source distribution is not required. Typically, the source space is divided into a grid containing a large number of dipoles. The grid can either be uniformly distributed in the whole brain volume, or be constrained to the cortical surface, as reconstructed from anatomical MRI data (Dale et al., 1999; Fischl et al., 2001). The problem is highly under-determined, as the number of unknowns (grid points) is much greater than the number of measurement points (MEG sensors). In minimum norm approaches, the solution to the inverse problem is obtained by finding the source configuration that explains most of the data while minimizing the norm of the current distribution (Hämäläinen and Ilmoniemi, 1994). The solution has an inherent bias towards superficial currents, which can be reduced by depth-weighting.

In calculating the estimate, different norms can be used. For example, the solution can be obtained either with respect to the L_2 norm, or with respect to the L_1 norm. The traditional minimum norm estimate (MNE) utilizes an L_2 norm (Hämäläinen and Ilmoniemi, 1994), which has the advantage that it provides a linear solution. The L_2 norm has relatively low spatial resolution, resulting in a distributed reconstruction even if the true source is focal. In Studies P4 and P5, we applied an anatomically constrained minimum L_2 norm approach, which uses grid points that are confined to the cortical surface. Noise-normalized MNEs were obtained by dividing the activity estimate at each source location by the noise sensitivity estimate (dSPM, dynamic statistical parametric mapping; Dale et al., 2000), thus representing an estimate of the signal-to-noise ratio at each source location as a z -score. This approach was used to obtain distributed source models of the activation sequences.

The minimum-current estimate (MCE; Uutela et al., 1999) utilizes a minimum L_1 norm, which minimizes the absolute value of the source strength. As an L_1 minimum-norm approach is employed, a solution with a few distinct source points is favored, resulting in more focal source estimates. A limitation of the method is that the dipole orientation at each grid point must be known, or determined iteratively. For example, the dipole orientation at each grid point can be obtained from the minimum L_2 norm solution (Uutela et al., 1999), and the minimum L_1 norm estimates can then be calculated with respect to these current orientations using linear programming.

For localization of rhythmic activity, Jensen and Vanni (2002) have developed a method utilizing minimum-current estimates in the frequency domain (MCE_{FD}). In MCE_{FD} , the data are divided into partly overlapping subsections in time, and transformed to frequency space. The minimum-current estimates for each data segment are calculated at the frequency of interest, and averaged (Jensen and Vanni, 2002). With MCE_{FD} , oscillatory activity of a certain frequency can be localized simultaneously in different brain regions. This approach was used in Study P1.

Beamformers

Another family of source localization algorithms is beamformers, or spatial filters, which are particularly useful for localization of rhythmic activity. A spatial filter passes signals originating from a certain spatial location, while attenuating those originating from other locations, using a weighted sum of the sensor signals (Van Veen et al., 1997). A map of neural power as a function of location is obtained by designing multiple spatial filters, each passing signals originating from a specified location.

Spatial filters can be implemented in the time domain (Robinson and Vrba, 1999) or in the frequency domain (Gross et al., 2001). In dynamic imaging of coherent sources (DICS; Gross et al., 2001; Kujala et al., 2008), a linear transformation that acts a spatial filter in the frequency domain is used. A three-dimensional grid that covers the entire brain is defined, and at each grid point the coherence with respect to a specified reference point and the power are calculated. Both measures can be computed from the solution to the forward problem at the respective grid point and the cross spectral density averaged over the frequency range of interest (Gross et al., 2001). DICS does not require any prior assumptions about the number of sources. In Study P1, we used DICS to localize sources of rhythmic activity. The cross-spectral density was first calculated between all combinations of MEG signals, and averaged over the whole time span. The mean power for the selected frequency bands was then extracted and the spatial filter was applied for each grid point. The power was noise normalized, and displayed superimposed on the MR images as a power statistical parametric map (pSPM). For calculation of the forward problem, two orthogonal dipolar sources were used.

A related approach is synthetic aperture magnetometry (SAM), which utilizes a nonlinear minimum-variance beamformer (Robinson and Vrba, 1999). This approach has been used, for example, to compare the amount of rhythmic activity between different experimental conditions (Singh et al., 2002; Gaetz and Cheyne, 2006). Unlike DICS, the SAM analysis is performed in the time domain, and the sensor-level data is represented by the covariance matrix.

The main limitation in beamformer approaches is that perfectly correlated sources cannot be identified (Van Veen et al., 1997). However, oscillatory sources in

distant areas are not likely to reach a level of coherence that would cause problems. Even for highly correlated sources complete attenuation is unlikely, although significant localization and amplitude biases may occur (Quraan and Cheyne, 2009).

2.3 Instrumentation and recordings

MEG recordings

Neuromagnetic signals are typically in the order of 50–500 fT (Hämäläinen et al., 1993). These extremely weak magnetic fields can be measured using SQUID sensors (Zimmermann et al., 1970). SQUID sensors are sensitive detectors of magnetic flux that consist of a superconducting loop, interrupted by two (DC-SQUID) Josephson junctions. The voltage across the SQUID is a periodic function of the flux. The SQUID sensor is kept at the working point by a feedback current. The sensors are immersed in liquid helium to obtain the superconducting properties. In order to reduce the impact of environmental noise the device is placed in a magnetically shielded room with mu-metal and aluminum.

The magnetic field is coupled to the SQUIDs through flux transformers, consisting of a pickup coil and a signal coil. The shape of the pickup coil determines the spatial sensitivity pattern of the sensor. Disturbances by distant sources can be reduced by selecting a suitable design for the pickup coils. A first-order planar gradiometer has two opposite coils next to each other. This configuration is most sensitive to sources located near or directly below the sensors. A magnetometer contains a single pickup loop and is sensitive also to more distant signals. In Study P2 we examined the differences in localization error for different kinds of pickup coils.

In Studies P1, P2, P4, and P5, we employed a Vectorview whole-head MEG device (Elekta Neuromag Oy, Helsinki, Finland), which has 102 triple sensor elements arranged in a helmet-shaped array. At each location there are two orthogonal planar gradiometers and one magnetometer. The head position with respect to the sensor array can be determined by head position indicator coils attached to the subject's scalp, and the locations of the coils with respect to anatomical landmarks (nasion and preauricular points) can be found with a 3D digitizer. Identifying these same anatomical points on the subject's MR images enables co-registration with structural images. For rejection of epochs contaminated by eye blinks or saccades we recorded electro-oculograms (EOG). Epochs with excessively large MEG amplitudes (exceeding 3,000 fT/cm) were also rejected.

For calculation of evoked responses in Studies P4 and P5, the MEG signals were sampled at 600 Hz and filtered to 0.03–200 Hz. Averages were calculated for each condition in a time window from –200 to 1000 ms with respect to the stimulus onset. The averaged responses were baseline-corrected to the 200-ms interval preceding stimulus onset (defined as the zero level) and low-pass filtered at 40 Hz.

EEG recordings

EEG measures the potential difference between two electrodes at the scalp with high temporal resolution. EEG is generally recorded from multiple electrodes placed on the

scalp. The placement of the reference electrode largely determines the observed distribution of the signals in EEG. Typical EEG signals are on the order of 10 to 100 μ V. In Study P5, we measured EEG simultaneously with the fMRI and MEG data. During the MEG measurement, EEG data were acquired using a 64-channel EEG cap (Elekta Neuromag Ltd, Helsinki, Finland). During the fMRI measurement, EEG data were recorded using a 32-channel customized EEG cap (BrainCap MR, Falk Minow Services (FMS), Herrsching, Germany) and a 32-channel EEG amplifier (BrainAmp MR Plus, BrainProducts GmbH, Munich, Germany). An additional EEG reference electrode was located between electrodes Fz and Cz during the MEG and fMRI measurements. In the analysis, we used the calculated average signal of all sensors as a common reference.

In simultaneous EEG and fMRI measurements, severe artifacts are induced in the EEG by the rapidly changing gradient fields. These artifacts can be removed from the EEG time series by subtracting an estimated artifact template from the measured signal. In Study P5, we used a time-continuous spline function (Koskinen and Vartiainen, 2009) to model the artifact signal in the EEG recorded simultaneously with fMRI. Other artifacts are caused by cardiac-related body movements (ballistocardiogram artifact). In Study P5 the ballistocardiogram artifact was considered to have only a negligible effect on the averaged evoked responses, and was not removed.

3 Evaluating source localization accuracy in MEG

The accuracy of the source estimation procedure in MEG depends on many factors, such as the location, orientation and spatial extent of the true underlying neural currents, and the accuracy of the head conductor mode. In addition, the localization accuracy depends on the validity of the underlying assumptions of the source model in explaining the data. Each source modeling technique has its own strengths, and choosing an appropriate strategy for analyzing the data requires thorough knowledge of the underlying assumptions. In this Thesis, we investigated two specific issues in source localization accuracy in MEG, namely source localization of ongoing rhythmic activity (Study P1), and the 3D topography of localization accuracy as affected by the choice of conductor model (Study P2). In this chapter, I will outline these studies and discuss the main results.

3.1 Localization of rhythmic activity (P1)

A growing number of studies have investigated the task-induced changes in cortical rhythmic activity with MEG (e.g. Salmelin et al., 2000; Gaetz and Cheyne, 2006; Longcamp et al., 2006; Osipova et al., 2006; Saarinen et al., 2006; Mazaheri et al., 2009). A rough estimate of the modulations of rhythmic activity can be obtained by inspecting the signals at the sensor level. However, for an accurate description of rhythmic activity in specific brain regions localization of rhythmic activity is essential. In Study P1, we compared the performance of three approaches for localization of cortical oscillations from MEG data: a) equivalent current dipoles (ECDs), using sequential ECD modeling b) minimum norm solutions using Minimum Current Estimates in the frequency domain (MCE_{FD}; Jensen and Vanni, 2002), and c) beamformers, using DICS (Dynamic Imaging of Coherent Sources; Gross et al., 2001; Kujala et al., 2008). The evaluation was performed using real data from four healthy subjects performing simple ongoing tasks (resting with eyes open or closed, and left or right index finger lifting). In such tasks, the main oscillatory sources are the mu rhythm, consisting of 10-Hz and 20-Hz components in the sensorimotor cortex, and the 10-Hz alpha rhythm, observed in the parieto-occipital cortex (Hari and Salmelin, 1997). In addition, we evaluated the performance of the three methods in simulations of rhythmic activity. The simulated sources were represented by equivalent current dipoles.

The main results were consistent across methods for both measured and simulated data. In the sensorimotor cortex the differences between the methods were typically a few millimeters in data with good signal-to-noise ratio (Figure 3.1). In the parieto-occipital cortex the differences in source localization were larger, and the number of localized sources varied. This result indicates a more complex activation pattern in the parieto-occipital areas than a single source can account for, making the selection of the correct source areas increasingly difficult. Using DICS, some additional sources were identified in the inferior sensorimotor or in the superior temporal cortex. These sources were not identified using the other methods.

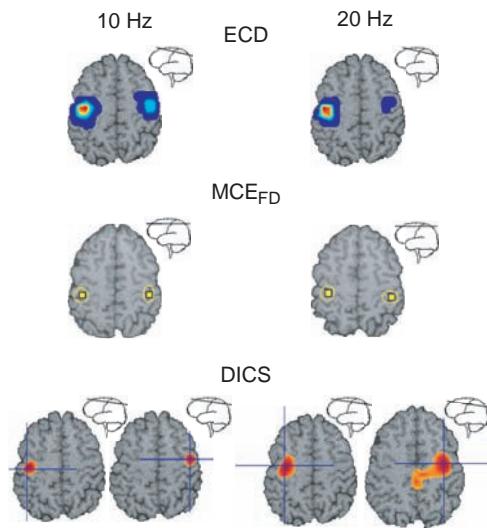


Figure 3.1. Sources in the sensorimotor cortex in one subject. The ECD clusters are shown as color-coded dipole density plots superimposed on the individual MR images. From Study P1.

Due to the limited spatial discrimination in MEG, source localization in areas with several simultaneously active sources is highly ambiguous. In simulations, we tested how well the methods were able to separate two sources (Figure 3.2). For separating the neighboring source areas, DICS performed better than the two other methods. In DICS, localized sources were removed before localization of subsequent sources by including the field produced by this source in the noise estimate before noise normalization. This approach should, however, be used with caution, as removal of already localized sources may affect identification of subsequent sources, especially in regions where several sources are located close to each other.

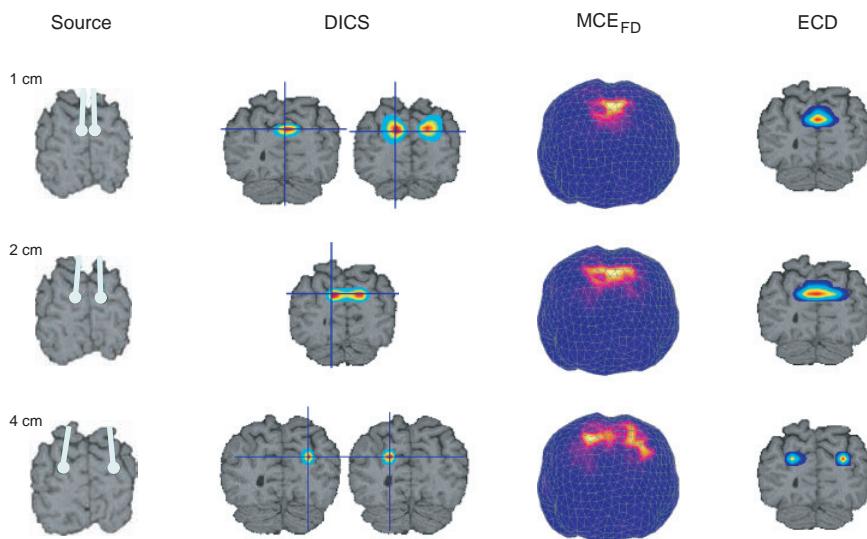


Figure 3.2. Separability of simulated sources in the parieto-occipital cortex situated 1 cm, 2 cm and 4 cm apart. At the 1-cm distance, all three methods failed to identify the correct sources. When the sources were 2 cm apart, DICS was the only method that could separate the two sources. At the 4-cm distance, all methods correctly identified the two sources. From Study P1.

In conclusion, it appears that with a fairly simple, single area of activation, the methods perform equally well, but with a more complicated distribution of active areas, the differences between the methods become evident. DICS was shown to be more sensitive to weak sources than the two other methods, both in measured and in simulated data. Using MCE_{FD} , sources could be found simultaneously in parieto-occipital areas and bilaterally in the hand areas. MCE_{FD} was thus the fastest of the three methods. However, it was difficult to separate sources in posterior regions. Since the scaling is done according to the stronger source, a weaker source might not be detected. Using the ECD approach, the current dipole clusters from sources located close to each other often overlapped. In addition, the ECD approach requires that appropriate subsets of sensors are selected by the researcher prior to localization, in order to minimize interference from simultaneously active sources. In neither MCE_{FD} nor DICS need assumptions be made about how many sources are active, or in which general areas these sources can be found. In this sense, DICS and MCE_{FD} are less prone to errors caused by the subjective bias of the researcher.

In our study, we focused on localization of ongoing cortical oscillations. However, a recent development of the DICS method towards characterization of task-related modulations in rhythmic activity (event-related DICS, or erDICS; Laaksonen et al., 2008) shows promise for future use of this technique in more complex tasks. Using the ECD approach, movement-related increases in rhythmic activity in the motor cortex have been characterized (e.g. Salmelin and Hari, 1994b, 1994a). However, the ECD approach cannot identify areas with a decrease in cortical rhythms, due to the low signal-to-noise ratio. With the erDICS approach it is possible to localize also task-related decreases in the level of rhythmic activity. A related technique, SAM, has also been applied to comparisons of rhythmic activity between conditions (e.g. Cheyne et al., 2006).

3.2 Localization errors: Effect of head conductor models and noise (P2)

The spherically symmetric model is the most commonly used conductor model in MEG source localization, partly due to the ease of creating the model. The main advantages of this model are that it is computationally fast, and easy to create. A spherical conductor is also a reasonable approximation of the head. Realistic BEM models offer a more accurate description of the shape of the conductor, utilizing anatomical information from e.g. MR images, but are computationally more time consuming, and are more difficult to create. However, faster computers and new (automated) segmentation algorithms are making the use of realistically shaped head conductor models more feasible than ever before.

In Study P2, we used computer simulations to estimate the source localization accuracy in MEG throughout the whole brain volume. The main goal was to evaluate the effect of the head conductor model on source estimation, under realistic conditions. In addition to evaluating the localization, orientation, and amplitude errors related to different head conductor models, we included a comparison of different sensor types by using either first-order planar gradiometers, or magnetometers, or a combination of both.

To mimic real data, we included noise taken from an MEG recording. We evaluated the performance of 13 different conductor models, including spherically

symmetric conductor models, one-layer realistically shaped boundary-element conductor models, and three-layer realistically shaped boundary-element conductor models. In the simulations, we first calculated the magnetic fields evoked by current dipoles situated on an evenly spaced grid with 5-mm spacing, covering the entire brain. We used the single dipole model due to the simplicity of this model, its wide usage, and the ease of quantifying the associated errors. As the reference model, we used a highly refined three-layer realistically shaped boundary-element conductor model. In the reference model, each compartment, i.e. brain, skull, and scalp, was modeled with triangles having a side length of 8 mm. To achieve realistic conditions, noise from a MEG measurement was re-averaged at randomly picked time points, and added to the simulated magnetic fields. Source parameters (location, strength, orientation) were then estimated from the noisy signals. To study how estimation errors depend on the signal-to-noise ratio of the MEG signals, we varied the frequency band of the noise and the original source strengths.

Our simulations showed that, without noise, the three-layer realistic model outperformed the other models (Figure 3.3, left column, dashed line). However, adding noise effectively masked the differences in source localization error between the different conductor models so that the advantages of using a three-layer realistic model were almost negligible (Figure 3.3, middle and right column).

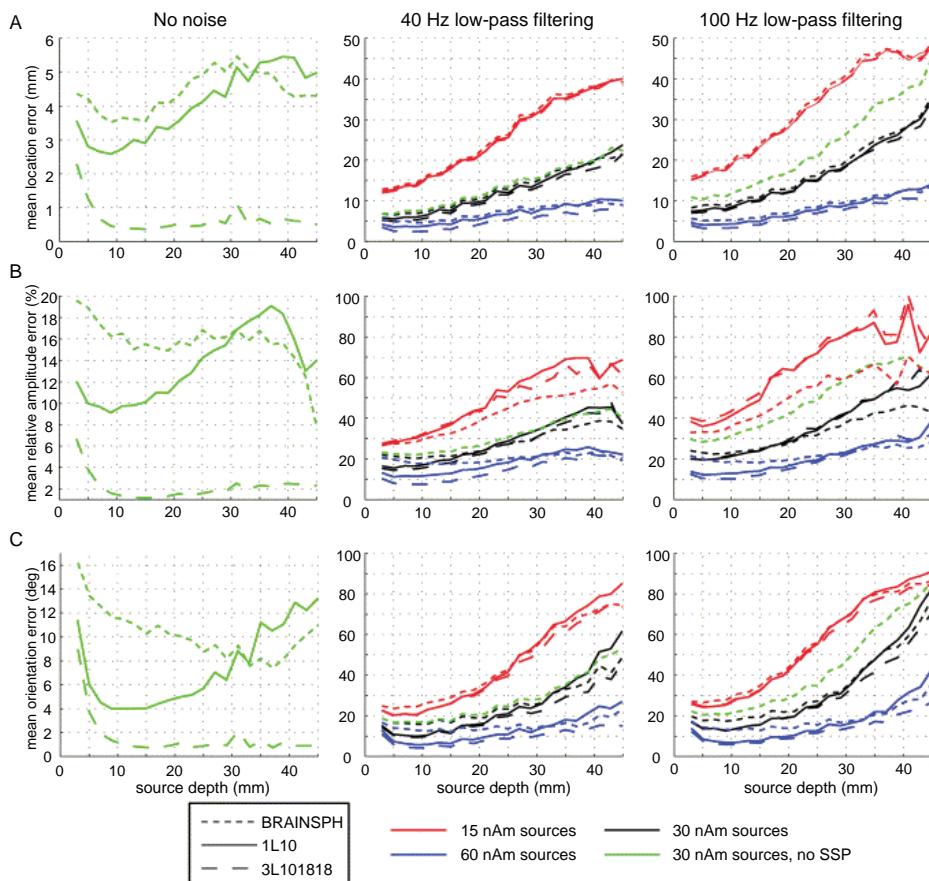


Figure 3.3. The mean errors in A) source location, B) amplitude, and C) orientation for a spherical model (BRAINSPH) (dotted line), a one-layer BEM model (1L10) (solid line), and a three-layer BEM model (3L101818) (dashed line) for different noise conditions. The source depth is measured as the distance from the surface of the brain triangle mesh. The amplitude errors are given relative to the original amplitude. Only gradiometers were used in the source estimation. From Study P2.

As expected, there were considerable variations in localization accuracy between different brain regions (Figure 3.4). Sources in cortical areas close to the vertex, and in temporal, frontoparietal, and occipital regions were localized with high accuracy (typically 2–4 mm), whereas source estimation in anterior frontal regions, and in deep brain structures produced errors exceeding 2 cm. Localization errors increased with source depth which, to a large extent, can be explained by decreasing signal-to-noise ratio, as the distance between the current source and the sensors increases.

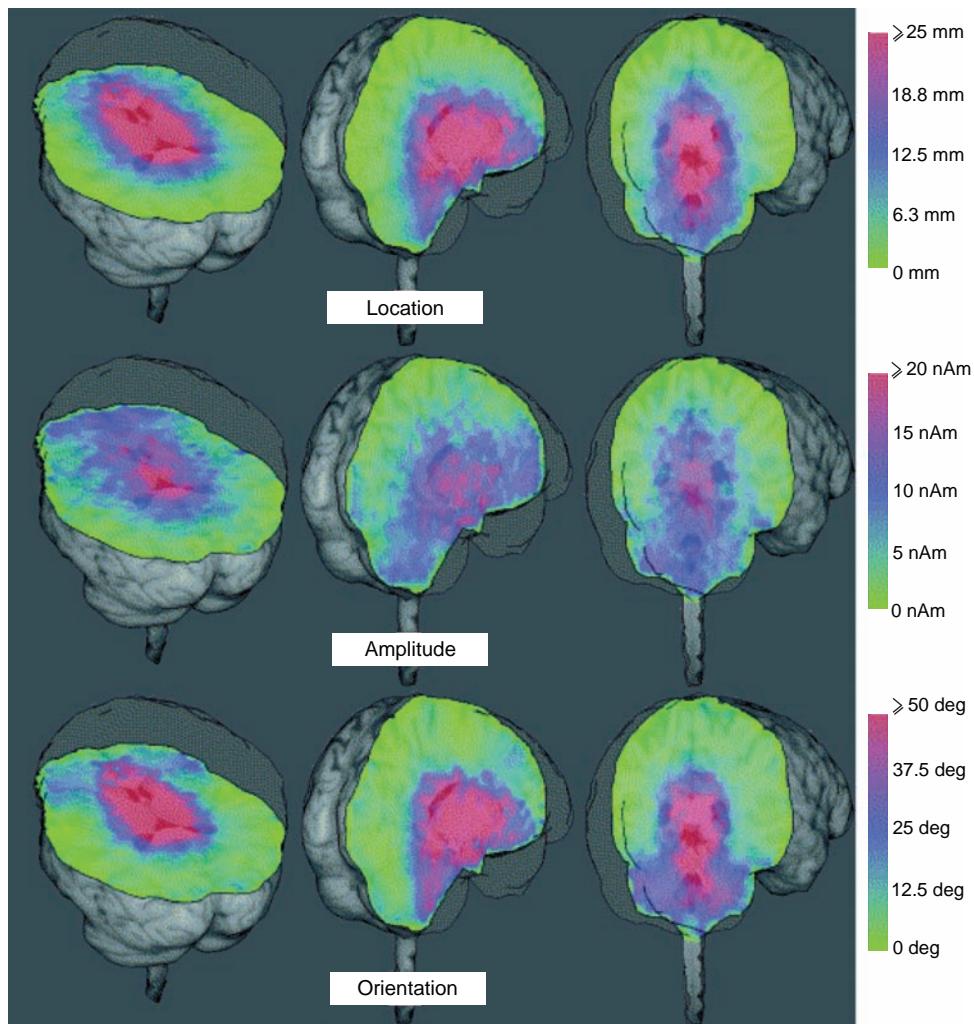


Figure 3.4. The distribution of the source estimation errors using a spherical conductor model (BRAINSPH) for 30 nAm sources. The added noise was low-pass filtered at 40 Hz. Adapted from P2.

Our tests did not show any general improvement by using magnetometers in addition to gradiometers—not even for deep source areas, most probably due to the smaller noise sensitivity of the gradiometers. The theoretical advantage of magnetometers for seeing activity originating from deep brain structure may have been nullified by interfering brain signals from the cortex. However, by eliminating cortical interference through high-pass filtering the magnetometers might yield better results for localization of deep sources (Parkkonen et al., 2009).

In conclusion, our results show that the traditionally used sphere model is adequate for many practical measurement situations, such as for the analysis of signals from visual, auditory, or sensorimotor cortices. In these cortical regions, the active source areas can often be found with 2–4 mm accuracy, leaving only little room for improvements from the use of realistically shaped models. These results are in agreement with previous findings (Leahy et al., 1998; Crouzeix et al., 1999). In anterior frontal regions, or in deep brain structures, localization may benefit most from the use of more advanced conductor models.

As our results show, the most efficient way to increase localization accuracy is to enhance the signal-to-noise-ratio by increasing the number of collected averages, through effective shielding of external noise, filtering, or by applying noise reduction techniques (Uusitalo and Ilmoniemi, 1997; Taulu et al., 2004). In this study, the effect of interfering activation from other brain areas was not specifically taken into account. In analysis of real data, such simultaneously active areas increase the possibility of source localization errors. In real data the benefit of using a realistic model may thus be more pronounced (Henson et al., 2009).

4 Functional magnetic resonance imaging

Magnetic resonance imaging (MRI) (Damadian, 1971; Lauterbur, 1973; Mansfield, 1977) is based on the property of nuclear magnetic resonance (NMR). In MRI, the hydrogen nuclei, or protons, are magnetized by a strong external magnetic field. The MRI scanner detects the signal created by alignment changes in the protons following excitation by brief radio frequency pulses. Through this phenomenon, it is possible to acquire both anatomical and functional images of the human body. The blood-oxygen-level-dependent (BOLD) signal (Ogawa et al., 1990; Belliveau et al., 1991; Bandettini et al., 1992; Kwong et al., 1992) is the most widely used technique for functional imaging of the brain. The fMRI BOLD signal is an indirect measure of neuronal activity that relies on the coupling between neural activation and blood flow.

This chapter briefly describes fMRI signal formation and recordings, and reviews the current literature on the relationship between the fMRI signal and neurophysiological measures. The following description on MR signal formation is mainly based on comprehensive texts by (Huettel et al., 2004) and (Logothetis, 2008).

4.1 MR signal formation

Nuclear magnetic resonance

Water molecules, and thus also protons, are abundant in biological tissue. Protons possess a spin angular momentum and a related magnetic moment. When placed in an external magnetic field, B_0 , the protons start precessing around the axis of the magnetic field at the resonance, or Larmor, frequency, f . The Larmor frequency is related to the magnetic field through the gyromagnetic ratio, γ . The gyromagnetic ratio of protons is 42.58 MHz/T.

The protons are aligned either parallel or antiparallel to the magnetic field. The parallel state has a lower energy, and is therefore slightly favored, resulting in a net magnetization, M_0 , in the direction of the main magnetic field. Applying a radio-frequency (RF) electromagnetic pulse at the Larmor frequency causes some protons in the parallel state to absorb energy and enter the antiparallel state. After the excitation the excess protons gradually return to the lower energy level, re-emitting the electromagnetic energy at the Larmor frequency. Applying an RF excitation pulse that is orthogonal to B_0 rotates the net magnetization from the longitudinal plane to the transverse plane, thus producing a measurable signal. Immediately after excitation the spins are in phase, but the synchrony is gradually lost. Recovery of the longitudinal magnetization along the main magnetic field is described by the time constant $T1$ (longitudinal relaxation, spin-lattice relaxation). The decay of the transverse magnetization (transverse relaxation, spin-spin relaxation) is described by the $T2$ time constant. $T2$ decay is caused by interactions between the spins. Inhomogeneities in the main magnetic field cause additional dephasing. The $T2^*$ time constant describes the

signal decay in the presence of such field inhomogeneities. The T2/T2* relaxation is a faster process than the T1 relaxation.

Magnetic resonance imaging

MR image contrast is dependent on the variations in the relaxation rates for different tissues. With a careful choice of RF pulse sequences (or applied gradient magnetic fields) it is possible to create MR images that are sensitive to different tissue-specific properties, such as proton density, T1, T2 or T2* relaxation, perfusion, or diffusion. For example, typical anatomical images are T1-weighted images, which rely on the differences in T1 relaxation of gray and white matter.

Two parameters are of particular importance for the timing of the pulse sequences. Repetition time (TR) is the time between two successive excitation pulses, whereas echo time (TE) is the time between the RF excitation pulse and the data acquisition. The difference in signal strength between tissue types, i.e. tissue contrast, is maximized by selecting suitable values for the parameters TR and TE.

Spatial locations are encoded by applying weaker magnetic field gradients superimposed on the main magnetic field (as first proposed by Lauterbur in 1973). To obtain two-dimensional images, the spatial information is encoded in terms of frequency in one direction ("readout", x), and in terms of phase in the other direction ("phase-encoding", y). Encoding in the direction of the third dimension, i.e. slice selection, is accomplished by applying a slice selection gradient and using an RF excitation with narrow bandwidth to selectively excite nuclei within a plane with the corresponding resonance frequency.

The Fourier transform of the image space is referred to as k-space. In magnetic resonance imaging, k-space is defined by the frequency and phase encoding directions. From the acquired k-space image, the MR image can be reconstructed by a two-dimensional Fourier transform.

Echo-planar imaging (proposed by Mansfield in 1977) enables fast imaging by recording an entire image in a TR period. In echo-planar imaging, the decay of the signal is recovered by refocusing the dephasing spins repeatedly. Gradient-echo sequences refocus the spins via gradient reversals, whereas spin-echo sequences refocus the spins using additional RF pulses. By repeating this process a train of echoes can be generated, and the entire k-space can be filled following a single excitation.

4.2 The fMRI BOLD effect

The fMRI BOLD signal is an indirect measure of neural activity, exploiting the relationship between the hemodynamic response and neural activity. The BOLD response is influenced by several factors, such as cerebral blood flow, cerebral blood volume, and blood oxygenation.

The activity of the neurons increases their metabolic requirements. In order to meet these requirements, energy must be provided in the form of glucose and oxygen, supplied by the vascular system. Oxygen is supplied bound to hemoglobin molecules. Hemoglobin is diamagnetic when it is oxygenated and paramagnetic when it is deoxygenated. The paramagnetic deoxyhemoglobin affects magnetic susceptibility, inducing local inhomogeneities in the magnetic field. Following neural activity, the

increase in oxygen usage is accompanied by a larger fractional increase in blood flow and blood volume. The resulting net decrease of the local deoxygenated hemoglobin is seen as a signal increase in T2*-weighted MR images.

The time course of the hemodynamic response is relatively slow: following stimulus onset, the hemodynamic response starts increasing after 1–2 s and reaches its maximum after 5–10 s (Buxton et al., 2004). An initial decrease of the hemodynamic response is observed in some experiments (Buxton, 2001). The signal returns to baseline after a post-stimulus undershoot 15–20 s after the stimulus offset.

The temporal resolution of fMRI is in the order of seconds. At best, a temporal resolution in the order of a few hundred milliseconds can be achieved by detecting latency differences in onset times for the hemodynamic response in event-related fMRI studies (e.g. Formisano and Goebel, 2003).

4.3 The relationship between neural activity and the fMRI BOLD signal

The exact relationship between neural activity and the measured BOLD signal is still unclear. Estimates of the energy expenditure in neural signaling suggest that fMRI signals are dominated by postsynaptic currents and action potential propagation rather than by presynaptic or glial activity (Attwell and Laughlin, 2001; Attwell and Iadecola, 2002). In addition, it seems that the hemodynamic response is driven by signaling related to neurotransmitters, rather than by local energy needs (Attwell and Iadecola, 2002).

Electrophysiological recordings of the monkey visual cortex have suggested that the hemodynamic response is correlated with local field potentials (LFPs) rather than with single-unit (SUA) or multi-unit spiking activity (MUA) (Logothetis et al., 2001). Local field potentials are related to subthreshold integrative processes in areas such as dendrites and reflect the summation of post-synaptic potentials. Thus, the BOLD signal would reflect information processing within active cortical regions, rather than the output, or spiking, of the principal neurons.

Similar results have been found in other studies relating the fMRI BOLD signal to electrophysiological measures in animals (Niessing et al., 2005; Goense and Logothetis, 2008), and in humans (Mukamel et al., 2005; Nir et al., 2007; Ojemann et al., 2009). These studies have generally reported a positive correlation between LFP and BOLD signal especially at high frequencies (e.g. 40–130 Hz; Mukamel et al., 2005; Niessing et al., 2005), and negative or low correlation between LFP and BOLD signals for low frequencies (e.g. <20 Hz; Mukamel et al., 2005; Goense and Logothetis, 2008). Several studies have reported highly variable correlations between spiking activity and fMRI BOLD (e.g. Nir et al., 2007), especially during time periods when LFP and MUA are dissociated (Goense and Logothetis, 2008), showing that under some physiological conditions, and in some brain regions there can indeed be a decoupling between spiking activity and fMRI BOLD signal.

Most comparisons between fMRI BOLD and electrophysiology have explored the primary sensory cortices (in both animals and humans), but there are some exceptions. For example, in a pair association task, Ojemann et al. (2009) found co-localized increase in LFPs in the 50–250 Hz range and the fMRI BOLD response in the temporal lobe. In a semantic decision task, Lachaux et al. (2007) also found a close spatial correspondence between fMRI activations and intracranial EEG (iEEG) modulations in the gamma range (>40 Hz). This relationship may not hold for all

brain regions. A study by Ekström et al. (2009) found a positive correlation between LFP power changes in the theta band (4–8 Hz) and BOLD signal intensity in the parahippocampal gyrus during a navigation task in a virtual environment. Yet, in the same task, LFP power changes in the hippocampus were only weakly correlated with BOLD signal intensity. There was no significant relationship between BOLD activity and neural firing rate.

There are also some other exceptions to the correspondence between electrophysiology and BOLD signal. Recent work has demonstrated that, in certain tasks, such as perceptual suppression (Maier et al., 2008), fMRI BOLD signals in the primary visual cortex diverge from electrophysiological signals (both MUA and LFP) in monkeys, although the two measures show good agreement during conventional stimulus presentation. A task-dependent divergence between hemodynamics and electrophysiology was also indicated in a study by Sirotin and Das (2009). Using simultaneous optical imaging and electrophysiological recordings in the monkey visual cortex they found a task-related hemodynamic response showing increased cerebral blood flow in anticipation of trial onset. These studies show that the coupling between the fMRI BOLD signal and electrophysiological signals can be highly context-dependent.

In this Thesis, the relationship between the fMRI BOLD signal and MEG evoked responses in language tasks was investigated in Studies P4 and P5.

4.4 Instrumentation and fMRI data analysis

Modern MRI scanners are typically within the range of 1.5 to 4 T, with systems of 7 T becoming more common. The major components of the MRI system are the main magnet, the gradient coils, and the RF transmitting coils.

In Studies P3, P4, and P5 MR images were acquired using a 3.0 T Signa EXCITE scanner (GE Healthcare, Chalfont St Giles, UK). In Study P3 images were acquired using a quadrature transmitting-and-receiving head coil, whereas in Study P5 an 8-channel head coil was used.

For functional images, we used a single-shot gradient-echo echo-planar imaging (GRE-EPI) sequence, with 39 oblique axial slices covering the entire brain, measured in an interleaved order. The matrix size was 64×64 , with in-plane resolution $3.4 \text{ mm} \times 3.4 \text{ mm}$ or $3 \text{ mm} \times 3 \text{ mm}$ (8 subjects in Study P3). The slice thickness was 3 mm with no spacing between the slices. The functional images were acquired using the following parameters: TR = 3 s, TE = 32 ms, flip angle = 90° (Study P3) or TR = 2.4 s, TE = 32 ms, flip angle = 75° (Study P5). Anatomical images were acquired using a T1-weighted 3D SPGR sequence.

The imaging data were analyzed with standard preprocessing and statistical methods. In order to eliminate the T1 saturation effects the first four volumes of the functional images were discarded and the data were corrected for head movements. The anatomical and functional images were co-registered, and the data were high-pass filtered to reduce the effect of slow drifts. Serial correlations were compensated for by using a first-order autoregressive model. In Study P3 the images were spatially normalized to the MNI (Montreal Neurological Institute) template image, whereas in Study P5 the images were transformed to the Talairach space (Talairach and Tournoux, 1988). For group-level fMRI analysis, the data were spatially smoothed with an 8-mm full width at half maximum Gaussian kernel.

In fMRI, the measured signal changes are relatively small: only a few percentages of the mean signal amplitude. Thus, statistical analysis is required. Statistical analysis was performed within the general linear model (GLM) framework. Regressors for each condition were entered into the design matrix and convolved with a canonical hemodynamic response function. At the group level, a random-effects analysis was performed. For correction of multiple comparisons we used false discovery rate (FDR; Genovese et al., 2002) or family-wise error (FWE).

In Study P3 the fMRI analysis was performed using statistical parametric mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK). This same approach was used in Study P4 for re-analyzing the data for the smaller subgroup of subjects who had participated also in the MEG measurements. In Study P5 the fMRI analysis was performed using BrainVoyager QX (Brain Innovation, Maastricht, Netherlands).

5 Cortical processing of verbs, nouns, and written words

Language processing involves multiple brain regions in a predominantly left-lateralized cortical network, as shown initially by studies of brain-damaged patients (Broca, 1861; Wernicke, 1874). For mapping the cortical regions involved in language processing and their functional roles in the healthy human brain, neuroimaging studies have employed a wide variety of linguistic tasks in speech production, comprehension, and reading (for extensive reviews, see e.g. Price, 2000; Bookheimer, 2002; Friederici, 2002; Jobard et al., 2003; Indefrey and Levelt, 2004; Vigneau et al., 2006; Salmelin, 2007).

In this Thesis, we have focused on two specific linguistic tasks, picture naming and reading. Both these tasks rely on visual information, and involve accessing meaning (semantics) from a visual stimulus. In the following, I will review the existing literature on these tasks, as relevant for understanding the background of experiments P3, P4 and P5. I will also discuss the verb/noun dissociations found in picture naming tasks in the patient and neuroimaging literature, and the aims and results from Studies P3 and P4 on action and object naming.

5.1 Neural mechanisms of reading and picture naming

Visual perception of objects and words

Visual processing of objects involves multiple cortical regions with different functions. Visual information, initially processed in the retina, is relayed through the lateral geniculate nucleus of the thalamus to the primary visual cortex (V1, striate cortex), located in the calcarine sulcus of the occipital cortex. The neurons located in V1 are organized in a retinotopical manner, so that adjacent cortical patches are sensitive to adjacent regions in the visual field. The neurons in area V1 are sensitive to simple visual features, such as lines with a specific orientation. Cortical responses measured with EEG or MEG within the first 100 ms after visual stimulus onset show sensitivity to the amount of visual features to process (e.g. Tarkiainen et al., 1999; Tarkiainen et al., 2002). At this latency, responses do not differentiate between classes of objects (Allison et al., 1994; Tarkiainen et al., 2002).

There are two main visual pathways: the dorsal and ventral streams. Different roles for the two streams have been proposed (Mishkin et al., 1983; Goodale and Milner, 1992). The dorsal stream, or the 'where' pathway, projects via the motion sensitive area MT/V5 to the posterior parietal cortex. The dorsal stream is associated with spatial awareness and guidance of actions, whereas the ventral stream, or the 'what' pathway, extending from the occipital cortex to ventral and lateral regions of the temporal cortex plays an important role in object recognition.

A number of studies have reported that distinct areas within the ventral stream in the temporal lobe are selective to certain categories of objects, such as faces in the fusiform face area (Kanwisher et al., 1997), places or buildings in the parahippocampal place area (Epstein and Kanwisher, 1998), or words in the visual

word-form area (VWFA; Allison et al., 1999; Cohen et al., 2002). Around 150–200 ms after stimulus presentation responses show sensitivity to object identity (Allison et al., 1994; Tarkiainen et al., 1999; Tarkiainen et al., 2002).

Cortical processing of written words

Processing of written words is assumed to advance from visual feature analysis to letter and word-level analysis, and analysis of the word's meaning and sound form. According to an influential theoretical model on reading (the dual route model; Coltheart et al., 1993), words can be processed through two different routes, depending on the familiarity of the word. In this model, unfamiliar words are converted letter-by-letter from graphemes to phonemes, whereas familiar words may be recognized based on the visual word form.

Cortical processing of reading has been studied extensively with both MEG and fMRI. MEG studies have shown a cortical activation sequence in reading advancing from the occipital cortex at ~100 ms after stimulus presentation (reflecting visual feature analysis; Tarkiainen et al., 1999), to the left occipito-temporal cortex peaking around ~150 ms (sensitive to letter strings; Tarkiainen et al., 1999; Cornelissen et al., 2003), and further to the superior temporal cortex at 200–800 ms (the so called N400m response; Helenius et al., 1998). Both MEG and fMRI consistently show activation of the occipital and inferior occipito-temporal cortex in reading (for reviews, see e.g. Jobard et al., 2003; Salmelin, 2007). However, there are some systematic discrepancies between the results obtained with each technique. In fMRI, differentiation between words and consonant strings has been found in the left occipito-temporal cortex (visual word-form area; Cohen et al., 2002; Vinckier et al., 2007). In contrast, MEG responses in the left occipito-temporal cortex at ~150 ms after word onset are equal to all letter strings (Tarkiainen et al., 1999; Cornelissen et al., 2003). In addition, involvement of the left inferior frontal gyrus is consistently observed in fMRI in response to visually presented words. Activation in this region has been associated with high-level linguistic analysis, such as semantic, phonological, and morphological processing (Jobard et al., 2003). In MEG, studies employing silent reading tasks have typically not reported frontal activation (Salmelin, 2007). The MEG activation found in the left superior temporal cortex around 400 ms, instead, shows sensitivity to semantic, phonological, and morphological manipulations (Helenius et al., 1998; Vartiainen et al., 2009a; Vartiainen et al., 2009b). In Study P5, we investigated whether these discrepancies remain when MEG and fMRI are measured in the same participants, controlling for the experimental paradigm, task, and language.

Picture naming

Picture naming is assumed to include several processing stages, proceeding from conceptualization to formulation and articulation (Harley, 2001). In a cognitive model by Levelt and colleagues (Levelt et al., 1999; Indefrey and Levelt, 2004) the main stages of word production proceed through visual object recognition, conceptual preparation and lexical selection, to form encoding, involving the retrieval of phonological codes, syllabification, and phonetic encoding for articulation. During lexical selection, it is assumed that related concepts are coactivated, and that

activation spreads to the corresponding lexical items ("lemmas") in the mental lexicon. In this model, the syntactic properties are specified at the lemma level and the target lemma is selected under competition.

Picture naming is a widely used task in assessment of patients with brain damage. Difficulties in naming pictures may occur for different underlying reasons in patients, as revealed by distinct patterns of performance between patients across behavioral tasks (e.g. Caramazza and Mahon, 2006; DeLeon et al., 2007; Mahon and Caramazza, 2009). For example, patients with a deficit at the visual recognition level may not be able to perform visual matching tasks, whereas patients with impairments of semantic representations might perform poorly on various semantic tasks, such as naming to definition. Other patients with disrupted performance in picture naming may perform well in comprehension tasks such as word-to-picture matching, but be unable to retrieve the spoken or written word form. As shown by lesion studies, damage to specific brain regions, in particular regions of the left temporal cortex, inferior frontal and inferior parietal cortex correlates with disruption at different levels of the naming process (DeLeon et al., 2007).

Picture naming is also commonly used in neuroimaging studies investigating speech production. fMRI studies aiming at finding the cortical areas involved in picture naming in healthy subjects have consistently revealed activations in a distributed cortical network including the bilateral occipitotemporal cortex and parietal cortex, left inferior frontal and dorsal premotor areas (Murtha et al., 1999; Abrahams et al., 2003; Price et al., 2005). These regions are typically involved in a wide range of linguistic tasks, including semantic and phonological processing and verbal working memory (Vandenbergh et al., 1996; Cabeza and Nyberg, 2000; Bookheimer, 2002; Jobard et al., 2003). The fusiform gyrus, inferior occipitotemporal cortex, and the superior/middle occipital gyrus are also consistently activated in object identification (Price et al., 1996; Whatmough et al., 2002; Grill-Spector, 2003). In MEG studies, the activation has been shown to proceed from the occipital cortex (< 200 ms) to parietal and temporal regions (> 200 ms) and further to frontal regions (> 300 ms) (Salmelin et al., 1994; Sörös et al., 2003; Vihla et al., 2006; Hultén et al., 2009).

A meta-analysis based on neuroimaging and behavioral studies of word production by Indefrey and Levelt (2004) suggested that regions in the occipital and ventral temporal cortex are associated with visual object recognition and conceptualization within 175 ms after stimulus onset, whereas word selection was associated with the left middle temporal cortex at 150–250 ms. Access to the phonological word form was suggested to involve left posterior middle and superior temporal cortex at 200–350 ms, whereas preparation for articulation may involve the left inferior frontal cortex from about 300 ms onwards.

In Studies P3 and P4, we employed picture naming in both fMRI and MEG to explore the differences in naming actions and objects in the healthy human brain.

5.2 Verbs and nouns in the brain

Neuropsychological studies of aphasic patients have shown that damage to the brain can affect verb or noun processing selectively (Zingeser and Berndt, 1990; Caramazza and Hillis, 1991; Bird et al., 2000; Arevalo et al., 2007). Some patients show a disproportionate difficulty in processing verbs, as compared to their ability to process nouns. In others, the pattern is reversed (Zingeser and Berndt, 1990; Daniele et al.,

1994). In these studies picture naming has been the preferred task. Nevertheless, the dissociation between verbs and nouns has been observed in both production and comprehension tasks (Caramazza and Hillis, 1991; Silveri and Di Betta, 1997; Rapp and Caramazza, 2002).

The underlying reason for this dissociation is difficult to resolve, as verbs and nouns differ in a number of aspects, including semantics, morphology and syntax. In most languages, there are many more nouns than verbs but the verbs are used more frequently. Although verbs are more high-frequent than nouns, they are acquired later (Gentner, 1982). Verb processing is considered more demanding than noun processing (Gentner, 1981), partly because verbs have a more complex argument structure, which differs between different verbs. Generalizing the usage from one verb to the other is therefore difficult. Concrete nouns, in contrast, tend to behave grammatically similarly. Importantly, there is also a clear semantic distinction between verbs and nouns, i.e. verbs typically refer to actions or events, while nouns refer to objects or entities. Concrete nouns are also more imageable than verbs (Bird et al., 2000). In patients, verb processing deficits are more common than noun processing deficits, in agreement with the higher demands for processing verbs (Märtzig et al., 2009).

The existence of patients with selective impairments of grammatical categories has led to the suggestion that there are distinct cortical areas for processing verbs and nouns (Damasio and Tranel, 1993). Lesion data has implied a link between left frontal areas and verb processing, whereas noun processing seems to depend on the integrity of left temporal areas (Damasio and Tranel, 1993; Daniele et al., 1994). However, both lesion location and diagnostic classification are more variable in patients with selective verb deficits. Whereas noun deficits in picture naming tasks are almost always associated with temporal lobe damage, verb deficits may occur following damage in frontal or parietal regions, in the basal ganglia, and in some cases in the temporal lobe (e.g. review by Märtzig et al., 2009). The variability of lesion site in verb deficits may indicate that the underlying reasons for verb-specific deficits differ between patients. Within the class of nouns, dissociations of performance across different object categories can further occur, i.e. noun impairments can target specific semantic categories such as animals or tools. The most commonly reported deficit is a relative impairment for living things compared to nonliving things (Caramazza and Shelton, 1998).

Explanations for the double dissociations

Several alternative explanations for the double dissociation between verb and noun processing have been put forward. One possibility is that differences between verbs and nouns in the brain are of grammatical nature (Caramazza and Hillis, 1991; Shapiro et al., 2000). According to this view, such differences should turn up in production tasks that require access to grammatical information. For example, it has been demonstrated that some patients with difficulties in verb or noun naming show difficulties in using pseudowords as members of that category as well (Shapiro et al., 2000).

Another view maintains that verbs and nouns are organized according to semantic features, nouns typically referring to objects and verbs to actions (McCarthy and Warrington, 1985; Damasio and Tranel, 1993). According to this account, semantic information is stored in distributed networks in (or near) the same cortical

areas that are active during perception (e.g. Warrington and Shallice, 1984; Martin and Chao, 2001). Words could, for example, be organized according to sensorimotor features (Vigliocco et al., 2006). Observations of motor cortex activation in response to action-related words (e.g. Hauk et al., 2004) have been taken to support the view that words that share semantic attributes are represented similarly in distributed cortical networks, and that motor regions are involved in semantic processing of action words.

Nouns and verbs could also be impaired in brain-damaged patients for different underlying reasons (Märtzig et al., 2009). Producing a word, of any grammatical category, involves conceptual, semantic, syntactic and phonological processes (Levelt et al., 1999) and some of these features may be more relevant for processing one category but not the other. For example, while grammatical knowledge could be more important for verb production, (concrete) noun production may rely to a greater extent on e.g. visual-semantic knowledge. Thus, only if it can be shown that deficits in processing verbs or nouns are the result from the same underlying problem (such as semantic or morphological processes) should the double dissociation seen in patients with brain damage be considered as evidence that nouns and verbs are processed in segregated anatomical regions (Märtzig et al., 2009).

Neuroimaging studies on verb and noun processing

Neuroimaging studies have used a large variety of experimental tasks to study noun and verb processing in the healthy brain, in both production (e.g. Martin et al., 1995; Shapiro et al., 2005) and comprehension (e.g. Perani et al., 1999; Vigliocco et al., 2006). Typical tasks include lexical decision (Perani et al., 1999), semantic judgments (Tyler et al., 2001), picture naming (Saccuman et al., 2006), and morphological transformations on words (Shapiro et al., 2005).

The results from earlier neuroimaging studies on verb and noun processing have generally been quite inconsistent. While some studies have suggested that the same distributed cortical network is activated for nouns and verbs in both semantic categorization and lexical decision (Tyler et al., 2001), as well as in picture naming (Sörös et al., 2003), others have shown that the overlap between cortical activations evoked by noun and verb processing is not complete. For example, stronger activation related to verbs has been found in the left premotor areas and left posterior middle temporal lobe in lexical decision (Perani et al., 1999) and in verb generation (Martin et al., 1995; Warburton et al., 1996). Despite abundant evidence of deficits in patients with brain damage being specific to grammatical category, neuroimaging studies have generally failed to find a double dissociation between noun and verb processing.

Several previous studies have focused on determining whether semantics or grammatical class is the main organizational principle of linguistic knowledge. For example, in listening to verbs or nouns, Vigliocco et al. (2006) found no effect for grammatical class whereas motor words activated the left precentral gyrus and sensory words the left inferior temporal and left inferior frontal regions. Similarly, in a picture naming task, no significant differences were found between verbs and nouns, whereas manipulable, compared to non-manipulable, actions and objects elicited activation in a fronto-parietal cortical network (Saccuman et al., 2006). Such results have been taken to indicate that semantic features, rather than grammatical class, serve as organizational principles of words.

Contrary to these findings, Bedny et al. (2008) found stronger activations to verbs as compared to nouns in listening to word pairs in the left frontal and posterior temporal cortex, but words could not be separated based on their visual-motion information. Other studies have demonstrated that while activation elicited by passive perception of written verb and noun stems does not differ, inflected verbs generate stronger activation compared to inflected nouns in left frontal (Tyler et al., 2004) or frontotemporal areas (Longe et al., 2007). In addition, the left prefrontal cortex and left superior parietal lobule have been shown to be selectively activated when verbs were produced in the context of short phrases, whereas noun production activated the left inferior temporal lobe, irrespective of semantic and morphological variations in the stimuli (Shapiro et al., 2006). These findings suggest that grammatical class is an important organizational principle for knowledge of language.

Confounding factors in studying verbs and nouns

As described above, verbs and nouns may differ in a number of aspects, such as age-of-acquisition, word frequency, concreteness and semantics. Thus, care must be taken to eliminate these confounding factors when designing experimental tasks. For example, it has been argued that differences in imageability (how easily a word evokes a mental image) between verbs and nouns can explain the grammatical category deficits in aphasia (Bird et al., 2000).

A number of different approaches have been used to eliminate the effect of these confounding factors. For example, differences between verbs and nouns might be controlled for by using both concrete and abstract words from matched semantic categories (Perani et al., 1999). Another possibility is to use both words and pseudowords in the context of short phrases to eliminate semantic confounds (Shapiro et al., 2006). In picture naming, concrete words with high imageability are usually assessed, and the semantic distinction between verbs as actions and nouns as objects is difficult to eliminate. One possibility to eliminate this confound is to use both verbs and nouns that refer to events (Siri et al., 2008).

5.3 Naming actions and objects (P3, P4)

In addition to the confounding factors described above, most picture naming tasks investigating action and object naming use different sets of images for verbs and nouns. Differences in visual input thus make it difficult to determine whether the resulting differences are related to the properties of the visual image or to actual differences in retrieving verbs or nouns. To address this issue, we investigated how the content of the image affects the pattern of activation in action and object naming. We used two sets of images: action images and object-only images (Figure 5.1). The participants performed silent action and object naming from action pictures, and object naming from object pictures. The images were presented in blocks of 10 images from the same category, with a resting period between blocks.

We performed identical measurements in fMRI and MEG, on the same subjects and using the same paradigm. Fifteen healthy native Finnish speakers participated in the fMRI experiment (Study P3). Of these subjects, data from eleven participants were obtained in the MEG experiment (Study P4). The MEG evoked responses were modeled by equivalent current dipoles (ECDs) and by using cortically constrained

minimum norm estimates (dSPM). The fMRI data were analyzed with random-effects group analysis in SPM2 within the general linear model framework.



Figure 5.1 Examples of stimuli used in Studies P3 and P4. A) Action images. B) Object-only images.

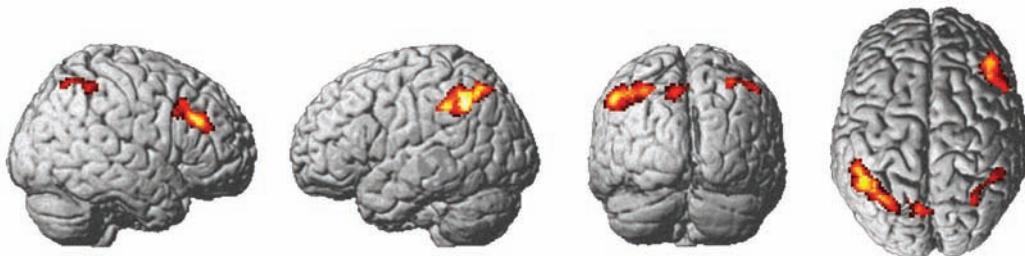
Action images vs. object images

In fMRI, action pictures, regardless of whether the subjects were instructed to name verbs or nouns, evoked stronger activation than pictures of isolated objects bilaterally in the posterior middle temporal cortex, in the left supramarginal gyrus, in the supplementary motor area, and in the left premotor cortex (for a surface view, see Figure 5.2B and C; for a schematic overview, see Figure 5.3A, blue color). Action pictures also evoked stronger activation in MEG in the left parietal and left frontal regions from about 250 ms onwards (see Figure 5.3B, blue color, and Figure 6.1).

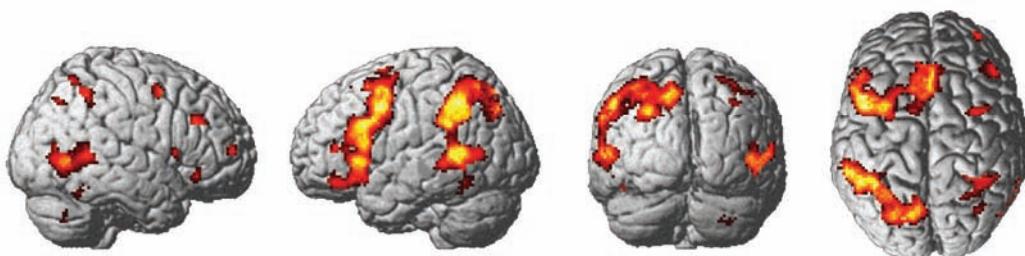
These results are in line with numerous previous studies showing that processing of action (or tool) knowledge involves cortical areas in the left premotor cortex (e.g. Valyear et al., 2007; Canessa et al., 2008), the left posterior middle temporal cortex (e.g. Martin et al., 1995; Martin et al., 1996; Kable et al., 2002), and the left parietal cortex (e.g. Noppeney et al., 2005). Several studies have also indicated these regions in processing verbs (e.g. Perani et al., 1999; Hauk et al., 2004; Corina et al., 2005; Shapiro et al., 2006), and in listening to action words and sentences (Noppeney et al., 2005; Tettamanti et al., 2005). Our data indicate that the activation pattern within these cortical regions in action and object naming relates to differential processing of the content of the image (action/object) rather than to computations specific to grammatical category or verb/noun retrieval.

In MEG, object images evoked stronger activation than action images in early visual regions in the time window 100–200 ms (Figure 5.3B, green color), probably reflecting increased processing of visual features for the object images where the shapes indicating action had been dissolved into random lines in the background (Figure 5.1B).

A Naming nouns from action images > Naming verbs from action images



B Naming nouns from action images > Naming nouns from object images



C Naming verbs from action images > Naming nouns from object images

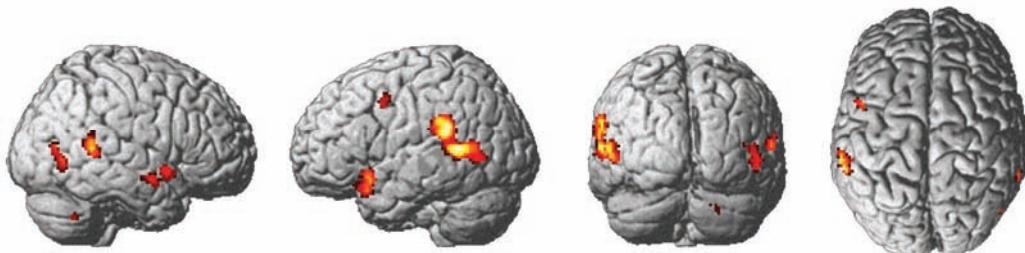


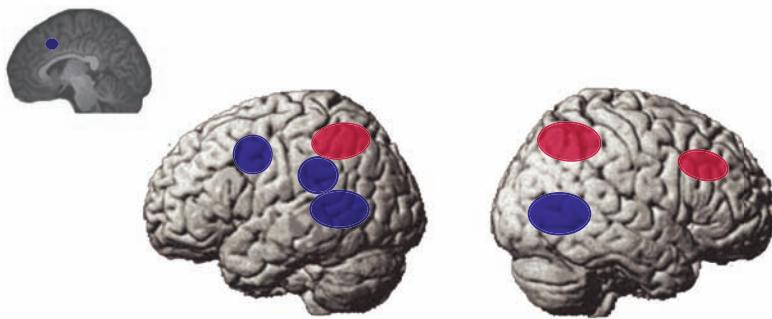
Figure 5.2. Results from the fMRI study. The results are shown at a significance level of $P < 0.01$, corrected for false discovery rate. Only the contrasts that revealed significant activation are shown. Adapted from Study P3.

Naming verbs and nouns from identical images

When the stimulus was the same (action image), retrieval of a verb did not reveal any significant activation increase compared to retrieval of a noun, neither in fMRI nor in MEG. Noun retrieval in the presence of action, however, revealed increased activation of the right frontal and bilateral parietal cortex in fMRI both in comparison to verb retrieval from the same set of images, and in comparison to noun retrieval from images with isolated objects (Figure 5.2A and Figure 5.3A, red color).

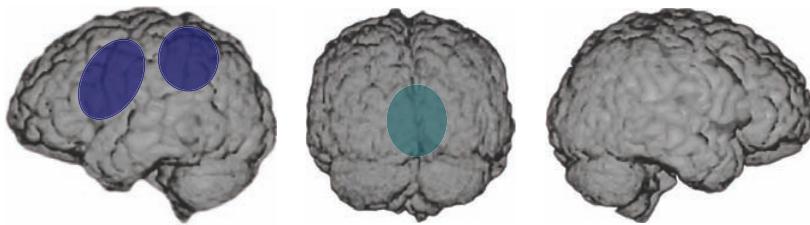
This activation pattern may reflect a visual search, or a shift of attention towards task-relevant objects (Nobre et al., 1997; Corbetta and Shulman, 1998; Beauchamp et al., 2001) when objects are named within an action scene. An alternative interpretation of the increased activation in the left posterior parietal cortex relates to

A



- Naming verbs and nouns from action images > Naming nouns from object images
- Naming nouns from action images > Naming verbs from action images
Naming nouns from object images

B



- Action image > Object image
- Object image > Action image

Figure 5.3. A) Results from the fMRI study. Schematic overview showing overlap in activation between contrasts comparing noun retrieval from action images to either verb retrieval from action images or noun retrieval from object-only images (red), and overlap between contrasts comparing verb or noun retrieval from action images to noun retrieval from object-only images (blue). Adapted from Study P3. B) Results from the MEG study. Schematic overview of areas showing significant differences between categories. Stronger activation for action images versus object images in the left frontal cortex (320–800 ms) and the left parietal cortex (260–320 ms) is shown in blue. Stronger activation for object images versus action images in the occipital cortex (100–200 ms) is shown in green. Adapted from Study P4.

the findings that this region is involved in explicit retrieval of actions associated with manipulable objects, as suggested by neuroimaging (Kellenbach et al., 2003; Boronat et al., 2005) and lesion data (Buxbaum et al., 2000; Buxbaum et al., 2005). Thus, naming objects in an action context may trigger access to knowledge about how

objects are used to a greater extent than when naming the same objects in isolation. The observed activations could, of course, also reflect both types of processes.

In fMRI, we did not detect any cortical area with increased activation when comparing noun retrieval from object-only images to verb or noun retrieval from action images. Thus, we found no regions specific to processing either verbs or nouns.

Conclusions

Our results, in both MEG and fMRI, demonstrate that image category (with/without action) has a stronger influence than naming category (verb/noun) on activation within the picture naming network. In lesion studies, verb and noun processing is typically assessed by asking the patients to name actions from action pictures and objects from object-only pictures. Based on our results, these two tasks do evoke different activation patterns also in the healthy human brain (Figure 5.2C). However, the differences do not seem to be specifically related to verb/noun retrieval, but may instead reflect conceptual processing of the image.

Our findings are in agreement with previous neuroimaging evidence (Hernandez et al., 2001; Sörös et al., 2003; Siri et al., 2008), showing that retrieval of verbs and nouns in the healthy human brain using identical stimuli in a picture naming task engages a similar distributed cortical network. Previous studies have suggested that verbs and nouns could be organized according to sensorimotor features (Vigliocco et al., 2006), or properties such as manipulability (Saccuman et al., 2006). These studies have been taken to indicate that semantic features, rather than grammatical class, serve as organizational principles of words. Our results further show that the context in which an object is presented affects the activation within the picture naming network.

6 Comparing MEG evoked responses and the fMRI BOLD signal

For a complete characterization of the cortical processes underlying language function an understanding of the "when" and the "where" in the brain is essential. Ideally, by combining the excellent temporal resolution of MEG and the spatial resolution of fMRI this could be achieved. Measurements combining different imaging techniques can be performed either simultaneously (e.g. combined EEG/fMRI or EEG/MEG measurements), or in separate sessions (e.g. MEG and fMRI). The implicit assumption in multimodal imaging is that the quantities measured by each imaging modality relate to the same neural activity in space and time. There are, however, several obstacles in merging, or even comparing, MEG and fMRI data.

Firstly, there is a need to bring the MEG and fMRI signals into a common reference space. The co-registration procedure of MEG and fMRI data to high-resolution MR images in itself may create some imprecision. In addition, imperfections in anatomical normalization (if applied), spatial smoothing (in fMRI), and the inexact spatial resolution in MEG may affect localization of corresponding activations. Secondly, and more importantly, due to the different nature of the signals, MEG and fMRI might be sensitive to different aspects of the overall neural activity. Most studies investigating the correlation between electromagnetic and hemodynamic measures have explored the co-localization of rhythmic activity and the BOLD response (e.g. Singh et al., 2002; Brookes et al., 2005; Winterer et al., 2007). We have focused on the correspondence between the most frequently used MEG measures, namely evoked responses, and the fMRI BOLD activation. In low-level sensory tasks MEG evoked responses and fMRI have shown relatively good agreement (e.g. Moradi et al., 2003; Brunetti et al., 2005; Sharon et al., 2007). In higher-level cognitive tasks that reach beyond early sensory or motor processing MEG and fMRI may, however, reveal greater divergence. For example, it has been shown that attentional modulation may affect both fMRI and late MEG responses, whereas early short-lasting activation detected by MEG may go undetected in fMRI (Furey et al., 2006). Studies P4 and P5 investigated the differences and similarities in the activation patterns obtained with MEG and fMRI in two relatively common language tasks: picture naming and reading.

6.1 MEG vs. fMRI in picture naming (P4)

In Study P4, our aim was to see whether fMRI and MEG results would yield the same pattern of activation in action and object naming when the experimental design and the participants were the same for the two imaging modalities. By introducing variations in the task (verb/noun retrieval) and the stimuli (action/object image) we asked whether functional differences between conditions in picture naming emerge in the same way in fMRI and MEG (see also Section 5.3).

As expected, there were many similarities in the overall activation patterns in MEG and fMRI (Figure 6.1). As shown by fMRI, the cortical network involved in picture naming included areas in the occipitotemporal, posterior and middle temporal, superior parietal, premotor and inferior frontal cortex, in line with previous fMRI

studies (e.g. Price et al., 1996; Murtha et al., 1999; Price et al., 2005). As shown by MEG, the focus of activation progressed from early visual areas (peaking around ~150 ms) to bilateral occipitotemporal cortex (around ~230 ms), and further to the parietal cortex (~300 ms). From about 300 ms onwards more sustained activations were observed bilaterally in the temporal and frontal cortex. These results are in good agreement with earlier MEG experiments on picture naming (e.g. Salmelin et al., 1994; Sörös et al., 2003; Hultén et al., 2009).

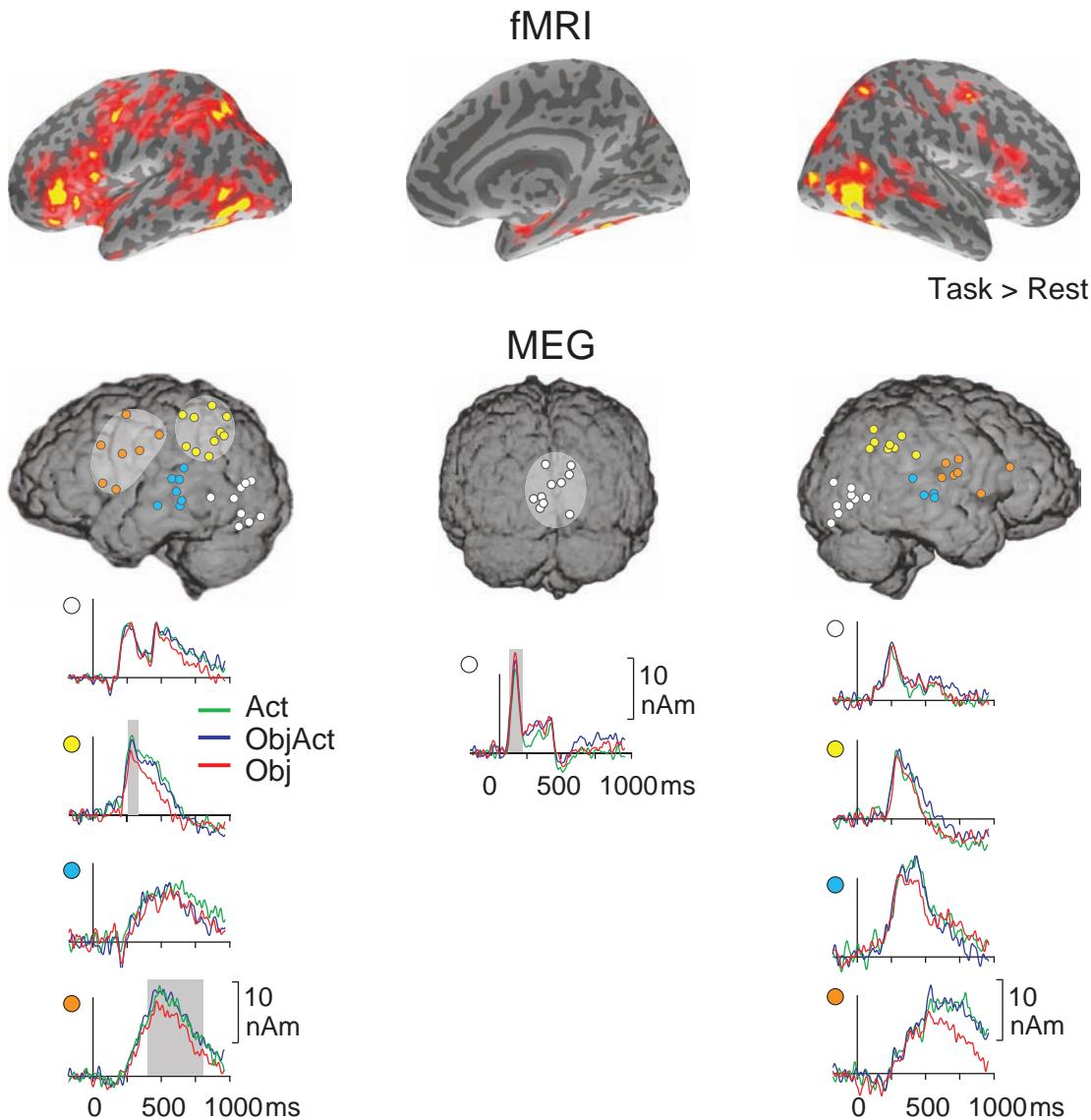


Figure 6.1. Group-level MEG and fMRI maps. Top: fMRI SPM2 analysis. Each view shows the Task > Rest contrast (FDR, $P < 0.01$). The results were visualized on a FreeSurfer-derived inflated cortex (Dale et al., 1999; Fischl et al., 2001). On the inflated view, dark gray areas represent sulci and light gray areas gyri. Bottom: MEG ECD analysis. The dots represent the centers of active cortical areas, and the colors the clustering based on location and time behavior. The curves depict the mean time course of activation in the clusters. The light gray shading denotes brain regions with significant difference between stimulus types. Obj – naming nouns from object-only images; Act – naming verbs from action images; ObjAct – naming nouns from action images. Adapted from P4.

As discussed in Section 5.3, the most prominent effect in fMRI was a weaker activation to naming nouns from object images than to naming verbs or nouns from action images in the frontal, inferior parietal and posterior temporal areas, particularly in the left hemisphere. A weaker activation to object images from about 250 ms onwards in the left frontal and parietal cortex was also the main finding in MEG (Figure 6.1). Although MEG and fMRI analyses agreed on stimulus differentiation in the left parietal and frontal cortex, fMRI data additionally revealed differentiation between action images and object images in the posterior middle temporal cortex. In MEG, activation of the temporal cortex from about 300 ms onward was observed, but it did not show task effects. The MEG left temporal activation was located approximately 2 cm anterior to the fMRI activation. Both localization and functional differences between these observations suggest that the left temporal activation in MEG seen in this time window may not correspond to the fMRI activation in the left posterior middle temporal cortex showing differentiation between conditions.

Even though fMRI and MEG showed involvement of a largely similar cortical network, there were differences between the methods in exact source locations, even in cortical regions where both methods showed similar task effects. At the group level, the average difference between MEG locations and fMRI local maxima was ~15 mm. The differences in location were slightly larger (~18 mm) in individual subjects than in the group-level data. These measures were calculated as the distance between the localized MEG activation and the nearest of potentially several fMRI local maxima, and should thus be considered as a lower limit for the observed mean differences in activation.

A number of systematic discrepancies between the MEG and fMRI activations were also observed. In the inferior frontal and premotor cortex, particularly in the left hemisphere, strong and extensive activation was seen in fMRI both at the group level, and in every individual. In MEG, frontal activation, as depicted by ECDs, was scattered, and was not observed in all subjects (Figure 6.1). MEG provides an estimate of the center of the active cortical patch but little or no information about its shape or extent. The scattered frontal ECDs may therefore also reflect an activation with large spatial extent, as suggested by the fMRI data, picking up the strongest source among active patches that are all likely to have fairly similar time courses.

In addition, fMRI revealed activation in several regions where MEG is known to show low sensitivity, such as the supplementary motor area, the hippocampus, and the cerebellum. As could be expected, these regions were not reliably detected with MEG. MEG, on the other hand, showed prominent early visual responses both at the group level and in all subjects, whereas fMRI group analysis did not display primary visual activation, as compared to the resting baseline. At the individual level, several subjects did show activation in early visual regions in fMRI. The lack of visual activation in the fMRI group data was probably due to the chosen resting baseline, depicting the Finnish word LEPO ("rest") during the whole resting period. Although instructed to look straight ahead, some of the participants may have performed saccades during the rest period. This visual stimulation during the rest block may well have masked the primary visual responses to the pictures presented during the task blocks.

6.2 MEG vs. fMRI in reading (P5)

Silent word reading has been studied extensively with both MEG and fMRI. Yet, despite many similarities, these two techniques have given partly diverging results on the cortical regions involved in reading, and on their functions. For example, MEG has revealed letter-string specific activation in the left occipito-temporal cortex that does not show differentiation between words and other letter strings (Tarkiainen et al., 1999), whereas fMRI has shown enhanced activation specifically to words in the visual word form area (VWFA; Cohen et al., 2002; Vinckier et al., 2007), situated slightly anterior the letter-string area observed in MEG studies. In addition, fMRI studies emphasize the role of the left inferior frontal cortex in reading, whereas MEG studies rarely reveal activation within this region in silent reading. Instead, MEG studies stress the importance of the superior temporal cortex in reading (Salmelin, 2007). To evaluate whether these discrepancies remain when the task, the participants, and the language are the same, we compared MEG evoked responses and fMRI BOLD signals in a one-back reading task. The fifteen participants were shown blocks of seven stimuli, each consisting of Finnish words, pseudowords, consonant strings, symbol strings, or words embedded in noise (Figure 6.2). The task was to detect an immediate repetition of the same stimulus. In addition, we measured EEG simultaneously with both MEG and fMRI to evaluate whether the subjects performed the task similarly in both environments. The MEG data were modeled by equivalent current dipoles (ECDs) and by using cortically constrained minimum norm estimates (dSPM). The fMRI data were analyzed within the GLM-framework in BrainVoyager.

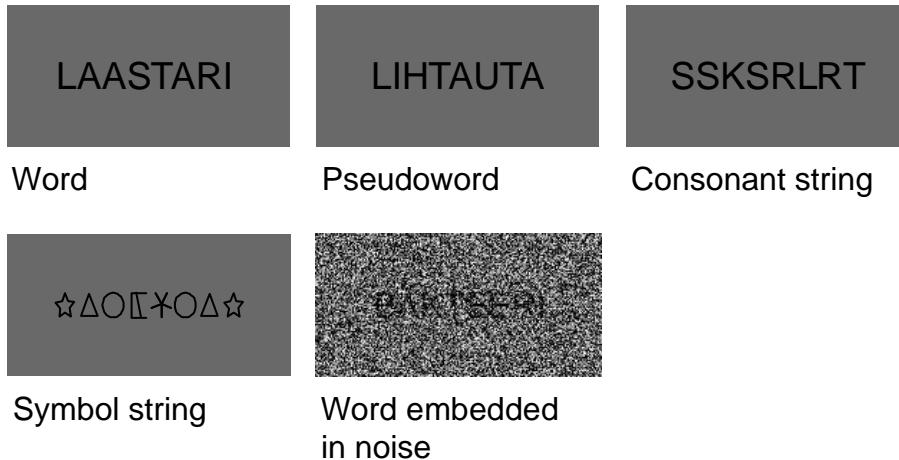


Figure 6.2. Example of stimuli used in Study P5.

In agreement with previous studies on reading (Jobard et al., 2003; Salmelin, 2007), our results in MEG and fMRI showed several cortical regions involved in processing written words, including regions in the occipital, left inferior occipito-temporal cortex, temporal cortex and left frontal cortex. In MEG, the activation advanced from the occipital cortex, peaking at ~100 ms after stimulus onset, to the bilateral occipito-temporal cortex, peaking at ~150 ms in the left hemisphere, and

~200 ms in the right hemisphere. From about 250 ms onwards, activation was seen in the temporal cortex, peaking around 400 ms. As expected, we found functional and spatial differences between MEG and fMRI within several cortical areas. Importantly, the EEG data showed no differences that could account for the observed differences.

Processing in the occipital and inferior occipito-temporal cortex

In the occipital cortex, the MEG and fMRI results were in good agreement both spatially and functionally, showing a bilateral activation with stronger activation to words embedded in noise than to other stimulus categories. This result is in line with previous studies that have shown similar localization of activation in the primary visual cortex with MEG and fMRI (Moradi et al., 2003; Sharon et al., 2007).

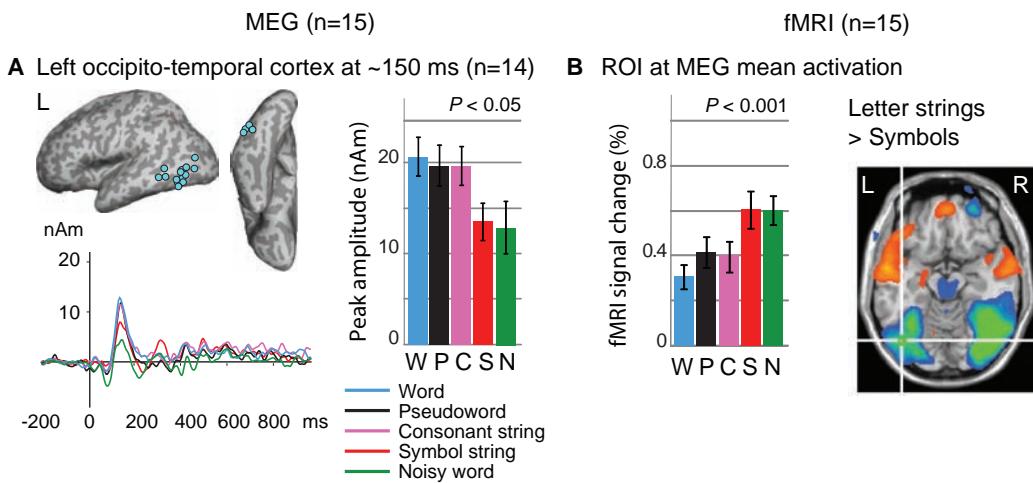


Figure 6.3 MEG and fMRI stimulus effects in the left occipito-temporal cortex. A) MEG results. The curves show the mean time course of activation. The bar graph displays the ECD maximum activation values (\pm SEM). B) fMRI results. The bar graphs display the fMRI signal change (%) in a $10 \times 10 \times 10$ -mm 3 region-of interest (ROI) centered at the mean MEG coordinate. (W=Words, P=Pseudowords, C=Consonants, S=Symbols, N=Noisy words i.e. words embedded in noise). Adapted from Study P5.

In the left occipito-temporal cortex MEG and fMRI showed opposite stimulus effects for letter and symbol strings (Figure 6.3). MEG responses around ~150 ms were stronger to letter strings than to symbol strings, in agreement with earlier MEG studies on reading (e.g. Tarkiainen et al., 1999). In contrast, fMRI activation within the same cortical area was stronger to symbol strings than to letter strings. There were no differences between real words, pseudowords and consonants strings. This effect extended also to the assumed visual word form area (VWFA; Vinckier et al., 2007). This result is in line with previous fMRI studies using similar tasks (Tagamets et al., 2000; Cohen et al., 2003), although other studies employing tasks with emphasis on perceptual processing of written words have found stronger activation to words than to other letter strings in the left occipito-temporal cortex (Vinckier et al., 2007).

We suggest that the MEG responses observed at ~150 ms in the left occipito-temporal cortex may reflect bottom-up processing of letter strings to a higher degree,

while the fMRI activation in the corresponding region showing the opposite stimulus effect may be dominated by additional top-down modulation. Such modulatory effects of attention have been shown to affect the fMRI activation and late, but not early, MEG activation in the left occipito-temporal cortex (Furey et al., 2006). In our one-back reading task, the participants may have attended the more demanding stimulus categories (symbol strings and words embedded in noise) more carefully, resulting in an increase of the fMRI activation.

Processing in the left frontal and temporal cortex

In the left inferior frontal gyrus, fMRI showed stronger activation to letter strings than to symbol strings or words embedded in noise. Among letter strings, words were further differentiated from consonant strings within this region (Figure 6.4). MEG activation in the left frontal cortex, slightly posterior to the fMRI activation, was weak and did not show stimulus effects. Strong frontal activation and stimulus effects in fMRI but not in MEG is a fairly common pattern in processing written words (Jobard et al., 2003; Salmelin, 2007).

From ~250 ms onwards, MEG activation was observed bilaterally in the middle part of the superior temporal cortex. This activation was stronger to words and pseudowords compared to consonant strings, symbols or words embedded in noise (Figure 6.4). Several MEG experiments have shown that activation within this region is sensitive to semantic, phonological, and morphological experimental manipulations of written words and pseudowords (Helenius et al., 1998; Wydell et al., 2003; Vartiainen et al., 2009a). The fMRI activation in response to words and pseudowords detected in the same location in the left temporal cortex did not differ with respect to consonant strings. These results confirm the dissociations between MEG evoked responses and fMRI activations in frontal and temporal regions in reading that have been observed in earlier studies, separately in each modality.

In conclusion, our results were in good agreement with previous MEG and fMRI experiments on reading, respectively, but revealed functional and spatial differences between MEG and fMRI in several cortical areas outside the visual cortex. The most striking difference was found in the left occipito-temporal cortex, where the two methods found opposite functional differentiation between symbols and letter strings.

6.3 Conclusions

Taken together, these two studies, investigating both language comprehension (Study P5) and production (Study P4), reveal differences between the MEG evoked response and the fMRI BOLD signal that cannot be explained by differences in paradigm, subjects or language. In addition, the EEG data, measured simultaneously with the fMRI and MEG in Study P5, showed no differences that could explain the divergence between the MEG and fMRI results. Instead, the observed differences are likely to reflect different sensitivity to different components of the overall neural activity between MEG evoked responses and fMRI BOLD signals.

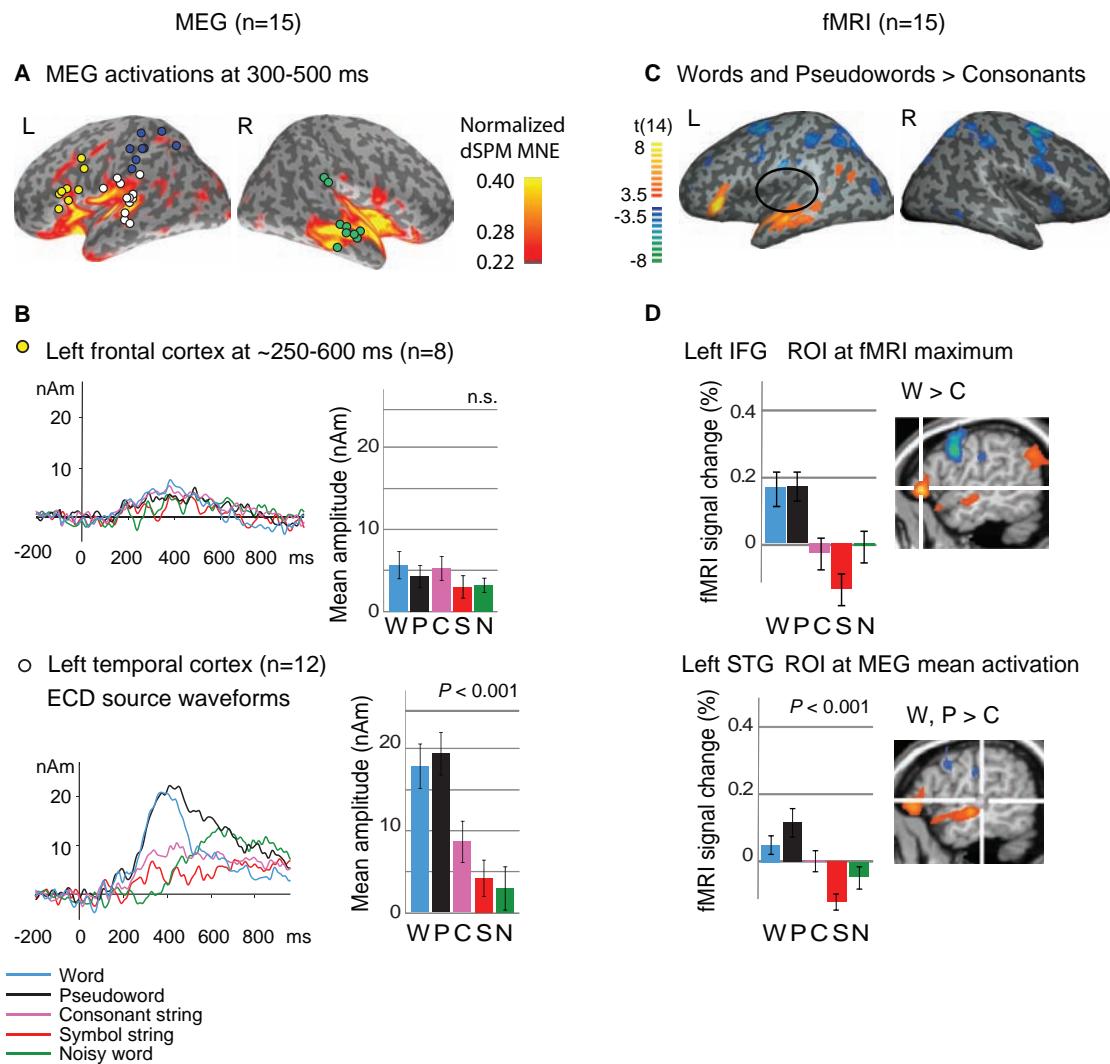


Figure 6.4. MEG and fMRI activations in the temporal and frontal cortex. A) MEG activations from ~250 ms onwards. The ECDs are overlaid on the mean MNE dSPM map for Words at 300–500 ms. The ECDs are color-coded by region (left temporal cluster in white, frontal cluster in yellow, parietal cluster in blue, right temporal cluster in green). B) MEG stimulus effects in the left frontal and temporal cortex. The curves show the mean time course of activation for the ECD clusters and the bar graphs the ECD mean amplitude values (\pm SEM) in the time window 300–500 ms. C) Group-averaged fMRI BOLD activations in the contrasts Words and Pseudowords > Consonants. D) The bar graphs display the fMRI signal change (%) in the ROIs centered at the fMRI activation maxima in the left frontal and for a ROI at the MEG mean activation in the temporal cortex. STG, superior temporal gyrus. IFG, inferior frontal gyrus. Adapted from Study P5.

Some of the discrepancies may derive from the fact that MEG and fMRI measure different aspects of brain function. The MEG signal reflects the synchronous activation of thousands of neurons, mainly of pyramidal cells (Murakami and Okada, 2006). Yet, non-synchronous activation that may remain undetected with MEG, may still contribute to the fMRI BOLD signal, for example through neuromodulatory mechanisms (Attwell and Iadecola, 2002; Logothetis, 2008). In reading as well as in picture naming a pattern of strong frontal activation in fMRI, but less pronounced

activation in MEG was observed. We thus confirmed the difference in emphasis on frontal activation observed in separate MEG and fMRI language studies before. A possible explanation for the different emphasis in activation in frontal regions between MEG and fMRI is that while MEG evoked responses reflect the part of the activation that is locked to stimulus timing, fMRI activation may, in addition, reflect long-lasting or multiple cognitive processes. In MEG, some of those processes might be captured by event-related modulations of cortical rhythmic activity, a measure of neural involvement that is less sensitive to small trial-to-trial variations in timing than evoked responses (see e.g. Salmelin and Hari, 1994a). Indeed, previous comparisons of electromagnetic and hemodynamic methods in cognitive tasks have emphasized co-localization of rhythmic activity (Singh et al., 2002; Brovelli et al., 2005; Lachaux et al., 2007). Other measures derived from the MEG signal, such as functional connectivity, may also show correspondence with the BOLD signal. For example, MEG evoked responses in the frontal regions are typically rather weak in silent reading but frontal regions do appear as nodes in functional connectivity analysis (Kujala et al., 2007).

Other discrepancies may be related to differences in the way the data are analyzed in the respective modalities. For example, event-related analysis is employed in MEG whereas fMRI signals are typically analyzed across blocks of several stimuli. Such differences may have caused the different activation pattern between MEG and fMRI in early visual regions in our picture naming study. In addition, inaccuracies in the co-registration of MEG and fMRI data are likely to produce errors in spatial correspondence.

Several studies have used fMRI BOLD maps as spatial constraints in MEG source localization (Liu et al., 1998; Korvenoja et al., 1999; Dale et al., 2000; Ahlfors and Simpson, 2004; Aurinen et al., 2009; Henson et al., 2010). Yet, MEG and fMRI may well give complementary information about brain function, the one method being able to detect activations that the other cannot, and vice versa. Such invisible sources in either MEG or fMRI pose a real challenge for using fMRI as a constraint in MEG analysis (e.g. Im et al., 2005). Differences in spatial location and functional differentiation between conditions between the two imaging techniques should be taken into account in conjoint analysis of MEG/EEG and fMRI.

7 General discussion

This Thesis considers cortical processing of language, as measured by neurophysiological (MEG) and hemodynamic (fMRI) measures. In MEG, the identification of the generators of neural activity requires localization with source modeling techniques. The accuracy of this procedure was explored in localization of cortical rhythms and for different head conductor models. Both MEG and fMRI have been extensively used in language research. Yet, a better understanding of the generation of these signals would be important for the interpretation of the results obtained with different brain imaging techniques. We asked how well the MEG evoked responses and the fMRI BOLD signal converged in two relatively common language tasks, picture naming and reading, when the experimental design and the subjects were exactly the same. A specific question in the picture naming studies was the processing of verbs (actions) and nouns (objects) in the brain.

Tracking brain dynamics with MEG

The combined temporal and spatial resolution of MEG allows tracking of complex activation sequences in the brain. In MEG, interpretation of the data critically depends on our ability to accurately estimate the underlying neural activity and localize it to a certain part of the brain, i.e. to solve the inverse problem. The precision of this procedure depends on many factors, such as the location and spatial extent of the underlying neural activity, and the head conductor model. Study P2 showed that in localization, performed under normal noisy conditions, a simple spherically symmetric conductor model is sufficient for many research applications.

Typical MEG and EEG experimental setups measure evoked responses. These measures provide a description of the cortical areas involved in a certain task that are strictly time- and phase-locked to the stimulus presentation. An important complement to the use of evoked responses is the characterization of ongoing rhythmic activation, which may provide the means to investigate cortical function in more natural, continuous tasks. In Study P1 a comparison of different source modeling techniques applied to simple ongoing tasks showed that rhythmic activity can be identified reliably with a variety of tools, such as equivalent current dipoles (ECDs), minimum norm approaches (MCE_{FD}), and beamformers (DICS). DICS was shown to be more sensitive to weak sources than the two other methods, both in measured and in simulated data. Recent studies have successfully applied these (and related) tools in, e.g., studying memory encoding and retrieval of visually presented images (Osipova et al., 2006), in error processing in a visual Go-noGo task (Mazaheri et al., 2009), and in motor cortex involvement of speech and non-speech mouth movements (Saarinen et al., 2006).

For the most part, MEG reports on rhythmic oscillations have focused on visual or motor tasks which affect the rhythmic activity in regions such as the sensorimotor cortex (mu rhythms) or visual cortex (alpha rhythms, gamma rhythms), in which these cortical rhythms are particularly prominent. A challenge for the use of cortical rhythms in studying language function is whether cortical rhythms can be identified

reliably using noninvasive measures in other brain regions, in which these rhythms are not equally prominent. Intracortical measurements (iEEG) (Lachaux et al., 2007; Dalal et al., 2009; Edwards et al., 2010) have revealed gamma band oscillations related to language function, but application of iEEG is highly restricted to patient groups, and to a limited area of the cortical surface in each study. Identification of gamma band oscillations using noninvasive measures is difficult, as the signal-to-noise ratio for gamma oscillations measured outside the head with MEG or EEG is poor (Hoogenboom et al., 2006). In addition, muscle activity and microsaccades, produce artifacts within the same frequency band (Trujillo et al., 2005; Hoogenboom et al., 2006). Indeed, simultaneous recordings of MEG and iEEG in attentive reading have shown that gamma band oscillations, although present at the cortical level, are difficult (but possible) to detect with MEG (Dalal et al., 2009).

Beamformer approaches, such as DICS, which was shown in Study P1 to be more sensitive to weak sources, may thus be an important asset in localizing these weak cortical rhythms. Through recent methodological improvements of the DICS algorithm this method can now also be applied in localizing task-related changes in rhythmic activity (erDICS, Laaksonen et al., 2008). Yet, the perhaps most important application of DICS in future studies is in the analysis of cortical coherence (Gross et al., 2001; Kujala et al., 2008). To date, most imaging studies have focused on mapping the areas involved in specific linguistic tasks. However, for a complete understanding of the processes that underlie complex cognitive functions, such as language, we need to characterize not only the areas involved, but also the interactions between these areas. This approach was taken in a recent study on reading, which demonstrated that a distributed cortical network of interconnected regions involved in continuous reading can be identified with the DICS method (Kujala et al., 2007). This approach shows promise for further characterization of the complex cortical networks involved in language perception and production.

Comparing MEG evoked responses and the fMRI BOLD signal

The most promising strategy for studying language function lies in the combined use of different techniques. For a full understanding of the processes underlying language function, we should therefore aim at integrating the results from both MEG and fMRI and take advantage of the possibility to gain complementary information from the two techniques, even beyond simply a combination of timing (MEG) and spatial location (fMRI).

For an efficient combined use of MEG and fMRI, we must first have a deep understanding of how these measures relate to each other. In this Thesis, we present a comparison between MEG evoked responses and fMRI BOLD signals in picture naming and reading. Through these tasks, we evaluated the correspondence of the overall MEG and fMRI patterns in language processing in order to find how the stimulus and task effects were manifested in the two imaging modalities.

As expected, we found many similarities between the results from each technique, in both picture naming and reading. Interestingly, we also found differences in both location and functionality in a number of cortical regions. In picture naming (Study P4), the overall activation pattern and functional differences in MEG and fMRI were similar, despite specific differences in exact spatial locations, and dissimilar functional differentiation between conditions in the middle temporal cortex. In reading, clear differences in the functional roles of the MEG and fMRI

activations were observed in a number of cortical regions outside the visual cortex, although the simultaneously recorded EEG was similar. The most remarkable discrepancy was found in the left occipito-temporal cortex, where MEG and fMRI activations showed opposite functional effects in response to symbols and letter strings. Study P5 thus demonstrated that differences seen earlier in reading, in separate MEG and fMRI experiments, arise also when the participants, paradigm, and language are the same. The observed differences are, instead, likely to reflect the different generation mechanisms of the MEG evoked responses and fMRI BOLD signals.

In this Thesis we focused on the relationship between the BOLD signal and the most common MEG measure, evoked responses. However, it is possible that some other MEG measure, such as task-related changes in rhythmic activity, may correspond better with fMRI BOLD activations. Indeed, studies investigating the correlation between electromagnetic and hemodynamic measures have generally indicated that cortical oscillations, particularly in the gamma range, are spatially and functionally correlated with hemodynamic changes in the cortex, especially in visual tasks (Brookes et al., 2005; Zumer et al., 2010). However, these studies also demonstrate that the relationship between the BOLD signal and electromagnetic measures may be quite complex, and depend on the frequency of the neural oscillations (Winterer et al., 2007; Zumer et al., 2010) as well as on the brain region (Ekström et al., 2009; Martuzzi et al., 2009). Recent studies of the monkey visual cortex also indicate that the coupling between the BOLD signal and electrophysiology depends on the task, and may be influenced by, e.g. perception (Maier et al., 2008) and anticipation (Sirotin and Das, 2009). Here, we demonstrate that while MEG and fMRI identify many of the same cortical regions involved in language processing, the MEG evoked responses and the fMRI BOLD signal can be dissociated in certain tasks and in certain regions, as shown by the opposite stimulus effects in the left occipito-temporal cortex in reading. Taken together, these studies suggest that any single measure (e.g. LFPs, MUAs, gamma rhythms, evoked responses), might not account for the whole BOLD signal, but most likely the BOLD signal reflects a combination or a mixture of these, and possibly other, measures.

In the studies presented in this Thesis, we have shown that the MEG evoked response and the fMRI BOLD signal differ in a number of aspects. In the future, we may be able to exploit differences between MEG and fMRI in designing experiments capitalizing on the different sensitivity of each measure to the overall neural activation pattern. Yet, such a full use of these methods would require a better understanding of which variables affect MEG and fMRI signals differently. By systematically exploring how changes between experimental conditions, for example in attention, affect the MEG and fMRI signals, we may gain a more complete understanding of the relationship between the MEG signals and the fMRI BOLD signal, necessary for the combination of these methods.

Perceiving and naming actions and objects

In this Thesis, we applied both fMRI and MEG to investigating action and object naming in healthy individuals. Differences in the neural representation of nouns and verbs have been studied extensively in patients with brain damage, but whether nouns and verbs are differentiated in cortical processing in the healthy human brain remains an unresolved question.

Studies P3 and P4 demonstrated that image category (action/object) has a stronger influence than naming category (verb/noun) on activation in picture naming, as measured with both fMRI and MEG. We did not find verbs and nouns differentiated in cortical processing in healthy participants, even though we employed picture naming, which has been the preferred task in patient studies indicating verb/noun dissociations. Instead, our studies show consistent activation related to action images in several cortical regions that have previously been identified in processing action (and tool) knowledge, irrespective of whether the participants were instructed to name verbs or nouns. The relatively late time window in which these conditions were separated shows that the differences were not related to early perceptual processing.

Our results imply that the dissociation between verb and noun naming observed in patients may, in some cases, reflect impairments in the way the specific images are processed and not in calculations specific to grammatical category as such. Whether differences in processing action and object images can be observed in patients suffering from a disproportionate deficit in processing either verbs or nouns would require further investigation. As patients show a large variety in lesion site and of the exact nature of the processing deficit in either production or comprehension it is, however, unlikely that this could explain the verb/noun dissociation in all patients. In addition, the activation patterns in a healthy and a lesioned human brain may not be directly comparable. For example, an MEG study of picture naming (Sörös et al., 2003) found divergence in the cortical routes of activation between object and action naming from identical images for an anomic patient who presented difficulties in object naming. Yet, the activation chains for both object and action naming deviated from those of the healthy controls performing the same task. Furthermore, in the healthy participants, the activation pattern between action and object naming from identical images did not differ, in agreement with the results presented in this Thesis. Such differences between processing in the healthy and damaged brain pose a challenge in reconciling results from neuroimaging and patient studies.

Our results in picture naming also highlight the importance of the context in which an object is presented. When objects were presented not as single entities but as part of images that also depict the relevant action, we observed increased activation in a number of regions within the cortical network involved in picture naming. Our results show that an object presented in a proper context is processed differently in the brain than an object presented in isolation – even for the simple line drawings in our experiment. This result emphasizes the need to move towards more realistic, natural experimental settings in the future.

Our studies did not reveal any cortical regions specific to processing either verbs or nouns that could explain the existence of a double dissociation between these grammatical categories in patients with brain damage. This may be because verbs and nouns are truly non-separable in the healthy human brain, but it may also be that differences between these grammatical categories would emerge in other types of tasks, for example in sentence production (Shapiro et al., 2006), or in another type of analysis, such as in the strength of cortico-cortical interactions (Kujala et al., 2007). Future studies investigating the connectivity between cortical regions in action and object naming in MEG may reveal distinctions between how these grammatical categories are processed in the brain that are not detected using conventional activation analysis.

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