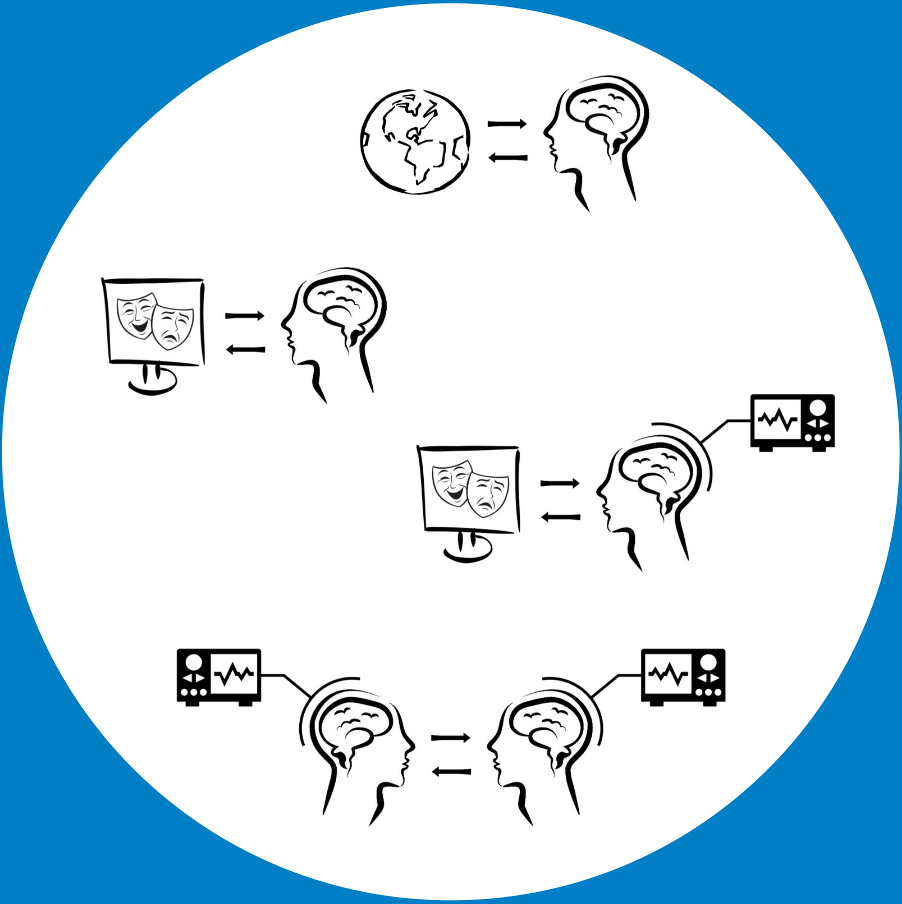
Capturing complex behavior in brain imaging: strategies and instrumentation

Andrey Zhdanov



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Capturing complex behavior in brain imaging: strategies and instrumentation

Andrey Zhdanov

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Abstract

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Abstract

Functional neuroimaging investigates the human brain through non-invasive recordings of brain signals or non-invasive stimulation. Traditionally, neuroimaging practitioners attempted to restrict the subject's behavior throughout the experiment to the point where it could be completely characterized by a few simple variables. Although this approach has its merits, it considerably limits the possibilities for investigating neural mechanisms underlying the organism's function under natural conditions. To overcome this limitation, researchers have increasingly focused on neuroimaging studies of subjects involved in complex ecologically-valid behavioral tasks. The shift from simple to complex behavior in neuroimaging studies brings along the demand for: (1) new instrumentation for handling the behavioral aspect of the experiment, and (2) new experimental designs that exploit the complexity of the participant's behavior instead of trying to suppress it.

The thesis comprises four publications that examine the capacity of video technology to provide new instrumentation and explore possibilities for new experimental designs utilizing rich behavioural information provided by video, in the context of magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS) methods. Additionally, it introduces the Helsinki VideoMEG Project---an open-source collaborative effort aimed at providing MEG practitioners with video recording and analysis tools.

The first part of the thesis (Publications I and II) examines the feasibility of augmenting TMS and MEG experiments with simultaneous synchronized video and audio recordings of the participant. The second part of the thesis (Publications III and IV) explores the possibility of using audio and video to link the participants in an MEG hyperscanning experiment---simultaneous recording of MEG signals from two interacting subjects.

The results presented in this thesis demonstrate the feasibility of augmenting TMS and MEG experiments with synchronized video and audio recordings.

Keywords magnetoencephalography, MEG, transcranial magnetic stimulation, TMS, complex behavior, video

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Preface

A preface to a doctoral thesis invariably tells a fairy tale of a Ph.D. student that is unlike any human that ever walked on Earth. This mythical creature spends most of it's time doing research that is both challenging and rewarding. Under the encouraging and enlightening guidance of it's supervisors it works in the laboratory that offers excellent experimental facilities, aided by resourceful lab engineers and friendly support personnel. In it's quest for knowledge it receives immeasurable support from highly skilled and devoted collaborators, whose friendship and advice it values so dearly. Every now and then the creature shares it's discoveries with the rest of the world by publishing scientific papers—the process that is greatly facilitated by constructive comments from infallibly insightful reviewers. And, of course, the whole undertaking is made possible by generous financial help of numerous benevolent research funding agencies.

While I would love to entertain the reader with another masterpiece of this genre, I am afraid that my fiction-writing skills are by no means up to the task. Therefore I decided to depart from the time-honoured tradition of the thesis preface writing by doing something I've never seen done before—using the preface to reflect upon the author's real experience as a Ph.D. student. I apologize to the reader for such a grave violation of his (or her) expectations.

Unlike my counterpart from the fairy-tale world of thesis prefaces, I could only dedicate a small fraction of my working time to the actual research. Most of my time was wasted doing things that were only tangentially related to science, like preparing grant applications or deciphering poorly-written articles, which, upon finally being deciphered, turned out to have little scientific merit.[1] Nonetheless, the real research, however little time I spent on it, was indeed challenging and rewarding.

Just like the fictional Ph.D. student, I was lucky to have excellent thesis advisers. I was equally lucky to have access to world-class research facilities of the BioMag laboratory at the Helsinki University Hospital, even though support provided by various hospital bodies was somewhat less than universally excellent.[2] And, naturally, Ph.D. studies offered me numerous opportunities for collaboration with other scientists, some of them quite outstanding (whether "outstanding" refers to "opportunities" or "scientists" depends heavily on the scientist in question).

Finally, my experience with publishing scientific papers and securing research funding also turned out to be notably different from that of my imaginary counterpart. (Detailed treatment of the topic is beyond the scope of this work; for a more comprehensive discussion I would like to refer the reader to numerous ranting posts on disgruntled scientists' blogs and cynical cartoons decorating the kitchen walls of any research laboratory worth it's salt.)

I would like to conclude by acknowledging the contributions of all those who helped me in the enterprise of writing the thesis. I want to express deep appreciation to my former and current supervisors, Academy Professor Risto Ilmoniemi and Professor Lauri Parkkonen, for trusting my ability to work independently and giving me complete freedom to plan and conduct my research without imposing any restrictive targets, milestones or deadlines. I am also greatly indebted to my thesis instructor Docent Jyrki Mäkelä and a key collaborator Academician Riitta Hari for not trusting my ability to work independently and providing me with a rigid framework of targets, milestones and deadlines that, embarrassing as it is, have proven crucial to the progress of my studies. I would like to thank all of my co-authors and other scientists who collaborated with me in my research. They all made my life easier; some from the very first day

---

[1] It should be noted that not all the scientific publications are worthless, only the vast majority. A diligent reader of scientific literature every once in a while happens to come across a paper from which he can actually learn something new. I myself have enjoyed the pleasure of several such encounters, although I am somewhat disturbed by the fact that too often the articles worth reading have titles like "Why Most Published Research Findings Are False" or "Why Current Publication Practices May Distort Science".

[2] For an illustrative example of support offered by the hospital IT department, the reader is advised to open the text of the novel "The Castle" by Franz Kafka in his or her favorite text editing software and perform the following modifications: replace every occurrence of "Castle" with "Helsinki University Hospital", "K." – with "the Ph.D. candidate", "messenger Barnabas" – with "laboratory engineer Juha Montonen", and "chief executive Klamm" – with "telecommunication specialist Kari Koivumäki".

of our collaboration, while others – from the moment the collaboration has ended.

The complete list of people who deserve credit for helping me along the road leading to this thesis—laboratory engineers, thesis pre-examiners, administrative assistants and many, many others—is too long to be printed here without turning the thesis into a phone directory with a small appendix on neuroimaging at the end. Nevertheless, I would like to express my gratitude to them all. There are two persons on that list, however, that I would like to single out; for in their efforts to help me they went far beyond anything I have expected. They are my good friend and collaborator Dr. Ritva Paetau and a former administrative assistant of the BioMag laboratory Pirjo Kari. Thank you so much!

It is also worth noting that the research described in this thesis was to a considerable degree facilitated by the fact that I was able from time to time to buy myself some food and pay an apartment rent. The credit for this accomplishment belongs, among others, to HUS Medical Imaging (product development grant M9200TK502), SalWe Research Program for Mind and Body (Tekes - the Finnish Funding Agency for Technology and Innovation grant 1104/10), Aalto Brain Center and the European Research Council (ERC Advanced Grant #232946 to Riitta Hari).

Helsinki, May 30, 2016,

Andrey Zhdanov

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6. Discussion and conclusions **41**

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List of Publications

This thesis consists of an overview and of the following publications which are referred to in the text by their Roman numerals.

I Lioumis P, Zhdanov A, Mäkelä N, Lehtinen H, Wilenius J, Neuvonen T, Hannula H, Deletis V, Picht T, Mäkelä J P. A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. *Journal of Neuroscience Methods*, 204, 2012.

II Zhdanov A, Wilenius J, Paetau R, Mäkelä J P. Quantifying the contribution of video in combined video-magnetoencephalographic ictal recordings of epilepsy patients. *Epilepsy Research*, 105, 2013.

III Baess P, Zhdanov A, Mandel A, Parkkonen L, Hirvenkari L, Mäkelä J P, Jousmäki V, Hari R. MEG dual scanning: a procedure to study real-time auditory interaction between two persons. *Frontiers in Human Neuroscience*, 6, 2012.

IV Zhdanov A, Nurminen J, Baess P, Hirvenkari L, Jousmäki V, Mäkelä J P, Mandel A, Meronen L, Hari R, Parkkonen L. An Internet-Based Real-Time Audiovisual Link for Dual MEG Recordings. *PLOS ONE*, 10, 2015.

Author's Contribution

Publication I: "A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation"

The author designed and implemented the instrumentation for augmenting TMS procedure with audiovisual recordings, and contributed to the manuscript preparation.

Publication II: "Quantifying the contribution of video in combined video-magnetoencephalographic ictal recordings of epilepsy patients"

The author developed the video-MEG instrumentation used in the study. He actively contributed to the study design, provided support for the data analysis, and is the principal author of the manuscript.

Publication III: "MEG dual scanning: a procedure to study real-time auditory interaction between two persons"

The author made a major contribution to the design and implementation of the experimental setup. He also contributed to the data analysis and manuscript preparation.

Publication IV: "An Internet-Based Real-Time Audiovisual Link for Dual MEG Recordings"

The author made a major contribution to the design and implementation of the experimental setup and data analysis. He is the principal author of the manuscript.

List of Abbreviations

1PN	One-person neuroscience
2PN	Two-person neuroscience
AV	Audiovisual
EEG	Electroencephalography
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
MEG	Magnetoencephalography
NIRS	Near-infrared spectroscopy
nTMS	Navigated transcranial magnetic stimulation
PET	Positron emission tomography
SQUID	Superconducting quantum interference device
TMS	Transcranial magnetic stimulation
VR	Virtual reality

1. Functional brain imaging

Functional brain imaging is a broad term. For the purpose of this thesis, I define functional brain imaging as the study of human brain function through either non-invasive recordings of brain activity or non-invasive stimulation with the characteristic time scale ranging from milliseconds to tens of minutes.

1.1 Brain activity recordings

Functional brain imaging can be performed by recording various signals that reflect physiological processes in the brain. For example, electroencephalography (EEG) records voltages on the scalp that result from the electrical activity of neurons (for a review, see Nunez and Srinivasan, 2007). Functional magnetic resonance imaging (fMRI) monitors the distribution of the oxygenated blood inside the brain, reflecting neuronal metabolic activity (reviewed by Ogawa and Sung, 2007). Positron emission tomography (PET) can measure the distribution of a number of different radioactive tracer molecules that reflect different aspects of brain's metabolic activity (reviewed by Ollinger and Fessler, 1997). Other commonly used functional brain modalities include near-infrared spectroscopy (NIRS; reviewed by Boas and Franceschini, 2009) and magnetoencephalography (MEG; reviewed by Hämäläinen et al., 1993; Cohen and Halgren, 2003).

1.2 Brain stimulation

As an alternative to recording brain activity, one can use non-invasive stimulation for studying the brain. The most widely used non-invasive stimulation technique is transcranial magnetic stimulation (TMS), which uses electromagnetic induction to create an electric current inside the brain without opening the skull (for a review, see Barker and Freeston, 2007).

1.3 General remarks

When talking about functional brain imaging one should keep in mind that the term "imaging" is somewhat misleading. In many disciplines imaging means measuring some quantity in a number of spatially different locations, usually regularly spaced, with each measurement being independent of others. This independence essentially means that imaging makes no a priori assumptions about the spatial distribution of the measured quantity. However, not all methods that are commonly referred to as "functional brain imaging", comply with this definition. For example, in EEG recordings, the signals originating from spatially distinct locations are mixed in a complex way and, in general, are inseparable. Although numerous methods exist for inferring the underlying spatial distribution of brain electrical activity (for a review, see Grech et al., 2008), they all rely heavily on a priori assumptions about the distribution they are trying to estimate, and therefore their estimates of brain activity at different locations are by no means independent.

Whereas functional brain imaging modalities differ in many respects, they all focus on the brain properties that change on a time scale ranging from milliseconds to tens of minutes. For comparison, longitudinal anatomical studies are similar to functional imaging studies in many respects—both study the brain by measuring certain brain parameters that change over time. However, unlike functional imaging, the longitudinal anatomical studies track the changes over the periods ranging from days to years.

Functional neuroimaging is mostly used in basic brain research. Additionally, it is being increasingly adopted in clinical practice. Clinical applications of functional neuroimaging include localization of the sources of epileptic activity in the brain with EEG and MEG, and functional brain mapping for preoperative planning with MEG, TMS, and fMRI. Functional brain mapping is a process of identifying brain areas that underlie specific behavioral or cognitive functions, such as production and comprehension of speech or motor control of a particular limb.

2. Basic principles of MEG and TMS

This chapter introduces the basics of two particular functional neuroimaging modalities—MEG and TMS—that were employed in the research described in the thesis.

Human brain consists of large number (estimated 10^{12}) of cells. About 2–10% of these are neurons—intricately interconnected cells that are generally agreed to be at the core of the information processing in the brain (Kandel, 1991). The rest are glial cells that are thought to provide support for neurons and participate in the information processing indirectly. The principal distinction between neurons and glial cells is the neurons' ability to fire or generate action potentials—short bursts of electrical activity that are believed to be at the core of the information processing in the brain. As a rough approximation, one can think of each neuron as a basic information processing unit that receives input represented by action potentials of antecedent neurons and performs a simple non-linear computation that results in the action potential either being produced or not. The resulting action potential (or the lack of thereof) in turn serves as the input to subsequent neurons. A neuron communicates the occurrence of the action potential to subsequent neurons through connections called synapses. A single neuron may form synaptic connections with up to 10^5 other neurons (Kandel, 1991).

The time that a single neuron needs to receive the inputs, perform the computation and produce the output is measured in single milliseconds. This defines the desirable temporal resolution of about 1 ms for functional brain imaging.

The neurons in the brain are not randomly scattered, but rather organized into a number of quite elaborate anatomical structures. One such structure—the cerebral cortex—is of particular interest to MEG and TMS. The cortex constitutes a large thin sheet of neuronal tissue comprising neurons organized in regular patterns. In humans, the cortical sheet spans a total area of about 2200 cm^2 and has a thickness between 1 and 4.5 mm (Brodmann, 1909). The human cortex is folded, resulting in the iconic pattern of sulci and gyri, and occupies the outermost part of the space inside the skull. The proximity to sensors or stimulation coils that can be non-invasively placed on the surface of the head and the relatively simple regular cellular structure of the cortical tissue make cortex the favourite target of many functional neuroimaging methods, such as EEG, MEG, TMS, and NIRS.

2.1 Magnetoencephalography (MEG)

2.1.1 Sources of MEG signals

MEG measures, outside of the head, the magnetic signatures of electric currents inside the brain (Hämäläinen et al., 1993; Cohen and Halgren, 2003). Although the relation between neuronal activity and the ensuing magnetic fields is rather complex (Murakami and Okada, 2006; Buzsáki et al., 2012), it is generally agreed that the magnetic fields observed by MEG reflect synchronized activity of large populations of cortical neurons. The fields arise from post-synaptic currents—electric currents produced inside a neuron when it receives a signal from an antecedent neuron through a synapse. The cortex contains large populations of neurons in which post-synaptic currents flow in the same direction; when a significant proportion of neurons in such a population simultaneously receive signals through their synapses, the magnetic fields of individual post-synaptic currents add up to the values that can be detected outside of the head. It has been estimated that simultaneous activation of as few as 10 000 neurons can produce a magnetic field that is strong enough to be detected with MEG (Murakami and Okada, 2006).

The simplest way to model the sources of MEG signals is in terms of current dipoles—infinitesimal units of electrical current characterized by their strength (absolute value of the dipole moment), position and orientation. When a compact population of cortical neurons activate in synchrony, they produce a net magnetic field that can be quite accurately modelled as a field of a current dipole with location and orientation corresponding to the location and orientation of the neurons. In the cortex,

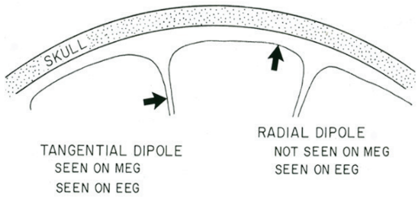

Figure 2.1. Dipole model for the MEG/EEG signal generation. Adapted from Cohen and Halgren (2003).

the dipoles are typically oriented normally to the surface of the cortical sheet. Because of the cortical folding, this does not mean that they are necessarily oriented normally to the skull (see Fig. 2.1).

In addition to the current of the dipole itself, each dipole induces a distribution of passive ohmic currents in the brain that close the current loop so that there is no build-up of charge anywhere in the brain. The spatial distribution of these so-called volume or return currents is determined by the dipole's strength, location and orientation, and by the conductivity distribution of the brain tissue. Assuming that the latter does not change over time, the distribution of the volume currents and the total magnetic field produced by the dipole and the return currents is uniquely determined by the dipole's location, orientation, and strength. This gives a rise to a somewhat confusing convention of omitting explicit mentions of return currents in the literature. Thus "magnetic field of dipole X" usually means "the magnetic field of dipole X and that of the associated return currents". This convention is used for the rest of the thesis.

The strength of the magnetic field produced by a neuronal population is proportional to the stength of the corresponding equivalent dipole and depends on the dipole's location and orientation (see Fig. 2.1). In the idealised case of a dipole inside a spherically symmetric conductor, radial dipoles produce zero field outside of the sphere. This phenomenon is caused by the return currents producing field that cancels out the field of the dipole everywhere outside of the sphere. Although a sphere provides only an approximate model of a human head, the conclusion about MEG's lesser sensitivity to radial dipoles holds to a large degree also in real MEG recordings.

2.1.2 MEG instrumentation

Magnetic fields produced by neuronal currents are extremely weak—on the order of 10^{-14} T. For comparison, the Earth's magnetic field is of the order of 10^{-4} T. Thus, recording of neuromagnetic signals requires extremely sensitive sensors and heavy shielding against environmental interference. Although first MEG experiments employed a room-temperature coil as a sensor (Cohen, 1968), MEG only became practical with the invention of a superconducting quantum interference device (SQUID)-based magnetic sensors (Zimmerman and Frederick, 1971; Cohen, 1972).

Modern MEG devices comprise hundreds of SQUID-based sensors located over a large part of the subject's scalp (Hämäläinen et al., 1993; Ahonen et al., 1993; Cohen and Halgren, 2003). To reduce the environmental interference, MEG measurements are usually conducted inside a magnetically-shielded room. MEG devices can sample the subject's neuromagnetic fields at frequencies up to several kHz, thus attaining the temporal resolution necessary to resolve the firing of a single neuron. Most modern MEG devices allow simultaneous recording of EEG and MEG.

2.1.3 Relation between MEG and EEG

Magnetoencephalography is closely related to the much older practice of electroencephalography, or recording electric voltages from the participant's scalp. It is widely agreed that MEG and EEG signals are produced by the same mechanism—postsynaptic currents of cortical neurons. However, since the two modalities observe different aspects of the neuronal current's signatures, the information they provide is complementary. In particular, the modalities have different profiles of sensitivity to dipole orientation. For example, EEG is more sensitive to radial dipolar sources than MEG, whereas the latter is more selective to the tangential dipoles (for an example, see Fig. 2.1). It has been demonstrated that each of the modalities provide information not available from the other and combined EEG-MEG recordings outperform each of the constituent modalities alone (Iwasaki et al., 2005; Sharon et al., 2007; Heers et al., 2010).

2.1.4 Applications

MEG is an established neuroimaging modality with commercial MEG scanners readily available and routinely used in both basic research and clinical practice. Clinical applications of MEG are dominated by preoperative localization of sources of epileptiform activity in epilepsy patients, where MEG was demonstrated to provide information that is unavailable

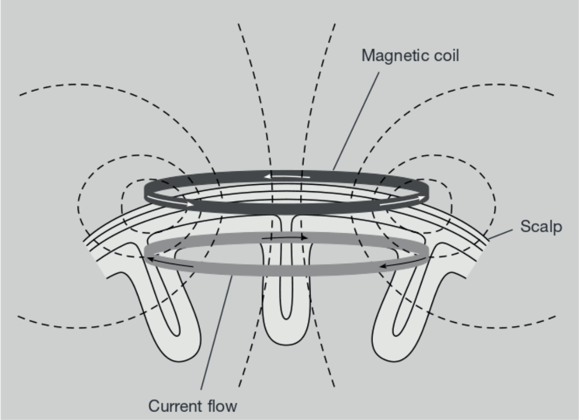

Figure 2.2. Physics of TMS. A current pulse in the stimulation coil outside of the head (dark gray) induces changing magnetic field (dashed lines), which, in turn, causes electric current inside the brain (light gray). Adapted from Hallett (2000).

from other modalities (Iwasaki et al., 2005; Heers et al., 2010) and is important for the epilepsy surgery planning (Sutherling et al., 2008).

2.2 Transcranial magnetic stimulation (TMS)

2.2.1 Physics of TMS

TMS is a non-invasive brain stimulation technique that employs a magnetic coil positioned close to the head to induce electric currents inside the brain (Hallett, 2000, 2007; O'Shea and Walsh, 2007). A brief (usually shorter than 1 ms) pulse of current driven through the coil induces a time-varying magnetic field that penetrates into the brain (see Fig. 2.2). According to Faraday's law, a time-varying magnetic field induces an electric field, which, in turn, causes electric currents inside the brain.

The geometric distribution of the TMS-induced current inside the brain depends on the coil geometry and conductivity distribution of the brain tissue. Out of several coil geometries proposed, the most widely used are the circular and the figure-of-eight coils. The latter offers the advantage of a more focused pattern of induced current.

Regardless of coil geometry, the ability of TMS to produce a spatially compact distribution of current is restricted to the most superficial parts of the brain. Therefore, most TMS studies restrict themselves to stimulating the cortex.

2.2.2 Physiological mechanisms of TMS

The physics that describes how TMS induces currents inside the brain is relatively simple and well-known. However, the mechanisms by which these currents affect the brain function are much more complicated and less explored. Depending on stimulation parameters, TMS has been reported to cause either an increase or decrease of neuronal activity. The exact nature of the underlying physiological processes remains unclear (Lisanby et al., 2000; Terao and Ugawa, 2002; Di Lazzaro et al., 2004).

2.2.3 Functional brain imaging with TMS

Most functional neuroimaging techniques adopt the experimental paradigm in which the experimenter manipulates the subject's behavior and measures the corresponding changes in the brain activity. TMS puts this approach on its head by allowing the experimenter to directly manipulate the brain activity. The functional role of the stimulated part of the brain reveals itself through the resulting effect either on subject's behavior or some physiological variables measured from the subject simultaneously with stimulation. Examples of such variables include electrical activity of peripheral muscles measured with electromyography (EMG) and brain signals recorded with various brain imaging methods.

Despite the technical challenges, TMS has been successfully combined with many other neuroimaging modalities such as EEG, fMRI, PET, and NIRS (Ziemann, 2011), combined TMS-EEG experiments (Ilmoniemi and Kičić, 2010) being by far the most common. Nevertheless, participant's behavior remains an important (and sometimes the only available) source of information in TMS experiments. For example, the TMS procedure for localizing parts of the cortex involved in speech production (Pascual-Leone et al., 1991) depends critically on detecting speech disruptions, which can be only performed by examining the behavior.

2.2.4 Navigated TMS (nTMS)

Obviously, many applications of TMS depend critically on the ability to accurately localize brain structures receiving the stimulation. A variation of TMS procedure that provides such a localization is known as a navigated TMS or nTMS (for a review, see Ruohonen and Karhu, 2010). nTMS tracks positions of the stimulation coil and the subject's head using, for example, optical tracking technology. Registration of pre-acquired anatomical (e.g. MRI) image of the brain to the head surface using anatomical landmarks allows nTMS to estimate the spatial distribution of the stimulation electric field with respect to the brain anatomy. nTMS visualizes the stimulation field overlayed on the anatomical image in real time during the stimulation procedure, providing guidance to the operator.

2.2.5 Applications

Like MEG, nTMS is an established neuroimaging method widely used in research and clinical practice. The most common clinical application of nTMS is a preoperative localization of the motor cortex—cortical areas, whose resection might result in a motor deficit in the patient. nTMS is the only non-invasive brain imaging method that shares the basic principle of operation with direct cortical stimulation—the current gold standard of the clinical motor-cortex localization. A high degree of agreement has been shown between the the two methods (Picht et al., 2009, 2011).

3. Neuroimaging of complex behavior

3.1 Behavioral aspect in functional neuroimaging: from simple to complex

One of the main goals of the neuroscience is to understand the neural mechanisms underlying organism's behavior. Functional neuroimaging typically approaches this goal by investigating relations between two sets of variables: (1) brain activity (parameters of brain measurements or brain stimulation), and (2) behavior-related variables that describe the stimuli presented to the participant and/or participant's actions. Although there is a considerable disagreement among behavioral biologists over the precise meaning of the term "behavior" (and, in particular, over the question whether passive perception of stimuli that does not result in any action constitutes behavior; for a discussion, see Levitis et al., 2009), in the context of the thesis I use that term to refer to both perception of the stimuli and the actions of the subject.

The classical approach to neuroimaging attempts to attain as much control over the subject's behavior as possible, making sure that only few parameters of interest vary during the experiment, and that they vary in a controlled fashion. For example, in an imaging study, the experimenter may try to ensure that all the stimuli presented to the subject are identical in every respect (presentation duration, size, spatial spectral content, etc.) except for one or two carefully controlled parameters of interest, such as the emotional valence of stimuli. With this approach, the requirements for the instrumentation handling the behavioral side of the experiment are quite straightforward: it should provide for presenting predetermined stimuli sequences in different sensory modalities to, and registering simple responses (e.g, button presses) by the subject.

The underlying philosophy of systematic and rigorous control of the experimental conditions, which is customary in many natural sciences, is motivated by the pursuit of clarity and simplicity in the interpretation of the results. However, these clarity and simplicity come at the price of restricting the research to very simple, unnatural behavior, which considerably limits its ability to explain the neural mechanisms underlying the organism's function under natural conditions. Electrical recordings from single neurons have demonstrated that models of brain function derived under simplified experimental conditions might perform poorly at explaining the brain's operation in natural environment (Rieke et al., 1995; David et al., 2004; Felsen and Dan, 2005).

An alternative to the classical approach suggests forfeiting some of the control over the experimental conditions (and the ensuing straightforwardness of the interpretation of the results) in favour of being able to probe neuronal mechanisms of more complex naturalistic behavior. The new approach calls for neuroimaging experiments with subjects involved in complex, naturalistic (also referred to as "ecologically valid") behavior such as maintaining a free conversation, and has recently been attracting an increasing attention (Hasson and Honey, 2012; Hari et al., 2015).

In addition to basic research, the need to handle complex behavior in neuroimaging experiments also arises in clinical practice. Clinical applications normally do not allow such behavior-control techniques as preselecting subjects based on their ability to conduct the behavioral task or discarding subjects with excessive movements. Additionally, complex uncontrollable behavior (such as complex movements during an epileptic seizure) might constitute an integral part of the very patho-physiological state that is being examined in the neuroimaging experiment.

The transition from the classical framework of simple controlled behavior to that of complex, naturalistic one necessitates radical changes in two aspects of the neuroimaging experiment:

1. Experimental strategies. The new approach requires different strategies in terms of experimental design and data analysis, suitable for experiments that debar straightforward interpretation of brain imaging or stimulation parameters in terms of simple behavioral categories.

2. Instrumentation. The transition to complex-behavior imaging re-

quires new instrumentation capable of adequately handling the behavioral aspect of the experiment.

Although in principle the question of instrumentation is subordinate to that of applications, in practice the availability of the instrumentation can considerably constrain the design of the application. Thus, the two questions are intricately entangled and have to be solved together.

3.2 Strategies

A number of strategies for complex-behavior neuroimaging have been reported in the literature. This chapter briefly reviews some of them.

3.2.1 One-person experiments

Within the domain of neuroimaging, “one-person neuroscience” or “1PN” concerns itself with the neuroimaging experiments in which only one subject is being recorded or stimulated at a time, as opposed to “hyperscanning”, or “two-person neuroscience (2PN)” experiments that involve simultaneous recordings of brain signals from multiple interacting subjects.

In a 1PN setting, the most obvious attempt at transitioning from simple to complex behavior starts with a classical simple-behavior experiment and proceeds towards making the behavioral aspect more complex and ecologically valid while trying to preserve the overall experimental framework. One relatively straightforward way to increase the complexity and ecological validity of the subjects behavior is by using video clips of natural scenes as stimuli. The experiments of Zacks and colleagues (2001) and Bartels and Zeki (2004) provide illustrative examples of this approach.

Further development of this idea places the participant in a virtual reality (VR) environment. The subject is no longer passively receiving the stimuli, but is actively interacting with the environment (Aguirre et al., 1996; Maguire et al., 1998; Spiers and Maguire, 2006; Naismith and Lewis, 2010; Shine et al., 2011). While these experiments accommodate for subject’s endogenous motor behavior, this behavior is very restricted and artificial, like button presses or joystick movements.

Despite the use of rich naturalistic stimuli, the experiments described above still follow the classical approach to neuroimaging, trying to reduce the complex behavior to a few simple variables before proceeding to investigate the relation between brain signals and behavior. This reduction is performed by various means, such as participants' verbal reports or content analysis. One particular method—classifying the behavior into several discrete categories by a trained expert—is dominant in clinical practice, such as long-term video-EEG monitoring or preoperative TMS mapping of the language-related cortical areas.

This forcing of complex-behavior neuroimaging experiments into the classical framework considerably restricts the experimenter's possibilities. In a sense, reducing complex behavior to a few manageable variables defeats the purpose of having it in the first place.

As an alternative to accommodating complex behavior into a classical neuroimaging framework, the experimenter may try something totally different—something that does not require characterising the behavior at all. There is a variety of ways to sidestep the explicit characterization of behavior. One can look at the correlations across the subjects (intersubject correlations; Hasson et al., 2004), and within the subject across different recording sessions and across different temporal structures (Hasson et al., 2008). Another possibility is to adopt a reverse-correlation approach similar to the spike-triggered averaging method used in single-cell electrophysiology (Hasson et al., 2004). For a more comprehensive review of different experimental strategies for complex-behavior neuroimaging, see Spiers and Maguire (2007).

3.2.2 Hyperscanning

One particular, but very important type of human behavior is social interaction. Traditionally, most neuroimaging studies of social behavior have adhered to the classical neuroimaging paradigm, where brain signals are recorded from a single subject following a carefully controlled but unnatural experimental protocol. More recently, a number of alternative approaches have been attracting the attention of the research community (Hari and Kujala, 2009; Dumas, 2011; Dumas et al., 2011; Hari et al., 2015). A notable example of such an approach is hyperscanning—simultaneous recording of brain signals from multiple interacting subjects.

Although electrophysiological experiments that can be retrospectively described as hyperscanning date at least half a century back (Duane and Behrendt, 1965), it was the fMRI community that first genuinely embraced this approach, starting with the seminal work by Montague and colleagues (2002) that coined the term "hyperscanning". Though constituting an important methodological advance, fMRI-based hyperscanning is handicapped by its low temporal resolution, which severely restricts the method's applicability to many types of social interaction.

More recently, the hyperscanning paradigm has been applied to a number of other neuroimaging modalities such as NIRS (Cui et al., 2012; Cheng et al., 2015), EEG (Babiloni et al., 2006; Lindenberger et al., 2009; Dumas et al., 2010, 2012; Jiang et al., 2012; Sänger et al., 2012), or MEG (Publications III and IV; Hirata et al., 2014).

3.2.3 Characteristic temporal scales

Virtually any ecologically-valid behavior, whether it is navigating a city in virtual reality, watching a movie, or playing a musical instrument in synchrony with a partner, involves events unfolding over timescales as short as tens of milliseconds. Naturally, this fast behavior must be effectuated by neuronal activity occurring on similar (or faster) timescales. For instance, in such an exemplary case of ecologically valid behavior as natural speech perception, the stimuli evolve on the millisecond timescale and are intricately entangled with various oscillatory processes in the brain (Giraud and Poeppel, 2012), spanning the frequency range from delta (1–3 Hz) to gamma (above 25 Hz).

Indeed, in many cases probing the neural mechanisms of such fast behavior is the primary reason for shifting from simple to complex behavior in a neuroimaging experiment. In an illustrative example, Spiers and Maguire (2006) describe the scientific contribution of their study as follows: "In this study, we have explored the second-by-second nature of human thought processes and their underlying brain dynamics . . . This fine-grained temporal characterisation of the unfolding navigation process permits new insights into the roles of specific brain regions that were inaccessible to previous studies . . . ". Yet neuroimaging research into this fine-grained temporal dynamics can be severely impeded by inadequate temporal resolution of the neuroimaging method. Certainly, it must have been quite challenging for Spiers and Maguire to "explore the second-by-second nature of human thought" with the reported fMRI sampling frequency of about 0.25 Hz.

Therefore, neuroimaging research into naturalistic behavior profoundly requires facilities for recording both the brain activity and the subject's behavior on millisecond timescales. This requirement raises the importance of fast neuroimaging modalities such as EEG or MEG.

3.3 Instrumentation

Transition to complex-behavior neuroimaging brings along the demand for instrumentation capable of handling the increased complexity of the behavioral aspect of the experiment and supporting the new experimental strategies.

3.3.1 One-person experiments

In the simplest (from the instrumentation perspective) case, the experiment attains ecological validity through the use of complex naturalistic stimuli while requiring no behavioral response. For example, in the experiment described by Hasson et al. (2004), the subjects were passively watching a fragment of a Hollywood movie while their brain activity was recorded with fMRI. This case requires little, if any, modification to the stimulation setup.

Moving from passive perception of complex stimuli to virtual reality introduces additional requirements for the instrumentation handling the behavioral aspect of the experiment. The important difference is the appearance of the endogenous component in the participant's behavior—it is no longer predetermined. This development brings along three new requirements:

1. The instrumentation needs to capture some aspect of the subject's endogenous behavior.
2. The stimuli need to be updated in real time in response to the subject's behavior.
3. The behavior needs to be recorded in a way that is synchronized with the neuroimaging device.

In most cases, the first requirement is addressed by employing a very simple and artificial, but readily available feedback channel, such as a button- or joystick-based controller (Aguirre et al., 1996; Maguire et al., 1998; Spiers and Maguire, 2006). Some experiments also capture additional behavioral variables, such as gaze direction (Spiers and Maguire, 2006), using standard off-the-shelf equipment. One group resorted to designing a custom feedback device—MR-compatible foot pedals—to increase the ecological validity of the subject's behavior (Naismith and Lewis, 2010; Shine et al., 2011). While pedals are more ecologically-relevant than a typical off-the-shelf MR-compatible controller for the particular research question—investigating freezing of gait—they still constitute a very artificial and restrictive way of capturing the subject's behavior.

In case of virtual reality, the second requirement essentially amounts to providing a VR environment. Computer games being among of the most prominent applications of VR, experimenters usually employ a modified version of a commercial computer game to address this requirement (Aguirre et al., 1996; Maguire et al., 1998; Spiers and Maguire, 2006; Naismith and Lewis, 2010; Shine et al., 2011).

The third requirement is typically handled in an ad-hoc fashion. For example, Spiers and Maguire (2006) employed "camera footage of the scan console and a stopwatch manually synchronized with the time stamp on debriefing video"; Maguire et al. (1998) used the built-in record function of the computer game used to create the VR.

The situation becomes more complicated once the requirement for the ecological validity is extended to the endogenous aspect of the subject's behavior. This case requires facilities for accurately documenting the subject's actions that in their complexity go far beyond button presses. Different research groups attempted to capture subject's motor activity with a variety of means such as accelerometers (Bowyer et al., 2007; Kim et al., 2014), driving (Haufe et al., 2011) and flight (Astolfi et al., 2011) simulators, video cameras (Publications I and II; Lüders, 1992; Karayiannis et al., 2005), and specialized 3D human motion tracking systems (Cunha et al., 2012).

3.3.2 Hyperscanning

In NIRS or EEG hyperscanning experiments brain signals can be simultaneously recorded from multiple participants sharing the same room. This arrangement makes the interaction between the subjects quite straightforward. The situation is more complicated with MEG or fMRI. Although dual-subject MEG (Hirata et al., 2014) and fMRI (Lee et al., 2012; Renvall et al., 2015) devices have been reported, they are scarcely available. In most cases, MEG or fMRI hyperscanning arrangement comprises two separate instruments located at geographically separated sites, necessitating some kind of a link to allow the subjects to interact. Due to its ubiquity and flexibility, the Internet is a natural choice for the underlying communication channel. The main disadvantage of this solution comes from relatively long and unpredictable delays that it might introduce.

4. Aims of the study

The general motivation of this thesis was to develop instrumentation that enables capturing complex naturalistic behavior of a subject in a neuroimaging experiment. The aims of the individual publications included in the thesis are:

Publication I

To design and validate instrumentation for documenting subject's performance in speech mapping TMS studies.

Publication II and the Helsinki VideoMEG Project

To design and implement the instrumentation for integrating video and audio recordings of the subject into the MEG procedure, and to quantitatively evaluate the added value of such recordings in a clinical MEG recordings of epilepsy patients.

Publication III

To implement and validate a simple MEG hyperscanning setup using audio-only link between the subjects.

Publication IV

To extend the setup described in Publication III to enable simultaneous MEG recordings of two subjects interacting over an audiovisual connection.

5. Summary of results

This chapter briefly describes the publications included in the thesis. Additionally, Section 5.2 introduces the Helsinki VideoMEG Project. Publications I and II, and the Helsinki VideoMEG Project pertain to documenting the participant's behavior with video- and audiorecordings in a single-subject setup; Publications III and IV relate to hyperscanning.

5.1 Publication I: "A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation"

This publication describes a setup for documenting participant's behavior during a nTMS language-mapping experiment. In this experiment, the subject is required to perform a language task, for example count aloud. While the subject performs the task, the experimenter stimulates the the subject's brain at different locations trying to identify the areas, the stimulation of which interferes with the speech production (Pascual-Leone et al., 1991). Such language-mapping procedure can be a useful tool in the basic research of brain mechanisms of speech as well as in clinical practice, where it can be used to delineate language-related brain areas that should be preserved during surgery.

Our experiment employed an object naming task in which the subject was required to name the object presented on a computer screen. Object naming has been argued to be an efficient task for mapping language areas with direct cortical stimulation (Petrovich Brennan et al., 2007), which shares the basic principle of operation with TMS. The experiment involves evaluation of the participant's performance in a relatively complex natural speech task. Such an evaluation should take into account at least the following aspects:

- Interference with the speech production can manifest itself as many different types of naming errors such as anomias (lack of response), semantic paraphasias, circumlocutions, phonological paraphasias, neologisms, and performance errors (Corina et al., 2010). The boundaries between errors and correct responses as well as between different error types are often fuzzy.

- In addition to the above errors, interference with speech mechanisms can produce more subtle effects, such as increased response times.
- Differences in the familiarity of the objects or in the phonetic complexity of the corresponding nouns might confound the evaluation of the subjects performance.
- Naming errors might also be caused by inadvertent stimulation of facial muscles or TMS-induced pain.

Despite the progress in the development of automated tools for objective analysis of TMS speech-mapping data (Vitikainen et al., 2015), manual annotation by a human expert remains the most widely used analysis method. Thus, recording video and audio of the patient synchronized to the stimulus presentation is a natural way to capture the behavioral side of the experiment. The publication describes a prototype implementation of such a video-nTMS setup (see Fig. 5.1). Our setup records the video of the patient with a consumer-grade camcorder and synchronizes with the visual stimuli presentation and nTMS system by cloning the monitors of these two within the camcorder's field of view. This simple construction circumvents the need to synchronize TMS, stimulation and video recording equipment. Despite the shortcomings of our prototype, we were able to successfully identify cortical language-sensitive sites in all the four subjects that participated in the experiment.

Video recordings proved to be a valuable tool for capturing the behavioral aspect of the experiment. In particular, some naming errors that were overlooked during the experiment, were discovered after reviewing the video.

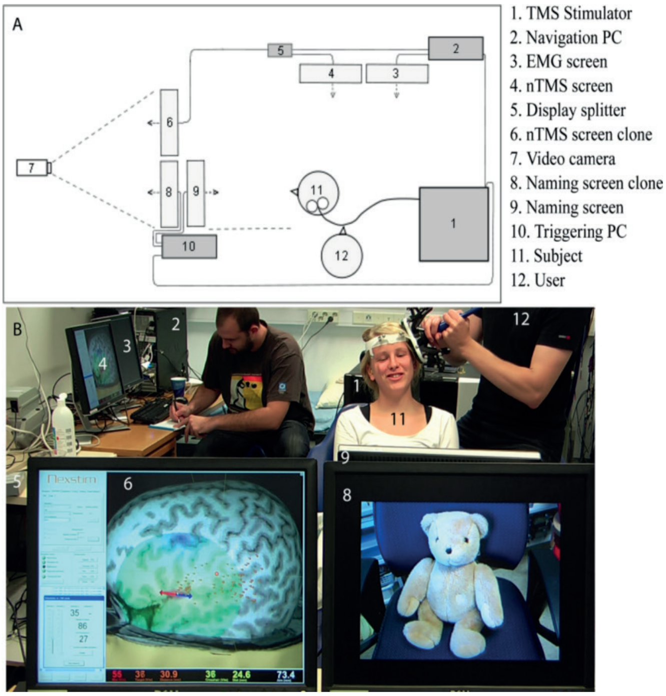

Figure 5.1. Prototype video-TMS system. (A) Schematic diagram of the setup, view from above. (B) Single frame from the video. Adapted from Publication I.

5.2 Publication II: "Quantifying the contribution of video in combined video-magnetoencephalographic ictal recordings of epilepsy patients" and the Helsinki VideoMEG Project

Another neuroimaging modality that may benefit from synchronized video recording is MEG. Particularly, clinical MEG recordings of epilepsy patients might involve complex behavioral patterns that have considerable implications for the analysis of the MEG signals.

The most prominent example of such a pattern is an ictal event—an episode of abnormal behavior caused by the epilepsy. Detecting such periods and accurately identifying the timing of their onset is an important part of the clinical MEG analysis routine. This task is challenging as ictal events can manifest themselves behaviorally in many different, sometimes quite subtle ways. Currently, the most reliable way to detect these events is a manual review of the recordings by a properly trained human expert who, in addition to MEG signals, takes into account information from a number of other sources: physiological signals, such as EEG and electromyograms (EMG), patient's clinical history, etc. Since ictal episodes are defined in terms of the patient's behavior, one can expect video recording of the patient to be of crucial value for their detection.

In addition to ictal events, video can reveal other behavioral patterns that are important for analysing clinical MEG recordings; for example, subject's movements or failure to maintain a proper head position inside the sensor helmet.

Considering the potential clinical value of synchronized video recordings in MEG, one would expect the facilities for such recordings to be a standard part of the instrumentation at every MEG laboratory. Surprisingly, very few reports of such video-MEG setups have been published to date (Burgess et al., 2009; Wilenius et al., 2010).

The Helsinki VideoMEG Project (Zhdanov et al., 2014)[1] aims at remedying this situation. The goal of the project is to provide tools that will enable any MEG laboratory to augment the MEG procedure with synchronized video and audio recordings of the patient.

Integrating video into an MEG procedure requires technical solutions for:

1. recording video and audio of the patient simultaneously with MEG in a manner that allows synchronizing them to the MEG data;
2. analysing audio and video jointly with the MEG data.

The Helsinki VideoMEG Project addresses the first requirement by providing the hardware design and the software for the video-recording station that allows recording multiple video and audio streams. The video-recording station generates a timing signal that, when recorded with the MEG trigger channel, can be used for synchronizing audio, video and MEG data. This arrangement attains the synchronization accuracy of about 16 ms for audio, and about 1 frame (33 ms) for video, as measured using and external source of synchronized audio, video, and MEG events.

The second requirement is currently only partially fulfilled—the project provides MATLAB® and Python routines for loading, synchronizing and manipulating the data, but not a complete GUI (Graphical User Interface)-based tool. For MEG systems manufactured by Elekta Oy, a prototype of such a tool has been demonstrated by the company.

Publication II demonstrates the added value of the tools developed in the framework of the Helsinki VideoMEG Project in clinical MEG recordings of epilepsy patients. The publication focuses on MEG recordings of ictal events.

In Publication II, we compared the ictal events that were detected in

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[1] Available at https://github.com/andreyzhd/VideoMEG

Patient	Events without video	Events with video	Result changes due to video		
			Detected[a]	Discarded[b]	Changed[c]
1	1	1			
2	1	1			
3	1	1			
4	6	1		5	1
5	5	12	7		
6	1	3	2		
7	0	6	6		
8	1	1			
9	1	7	6		
10	0	5	5		

Table 5.1. Changes in the outcome of the ictal episode detection due to video.

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[a] Detected: events missed without video, detected after viewing the video.

[b] Discarded: false events detected without video, discarded after viewing the video.

[c] Changed: events for which the timing was changed after viewing the video.

the same recording with and without video. Adding video changed the number of detected events in 6 out of 10 patients, in all cases by more than 50%. The results are summarized in Table 5.1.

5.3 Publication III: “MEG dual scanning: a procedure to study real-time auditory interaction between two persons”

Publication III describes our first attempt to adapt the hyperscanning experimental paradigm to MEG. In our experiment, we simultaneously scanned two interacting subjects at two MEG sites—one at the MEG Core, Brain Research Unit, Aalto University, Espoo, and the other at BioMag laboratory at the Helsinki University Central Hospital, Helsinki. The sites are separated by approximately 5 km.

The principal technical challenge of MEG hyperscanning involving geographically separated sites is providing facilities for subjects to interact with each other. In the experiment described in Publication III, we restricted the interaction to audio-only communication and used fixed phone lines for establishing the connection between the two sites (see Fig. 5.2), attaining one-way communication latency of merely 12.7 ms. Such a lag is experienced in a face-to-face conversation by participants separated by approximately 4 m.

Another issue that needs to be addressed is synchronization of all the data streams. At each site, the MEG device, the audio recording com-

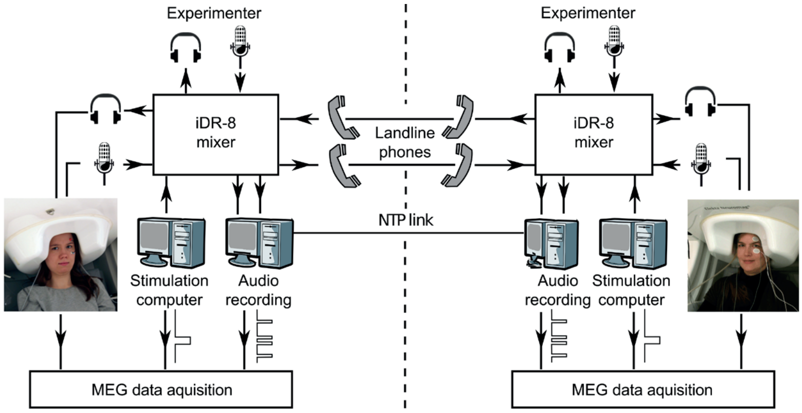

Figure 5.2. Schematic depiction of the experimental setup. Two similar sets of hardware are located at the two MEG sites and are linked over phone landlines. Adapted from Publication III.

puter, and the stimulus presentation computer are synchronized using trigger pulses. Between the sites, the audio recording computers are synchronized using GPS time sources.

We have validated the setup by a straightforward experiment where we recorded subjects' brain responses to simple auditory stimuli (50-ms long 500-Hz tone pips). We observed very similar responses to stimuli presented locally and remotely over the audio connection, suggesting that our setup is suitable for conducting auditory-based MEG hyperscanning experiments.

5.4 Publication IV: "An Internet-Based Real-Time Audiovisual Link for Dual MEG Recordings"

In Publication IV, we extended the research described in Publication III in two ways:

1. We augmented our hyperscanning setup with a video link between the two subjects.
2. We validated the setup using a task that requires genuine interaction between the subjects.

Fig. 5.3 presents our setup. We capture the video of the subject with a machine-vision camera mounted inside the magnetically shielded room. The camera transmits the video to the audiovisual (AV) computer located in the MEG control room via the optical fiber. To present the video from the other site we use a projector and a back-projection screen.

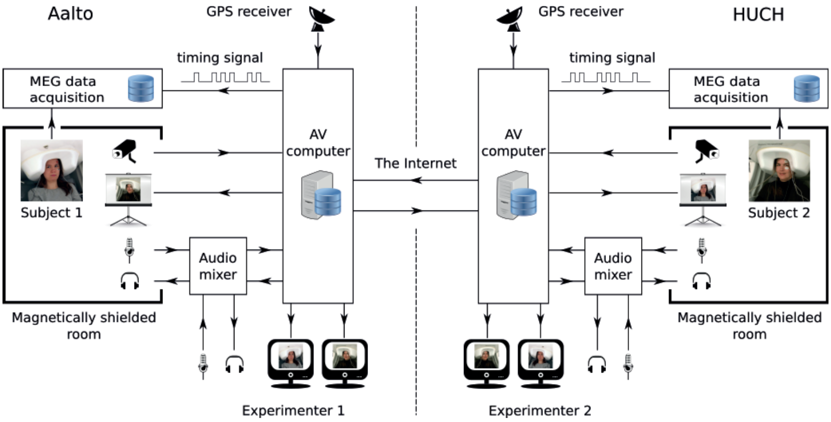

Figure 5.3. Schematic depiction of the experimental setup. Two similar sets of hardware are located at the two MEG sites and are linked over the Internet. Adapted from Publication IV.

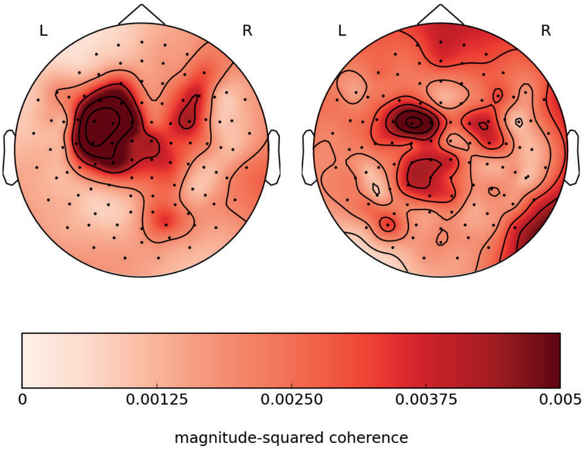

Figure 5.4. Inter-subject coherence for one subject pair. The flattened sensor-helmet maps show the average coherence in the 0.5–2-Hz band. At each location, the maps depict the average coherence value to all the planar-gradiometer channels from the other subject. Adapted from Publication IV.

Each AV computer streams the video to its counterpart at the other site over the Internet, which is the only practical way of transmitting the video data between the sites. Since we use the Internet for the video transmission, we decided to forfeit the phone-line-based audio link in favour of transmitting the audio over the Internet, too. This simplifies the setup and increases the audio quality at the expense of an increased audio delay. The latter, however, does not constitute a problem in combined audio-visual experiments, since the audio needs to be delayed anyway to keep it synchronized with the video, which introduces a much longer transmission lag.

To validate out setup, we asked the subjects to perform simple repetitive hand movements synchronously. By observing each other's hands over the video link, the participants were able to synchronize their movements to a sub-second accuracy (measured independently by accelerometers attached to the subjects' fingers).

The coherence analysis that we conducted for one pair of subjects revealed increased coherence between the signals from the MEG sensors located over the subject's motor cortex and the signals from the other subject (see Fig 5.4), occurring roughly at the frequency of the movement. This further demonstrates the suitability of our setup for MEG hyperscanning experiments.

6. Discussion and conclusions

The rising prominence of complex-behavior neuroimaging brings along the requirements for novel strategies and instrumentation for handling the behavioral aspect of the neuroimaging experiments. In the repertoire of possible instruments for registering the participants behavior—such as accelerometers, joysticks, pedals, etc—video cameras occupy a special place for a number of reasons:

- Video often provides richer information about the subject's behavior than the other available methods.
- Being ubiquitous technology, video benefits from extensive research and development efforts resulting in significant advances in sensor technology, video compression and processing tools.
- For a human observer, video provides arguably the most natural description of the participants behavior. This is particularly important for hyperscanning experiments, where the participants' behavior is not only recorded for subsequent analysis, but is also communicated in real time to their peers to enable interaction. Additionally, the interpretability of video by a human reviewer greatly facilitates its adoption in clinical practice.

Despite the low cost and the potential benefits of integrating video into neuroimaging procedures, the use of video in brain imaging is far from being widespread. In some areas, such as long-term EEG monitoring of epilepsy patients, video has long been a part of the established routine. Yet, in other fields, such as MEG, video has been mostly overlooked so far.

This thesis explores the possibilities for documenting complex behavior offered by video in clinical practice (Publications I and II), and in basic research (Publications III and IV). Additionally, the Helsinki VideoMEG project provides researchers and clinicians with tools for integrating video recordings into their MEG measurements.

Publication I demonstrates that video can be relatively easily integrated into a clinical nTMS procedure. The added value of video in TMS language mapping as demonstrated in Publication I has eventually led to the integration of video recording capabilities into a commercial TMS product (NexSpeech by Nextim Plc, Helsinki, Finland), which is currently used at more than 40 TMS installations around the world. Pre-operative localization of language areas performed with video-augmented nTMS provided maps that are in good agreement with the current gold standard of clinical language localization—intra-operative direct cortical stimulation (Picht et al., 2013; Tarapore et al., 2013). Although Publication I provides some qualitative evidence for the utility of video, it does not report any quantitative measures.

Publication II addresses this shortcoming while investigating the feasibility of integrating video with a different neuroimaging modality—MEG. The results reported by this publication suggest that video can contribute considerably to the interpretation of MEG data.

The experiment described in Publication III restricts itself to an audio-only configuration. However, it introduces a transition from recording audio of a single MEG subject to using audio as a communication channel in a hyperscanning experiment, where two subjects are simultaneously recorded at geographically separated MEG sites. The transitions from 1PN to 2PN experiment introduces additional challenges related to the communication latency and the requirement for synchronization between the sites. Publication III demonstrates that these challenges can be successfully addressed.

Finally, Publication IV extends the research reported in Publication III by adding video capability to the inter-subject communication channel and describing an example of inter-subject coherence in MEG signals resulting from the subjects interaction.

The most obvious direction for the future research seems to be development of automated tools for more quantitative and objective analysis of the video and audio recorded from the participant in the neuroimaging experiment. Another promising direction for future development of video in neuroimaging is fusion of video data with signals from different brain imaging instruments. For example, clinical video-EEG and video-MEG recordings of epilepsy patients may benefit from tools for automatic detection of seizures. Despite the long history of combining video with EEG, the tools that are currently used in clinical video-EEG practice for automated seizure detection (Gotman, 1982, 1999) ignore the video. Although there are a number of video-based seizure detection tools being developed (Pediaditis et al., 2012), none of these utilizes EEG data. By fusing the data from two modalities one can expect to develop video-EEG and video-MEG seizure detectors that outperform current methods.

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Errata for publications

Publication IV

The captions for the figures 6 and 7 should be swapped.

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