Transcranial magnetic stimulation and EEG in studies of brain function

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Aalto University

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Abstract

Transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) is a multimodal technique, with a temporal resolution of submilliseconds, for studying cortical excitability and connectivity. When TMS is combined with neuronavigation, resulting in so-called navigated TMS (nTMS), the technique becomes very powerful. However, despite the potential of TMS–EEG, its use for studying lateral areas has been restricted because the TMS pulse induces strong muscle artifacts, making the EEG data useless for further analyses. In this Thesis, methods for analyzing TMS-evoked EEG data from lateral areas are introduced. First, TMS–EEG is used to study Broca's area and dorsal premotor cortex. Due to the fact that those areas are close to cranial muscles, their stimulation evokes large muscle artifacts in EEG recordings. The behavior of the artifacts is described in detail. Two approaches to deal with large artifacts are presented. In the first approach, independent component analysis (ICA) is used. Here, FastICA algorithm is modified to make the search of the components more robust and easier, allowing one to get more stable results. The second approach presents methods for suppressing the artifacts rather than removing them. These methods were combined with source localization showing that the artifact suppression is efficient. The methods were tested with both real and simulated data, suggesting they are useful for artifact correction. For a better understanding of the effects of repetitive nTMS during naming tasks and the cortical organization of speech in general, here another study is introduced to understand the sensitivity of object and action naming tasks to repetitive nTMS. The distributions of cortical sites, where repetitive nTMS produced naming errors during both tasks, are compared. Thus, it is shown how this study can impact on both cognitive neuroscience and clinical practice. In the last part, the beamformer method is improved to study source localization, which makes it a robust method to study time-correlated sources. In this Thesis, I discuss how all these methods together can contribute to study brain connectivity of language and lateral areas with TMS–EEG, opening new possibilities for basic research and clinical applications.

Preface

I have said many times that in a thesis the preface is what people usually read. Therefore, I have decided to tell a nice story and hope my readers enjoy it.

Why did you decide to come to Finland? Why Finland? Why brain research? Those are the typical questions I am asked repeatedly. My story is not very different from many others or maybe it is.

I decided to study physics because I wanted to become an astronomer. However, I changed my direction during my undergraduate studies in Mexico when I heard about "electromagnetic stimulation" and "the brain." Since then, I have been intrigued by learning more about the interaction between the electromagnetic fields and biological systems.

Although my path to Finland took time, somehow it was in my heart to come to this country. In 2006, I went to Madison, Wisconsin, in the USA and worked in the lab of Prof. Ron Wakai as part of my Master's studies. It was there I learned that Finland is a strong country with a long tradition of brain research. At that time, I was working on magnetoencephalography. This was my first approach to brain research. Several months later, after obtaining my Master's degree, I began to look for an institution for studying my Ph.D. It was then in 2007 when I decided to contact some groups in Finland and inquire about opportunities for pursuing a Ph.D. there. A person who always replied to my emails and was very open and polite was Prof. Risto Ilmoniemi. Nevertheless, I was unable to complete the application process and decided to do my Ph.D. at the University of Guanajuato, the same place where I did my Master's degree. However, as I have mentioned before, Finland was in my heart, even when I only knew

this country was a good option for brain research (I didn't know anything else about Finland. I had no idea about the cold and darkness).

In 2008, I had the chance to travel to Japan to attend a conference. After many days of talks and poster sessions, one day during the late afternoon, I start to feel exhausted and decided to go to the hotel and rest. Nevertheless, I passed close to a room full of posters and had the feeling that I should go in and did so. I looked at a few posters and suddenly I saw the title of one that included "transcranial magnetic stimulation" and among the authors was the name "Risto Ilmoniemi." I asked the student who was presenting the poster two questions: "Is this your poster?"; "Do you know Prof. Risto Ilmoniemi?" His answers were: "Yes"; "Sure, Prof. Risto is there." Then he added: "Do you want me to introduce him to you?" I said: "Yes, please!" Then I said to Prof. Risto "I am Julio, the Mexican guy who contacted you more than a year ago who was interested in pursuing a Ph.D. in Finland." Then we had our first scientific discussion in person, and told him I was still interested in going to Finland and doing research. He told me it was possible to do an internship in his lab. Then it was the beginning of my new life and a year later I traveled to Finland.

I want to thank and to express my gratitude to Prof. Risto Ilmoniemi for being my supervisor and especially for giving me the chance to work in his group. He is the key person who helped me come to Finland. Prof. Ilmoniemi is an outstanding researcher; I have learned many things from him, not only about science but also about life. Prof. Risto is a great leader, because not only he is extremely smart, but also because he is very human. He has treated me first like a human being and as a friend and then, as a student. He is a wonderful person; I really admire how humble he is. Every time I have been at his office, it has been a pleasure to talk with him. He has a tremendous passion for his job, passion that transmits immediately. I really thank Prof. Ilmoniemi for all of his support, for trusting me, and additionally for giving me the chance to coordinate two science factories. I consider Prof. Ilmoniemi my "academic father", it has been an honor and pleasure to work with him.

My time in Finland has also been influenced by other people. In particular, there is a person who has highly been involved in my academic development. He is calm, wise, he has a good sense of humor; he is a good

storyteller. Usually, he starts our meetings talking about what he did with his family. He has a peculiar style and always wears "black Reeboks"; it is very easy to identify his steps when he is approaching the office or when he just walks into the corridor. He has a beautiful mind and is one of the most patient people I have ever met. I want to express my gratitude to Prof. Jukka Sarvas "my academic grandfather." It has been a great honor to work with him.

I would also like to thank my friends and colleagues from the Department of Neuroscience and Biomedical Engineering (formerly called Department of Biomedical Engineering and Computational Science): Johanna Metsomaa (she is brilliant and very humble. Thanks, Johanna, for being patient the time that we shared the office and all the nice discussions not only about work, but also about something else), Tuomas Mutanen (AKA many other names in the corridor, of course only by me. Thanks Tuomas for being a good office mate. I have to say Tuomas is not the typical quiet Finn, since many times I had to say, "Sorry I have to work" when he was so enthusiastic telling me about his weekends), Niko Mäkelä (for collaborating and giving some jazz and flavor to the lab), Jaakko Nieminen (thanks for sharing good moments both in and outside of the lab), Sergei Tugin (for the good moments and for being patient while I have been supervising him), Dr. Ilkka Nissilä (for recording the smiles and moments of the lab with his photos), Antonios Thanellas (for the nice discussions about any topic), Dr. Matti Stenroos (for collaborating and your positive feedback, it has been great collaborating with him).

I want to mention many other colleagues: Dr. Simo Monto (many years later I realized he was the person who was standing in the poster), Dr. Kalle Kotilahti, Koos Zevenhoven, Mikko Lilja, Mika Pollari, Andrey Zhdanov, Ville Mäntynen, Lari Koponen, all of the members of the TMS group and personnel of the Department of Neuroscience and Biomedical Engineering who have created a nice working atmosphere, in particular to Dr. Lauri Parkkonen, Marita Stenman, Eeva Lampinen, Mikko Hakala, Susanna Väänänen and Laura Pyysalo. I would like to thank my former colleagues and collaborators: Reeta Korhonen, Dr. Hanna Mäki, Dr. Juhani Dabek, Dr. Tiina Näsi, Dr. Panu Vesanen.

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Jyrki Mäkelä. Jyrki is a great scientist. He has a good view of science (thanks, Jyrki, for being patient and for the collaborations, it has been very fruitful to work with him).

I would like to thank pre-examiners: Prof. Christoph Herrmann and Prof. Aapo Hyvärinen for taking the time to read my thesis and giving their valuable comments that have further improved the introduction. I would like also to thank my opponent Prof. Samu Taulu for accepting the role of opponent.

I would like to express my gratitude to Leena Laine for all of her help during my arrival to Finland. I especially want to thank my two friends, colleagues, and TMS experts: Dr. Pantelis Lioumis (Amigo Griego, thanks for being always direct and your advice) and Dr. Dubravko Kičić (Thanks amigo Croata, he was also a key person for my visit to Finland).

I would like to thank my international collaborators, Dr. Vadim Nikulin, Prof. Paul B. Fitzgerald, Dr. Nigel Rogasch, and Dr. Neil Bailey. As well as local collaborator Henri Lehtinen.

During the past six years, I have met wonderful people in Finland who have influenced my life in different ways. The list is too long to be presented in this document. However, I will mention some of them and the rest should excuse me if I do not mention their names here, but they are in my mind and heart. I want to thank Nora Lillandt (for always being there), Heidi Uppa (for the smiles), Jenni Saarinen (for cheering me up), Emil Gil (for the good moments), Jesus Castro (for the good moments), Hanna Gil (for the good moments), Riikka Karjalainen (for the good moments), Juha Silvanto, Jessica Guzman, Nadia Catallo, Lizaveta Ihnatsyeva, Evelyn Guevara, Ana Grau, Anna Ahlava, Tiina Taskila, Mia Hovi (thanks for providing the skull of the cover), Marketta Kyttä.

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Last but not least, I want to express all of my gratitude to my sisters; Beatriz, Veronica, Guadalupe, and my brother Jesus and the rest of my family. I want to express with all of my heart and my love my gratitude to my parents, Jesus Hernandez Herrera and Josefa Pavon Roman. Thanks Dad and Mom for all of your support.

Quiero expresar mi gratitud y agradecimiento a mi familia. Mis hermanas; Beatriz, Veronica, Guadalupe, y a mi hermano Jesus y el resto de mi familia. Quiero expresar con todo mi corazón y amor mis agradecimientos a mis padres, Jesus Hernandez Herrera y Josefa Pavon Roman. Gracias Papa y Mama por todo su apoyo.

This is part of my story, part of my life during the past six years. Thanks all of you for being there!

<div align="center">

"A son never forgets!"

"Better to die on your feet than live on your knees!" Emiliano Zapata

"Be happy and enjoy life!" Mr. Pavon

</div>

Helsinki, Finland, July 21, 2015,

Julio César Hernández Pavón

Contents

List of Publications

This Thesis consists of an overview and the following Publications, which are referred to in the text by their roman numerals.

I Korhonen R, Hernandez-Pavon JC, Metsomaa J, Mäki H, Ilmoniemi RJ, Sarvas J. Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis. *Medical and Biological Engineering and Computing*, 49, 397–407, 2011.

II Hernandez-Pavon JC, Metsomaa J, Mutanen T, Stenroos M, Mäki H, Ilmoniemi RJ, Sarvas J. Uncovering neural independent components from highly artifactual TMS-evoked EEG data. *Journal of Neuroscience Methods*, 209, 144–157, 2012.

III Hernandez-Pavon JC, Mäkelä N, Lehtinen H, Lioumis P, Mäkelä JP. Effects of navigated TMS on object and action naming. *Frontiers in Human Neuroscience*, 8, 1–9, 2014.

IV Hernandez-Pavon JC, Sarvas J, Stenroos M, Ilmoniemi RJ. Beamformer with temporally correlated sources and iterative search in EEG. *To be submitted*, 2015.

Author's Contribution

Publication I: "Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis"

The author participated in designing and carrying out the measurements. He assisted the principal author in the data acquisition, in data analysis and interpretation, and in writing of the article. The author, the first and third authors developed the algorithm together. The author is the corresponding author of the manuscript.

Publication II: "Uncovering neural independent components from highly artifactual TMS-evoked EEG data"

The author performed the measurements and analyzed the data. He developed the main theory and performed the simulations with the second and last authors. The appendices and mathematical proofs were carried out by the last author. He wrote the article with the second and last two authors. He is the principal author of the article.

Publication III: "Effects of navigated TMS on object and action naming"

The author performed the measurements and analyzed the data with the second and fourth authors. He wrote the article with the other authors. He is the principal author of the article.

Publication IV: "Beamformer with temporally correlated sources and iterative search in EEG"

The author performed the simulations and analyzed the data. He participated in developing the main theory with the second author and wrote the article with the rest of the authors. The appendices and mathematical proofs were carried out by the second author. He is the principal author of the article.

List of Abbreviations

BA	Broca's area
BSS	Blind source separation
DCS	Direct cortical stimulation
dPMC	Dorsal premotor cortex
DTI	Diffusion tensor imaging
EDM	Enhanced deflation method
EEG	Electroencephalography
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
ICA	Independent component analysis
ICs	Independent components
LCMV	Linearly constrained minimum-variance
LORETA	Low resolution electromagnetic tomography
M1	Primary motor area
MAM	Manual method
MEG	Magnetoencephalography
MNE	Minimum norm estimate
MRI	Magnetic resonance imaging
MUSIC	Multiple signal classification
NIRS	Near infrared spectroscopy
nTMS	Navigated transcranial magnetic stimulation
PCA	Principal component analysis
PET	Positron emission tomography
RAP	Recursively applied and projected
RAP-MUSIC	recursively applied and projected multiple signal classification
rTMS	Repetitive transcranial magnetic stimulation
sLORETA	Standardized low-resolution brain electromagnetic tomography
TMS	Transcranial magnetic stimulation

1. Introduction

The human brain is composed of about 100 billion neurons, it controls feelings, thoughts, memories, perceptions, and other actions (Kandel et al., 2000). Despite great advances in neuroscience, there are still many open questions. In the past few years, different brain stimulation and neuroimaging techniques have been developed to study brain functions (Bestmann and Feredoes, 2013). Transcranial magnetic stimulation (TMS) is undoubtedly one of the most powerful *non-invasive* techniques to probe the brain. In a nutshell, TMS can be described in three steps: 1) a strong, brief, time-variant magnetic field is delivered to the brain by a coil; 2) the magnetic pulse induces an electric field on the cortex, 3) the electric field produces depolarization of pyramidal cells and inhibitory interneurons resulting in neuronal activation (Barker et al., 1985; Ilmoniemi et al., 1999). Neuronal activation consists of coherent activation of a large number of pyramidal cells (Baillet et al., 2001).

Transcranial magnetic stimulation can be combined with different neuroimaging techniques, either on-line or off-line, to measure changes in excitability, as well as hemodynamics and metabolic changes in the brain (Siebner et al., 2009). However, there are several technical difficulties to perform on-line studies with TMS. So far, the combination of TMS with electroencephalography (EEG) has been the most successful in comparison with other combinations (Ilmoniemi and Kičić, 2010). TMS combined with EEG allows one to study cortical excitability and functional connectivity of the brain (Ilmoniemi et al., 1997; Komssi et al., 2002). Furthermore, TMS combined with neuronavigation, resulting in so-called navigated TMS (nTMS), has made it possible to perform brain mapping of different areas (Ruohonen and Karhu, 2010). Consequently, basic research and clinical application on TMS–EEG have extensively been carried out (Ilmoniemi and Kičić, 2010; Miniussi and Thut, 2010; Rotenberg, 2010;

Hernandez-Pavon et al., 2014; Bortoletto et al., 2015).

The motivation of this Thesis came from our interest to study brain connectivity, in particular language areas. The question that we wanted to address was the following: is it possible to study connectivity between Broca's and Wernicke's areas with TMS–EEG? Although the answer to that question is still open, it has led to many studies, some of them carried out by myself, some by my colleagues; further work remains to be done. Here, TMS–EEG and nTMS are used to answer several questions that appeared. I will describe the methodological issues when language areas are stimulated with TMS–EEG. In particular, stimulation of Broca's area with TMS induces large muscle artifacts in the EEG recordings, making them useless unless they can be removed or sufficiently suppressed. This Thesis presents methods to remove or suppress the muscle artifacts. A study that compares the sensitivity of object and action naming tasks to repetitive nTMS for understanding the cortical organization of speech is described. Also a combination of the beamformer and RAP (recursively applied and projected) technique is introduced for investigating source localization. It will be shown how these techniques or methods can be integrated to study brain connectivity, functional excitability and brain mapping.

This Thesis contains several studies to carry out basic research and clinical applications, aimed to improve our understanding of the connections between cortical language areas in the brain, as well as to extend our knowledge of brain excitability and connectivity induced by TMS. The impact of these studies can be reflected at both scientific and clinical levels. From a cognitive point of view, this research provides information for understanding the language network, whereas in clinical practice patients that need to undergo a brain surgery can benefit from nTMS with a noninvasive functional mapping, and therefore replace standard invasive procedures. Patients with aphasia, stroke, Parkinson's, and Alzheimer's diseases can benefit from this research as well, since all these methods together could be utilized as diagnostics and therapeutical tools.

1.1 Aims of the study

This Thesis consists of Publications I–IV with the following aims:

I. To examine and to understand the TMS-evoked EEG responses after

stimulating language areas and to design a robust signal analysis method for removing muscle artifacts induced by the TMS pulse, Publication I.

II. To develop efficient algorithms to suppress large muscle artifacts from TMS-evoked EEG data of lateral areas and to uncover neuronal components masked by the artifacts, Publication II.

III. To compare the sensitivity of object and action naming tasks to repetitive nTMS in order to understand cortical speech organization and to use an optimal paradigm for mapping language areas, Publication III.

IV. To improve a source localization methodology in order to study temporally correlated sources arising from EEG data, Publication IV.

2. Background and Methods

This Chapter describes the theoretical framework and methods used to perform different experiments and data analysis of this Thesis. In the first part of this Chapter, the cerebral cortex is briefly described. In subsequent sections, an overview of the physical and biological principles of TMS and EEG, as well as other modalities of TMS, such as navigated and repetitive TMS, will be discussed. In the later part, I will introduce independent component analysis as a tool to remove artifacts. Thereafter, the basic principles of the beamformer and RAP techniques are presented.

2.1 Cerebral cortex

The cerebral cortex is the superficial gray matter layer of the brain. It is 2–4 mm thick and has a convoluted shape determined by bulges (gyri) and grooves (sulci) (Fischl and Dale, 2000). The deepest grooves between bulges are known as fissures; see Fig. 2.1 A. The longitudinal fissure is the most prominent and separates the cerebrum into the right and left halves known as cerebral hemispheres. The hemispheres are connected by the corpus callosum and each hemisphere is divided in four lobes: frontal, parietal, temporal, and occipital (Fig. 2.1 B). Anatomically, the cortical areas are localized in terms of the gyri and sulci (Tortora and Derrickson, 2008). For instance, the central sulcus separates the frontal lobe from the parietal lobe. A major gyrus, the precentral gyrus (located anterior to the central sulcus) contains the primary motor area (M1), and the postcentral gyrus, which is located posterior to the central sulcus, contains the primary somatosensory area of the cerebral cortex (Fig. 2.1).

The cerebral cortex is involved in most of the brain's highest functions such as memory, language, and sight (Kandel et al., 2000). The primary motor area controls voluntary contractions of specific muscles or groups

A) Superior view

ANTERIOR

Longitudinal fissure

Precentral gyrus
Central sulcus
Postcentral gyrus

Frontal lobe

Parietal lobe

Occipital lobe

Details of a gyrus, sulcus, and fisures

Gyrus
Sulcus
Cerebral cortex

White matter

Fissure

Left hemisphere

Right hemisphere

POSTERIOR

B) Left lateral view

Primary motor area (M1)   Somatosensory area

Frontal lobe

Parietal lobe

Broca's area

Wernicke's area

Temporal lobe

Occipital lobe

Cerebellum

Figure 2.1 A) Superior and B) left lateral views of the human brain. Modified from (Tortora and Derrickson, 2008) and 3D-Brain (2015), respectively.

of muscles (Rizzolatti and Luppino, 2001; Graziano et al., 2002). Electric or magnetic stimulation at any point in the M1 results in the contraction of specific skeletal muscle fibers on the opposite side of the body (Day et al., 1989). Histologically, the cerebral cortex is composed of six cellular layers, containing mostly two types of nerve cells: excitatory pyramidal cells and inhibitory interneurons. Each neuron communicates with other neurons through chemical or electrical signals that either inhibit or excite the next neuron (Kandel et al., 2000). The site of communication between two neurons is called a synapse. At a synapse between neurons, the neuron sending the signal is called the presynaptic neuron, and the neuron receiving the message is called the postsynaptic neuron.

2.1.1 Language areas

Producing and understanding language are complex activities that involve several sensory, association, and motor areas of the cortex (Geschwind, 1970; Pulvermüller, 2005). In 96–97% of the population, these language areas are located predominantly in the left hemisphere (Corina et al., 1992). The production of speech occurs in Broca's area, located in the inferior frontal gyrus (Broca, 1861). The understanding of spoken language is regulated by Wernicke's area in the superior temporal gyrus (Wernicke, 1874).

Recent studies by diffusion tensor imaging (DTI) have shown how Broca's and Wernicke's areas are connected by means of the arcuate fasciculus (Catani and ffytche, 2005; Catani and Mesulam, 2008; Catani and De Schotten, 2008). Cortical damage in or between these two main areas can cause a wide range of very specific language problems. For example, if the connections between Wernicke's and Broca's areas are damaged, a person may be unable to repeat what is said to her/him. This occurs because the incoming words (which are registered in Wernicke's area) cannot be passed on to Broca's area for articulation (Catani et al., 2005).

2.2 Principles of transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a powerful technique to non-invasively stimulate the human brain through the intact scalp with a strong and time-varying magnetic field in order to produce neuronal activity (Ilmoniemi et al., 1997). The first study where TMS was used to stimulate the motor cortex was carried out by Barker et al. (1985). They placed a coil of 100 mm outside diameter over the vertex of a normal subject and were able to produce hand movement and record evoked muscle action potentials. In the past thirty years, TMS has been extensively used to perform both basic and clinical research. There is a remarkable number of papers on basic research of TMS (Hallett, 2007; Ferreri and Rossini, 2013); on several clinical applications of TMS (Edwards et al., 2008; Wassermann and Zimmermann, 2012) as well as on some combinations of TMS with neuroimaging techniques (Ridding and Rothwell, 2007; Siebner et al., 2009; Ilmoniemi and Kičić, 2010).

2.2.1 Physics of TMS

In TMS, a strong, brief and time-varying magnetic field is delivered to the brain by means of a coil. The magnetic pulse induces an electric field in the cortex and this produces neuronal activation when pyramidal cells and inhibitory interneurons are depolarized (Ilmoniemi et al., 1999; Ridding and Rothwell, 2007). Transcranial magnetic stimulation is based on electromagnetic induction, described by Faraday's law,

$$\nabla \times \mathbf{E}_1 = -\frac{\partial \mathbf{B}}{\partial t} \ , \tag{2.1}$$

where a changing magnetic field $\mathbf{B}$ induces an electric field $\mathbf{E}_1$. The brain is a conductor; therefore, a current flow or eddy currents are produced in the brain. Consequently, the currents in turn produce neuronal activation.

When $\mathbf{B}$ changes slowly or is static, no neuronal excitation occurs. The strength of $\mathbf{B}$ used in TMS is of the order of 1–2 T; its rise time is about 100 μs. The spatial extent of the induced electric field varies from about 7 mm up to 3 cm, depending on the coil, stimulus intensity, and target area (Ilmoniemi et al., 1999; Deng et al., 2013). TMS stimulates superficial areas more strongly than deep areas. In addition, TMS does not activate only the target area, but also tissues around and above it, and indirectly distant interconnected sites in the brain, which is important for studies of brain connectivity (Ilmoniemi et al., 1997). The temporal resolution of TMS is submilliseconds, which allows for real-time modulation of the brain. The chain of events in TMS is depicted in Fig. 2.2.

The magnetic field produced by the coil can be computed by the law of Biot and Savart:

$$\mathbf{B}(\mathbf{r},t) = \frac{\mu_0}{4\pi} I(t) \oint_C \frac{\mathbf{dl}(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \ , \tag{2.2}$$

where the differential vector element $\mathbf{dl}$ is directed along the coil winding C, $I(t)$ is the electric current and $\mathbf{r} - \mathbf{r}'$ is the vector from the wire element ($\mathbf{r}'$) to the point at which the field is computed ($\mathbf{r}$). The distribution of the electric field induced in the tissue depends on (1) the shape of the induction coil, (2) the location and orientation of the coil with respect to the tissue, and (3) the conductivity structure of the tissue.

The total electric field $\mathbf{E}$ in the tissue is the sum of two parts, $\mathbf{E} = \mathbf{E}_1 + \mathbf{E}_2$. The electric field $\mathbf{E}_1$ is induced by the changing magnetic field $\mathbf{B}$ from the coil, and can be written in terms of the vector potential $\mathbf{A}$ as $\mathbf{E}_1 = -\partial \mathbf{A}/\partial t$. The current flow caused by $\mathbf{E}_1$ produces accumulation of electric

A)

TMS coil (produces a magnetic field)

Induced electric field

Neuronal activation

B)

Rate of change of
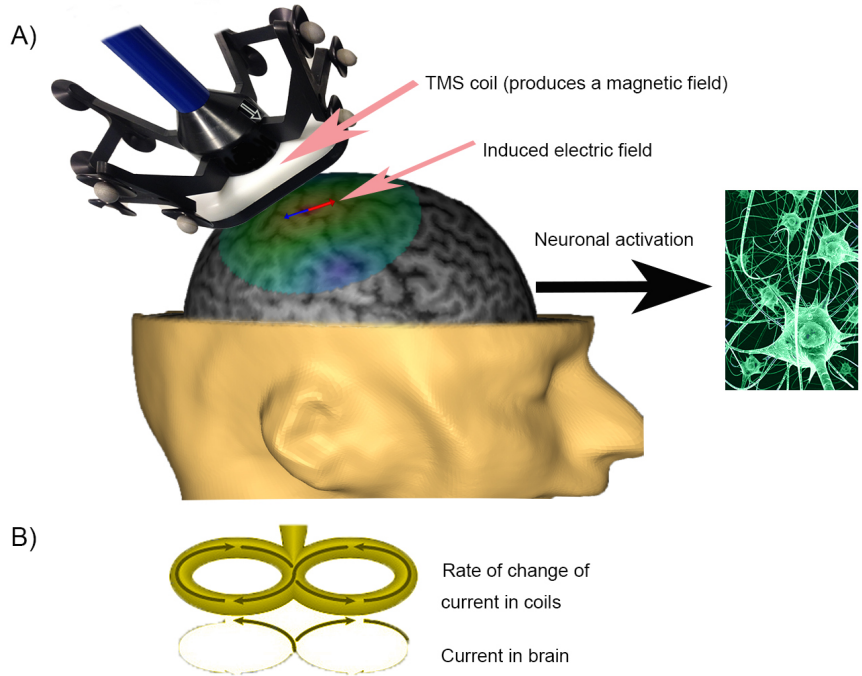current in coils

Current in brain

Figure 2.2 Chain of events due to TMS. A) An electric current flows in the TMS coil, generating a magnetic field that induces an electric field in the brain. The electric field produces movement of ions in the membrane of the pyramidal axons, leading to depolarization and subsequent neuronal activation. B) The electric field and resulting currents induced in the brain obey Lenz's law: they are parallel, but opposite in direction to the rate of change of currents in the coil.

charges on the conductor (*i.e.*, the head) or gradients of conductivity (σ) on the path of the currents and thereby the potential V. In the quasi-static situation $\mathbf{E}_2$ arises from the potential V and is expressed as the negative gradient of the scalar potential $\mathbf{E}_2 = -\nabla V$.

Then, the total $\mathbf{E}$ is:

$$\mathbf{E} = \mathbf{E}_1 + \mathbf{E}_2 = -\frac{\partial \mathbf{A}}{\partial t} - \nabla V \ . \tag{2.3}$$

The electric field strength for brain stimulation should be of the order of 30–100 mV/mm to elicit significant neuronal activation (Ilmoniemi et al., 1999; Hernandez-Pavon et al., 2014).

2.3 TMS pulses

2.3.1 Single-pulse TMS

When stimuli are applied at a low rate so that the activity produced by previous pulses does not interfere much with that of the new pulse, the stimulation is considered single-pulse TMS; the rate of these pulses is lower than 1 Hz. The pulse duration has been studied to assess possible changes in the effect of TMS (Rothkegel et al., 2010). Most knowledge about the effects of single-pulse TMS on the human cortex comes from studies performed on the primary motor cortex (M1) (Di Lazzaro et al., 2008). Stimulation of M1 evokes activity in muscles on the opposite side of the body, which can be measured by using electrophysiological methods such as electromyography (EMG) (Barker et al., 1985). In contrast, stimulation of most other parts of the cortex (at least with single pulses) has no obvious effects. One exception is the stimulation of visual cortex, which can elicit phosphenes (Silvanto et al., 2005; Silvanto, 2012).

TMS of M1 exhibits two effects that are likely to happen also when stimulating other cortical areas. The size of the response depends on the level of activity in the cortex at the time the stimulus is given, and it depends on the orientation of the TMS coil (Ridding and Rothwell, 2007). The orientation of the coil plays an important role in the response since pyramidal neurons are oriented mainly perpendicular to the cortical surface (Brasil-Neto et al., 1992; Amassian et al., 1992). Depending on the folding of the cortex, the neurons have specific orientations with respect to the TMS-induced currents that will favor one or another population (i.e., neurons oriented in one way or another) (Day et al., 1989; Maccabee et al., 1993; Ruohonen et al., 1996). As a consequence of this, the activation of the hand area of the motor cortex occurs at the lowest threshold when the stimulus induces posterior to anterior currents perpendicular to the central sulcus (Di Lazzaro et al., 2012).

2.3.2 Repetitive TMS

When a train of pulses is delivered, the TMS technique is called repetitive TMS or rTMS. Low-frequency rTMS refers to a train of pulses at frequencies of ≤ 1 Hz that tends to have an inhibitory effect, whereas high-frequency rTMS refers to a train of pulses delivered at frequencies

> 5 Hz and it usually has been found to have an excitatory effect (Siebner and Rothwell, 2003; Platz and Rothwell, 2010; Lefaucheur et al., 2014; Hernandez-Pavon et al., 2014). In the literature, low-frequency rTMS is defined as previously mentioned; however, since the frequency of single-pulse TMS and low-frequency rTMS is ≤ 1 Hz, strictly speaking, both definitions are equivalent. Due to the effects of rTMS that outlast the stimulation (for instance in modulating the brain activity) this technique has generated a lot of interest in studying cognitive processes and as a potential therapeutic tool for treatment of conditions such as stroke (motor recovery, dysphagia, aphasia) (Edwards et al., 2008), Parkinson's disease (bradykinesia, dyskinesia) (Filipović et al., 2010), Alzheimer's disease (Lefaucheur et al., 2014), schizophrenia (Barr et al., 2011), depression (George et al., 2010; Fitzgerald and Daskalakis, 2012), pain (Leo and Latif, 2007), tinnitus (Lehner et al., 2014) and other diseases (Wassermann and Lisanby, 2001; Platz and Rothwell, 2010; Lefaucheur et al., 2014). However, the duration of the outlasting effects is unknown.

In addition, rTMS is a promising tool for studying language at both the cognitive and neuronal level (Devlin and Watkins, 2007). Language research suggests that the left and right hemispheres are thought to support language recovery after stroke (Sparing et al., 2001; Crosson et al., 2007). Findings from neuroimaging studies in non-fluent aphasia patients have shown high activation in right hemisphere location homologue to Broca's area (Martin et al., 2004; Naeser et al., 2010); the high activation in right hemisphere might be due to transcallosal disinhibition. Therefore, reducing the excitability in these areas by rTMS might increase the activity of areas within the damaged hemisphere, thus promoting language recovery (Vuksanović et al., 2015).

2.4 Electroencephalography (EEG)

Despite developments in technology, the basic principles of EEG remain unchanged from Berger's time (Berger, 1929). EEG is a non-invasive technique with a temporal resolution of milliseconds and a spatial resolution of centimeters, and it consists of measurements of a set of electric potential differences between pairs of electrodes placed on the scalp. EEG has been widely used in both basic and clinical research (Niedermeyer and da Silva, 2005).

2.4.1 Biophysical aspects of EEG generation

The electrical activity of the brain consists of ionic currents generated at the cellular level. These ionic primary currents induce secondary currents in the head and these currents give rise to a magnetic field that can be measured outside the head. Roughly speaking, when a neuron is excited by other neurons, postsynaptic potentials are generated in the dendrites. As a consequence, primary electric current will flow in a direction determined by whether the synaptic action is excitatory or inhibitory. The changes in the electric potential recorded on the scalp by the electrodes are generated by the sum of the excitatory and inhibitory postsynaptic potentials of the nerve cells. The EEG technique mainly measures the potentials of pyramidal cells whose apical dendrites are oriented perpendicular to the surface of the cortex. The EEG signals reflect the dynamics of electrical activity in populations of neurons. A property of such populations that is of essential importance for the generation of EEG signals is the capacity of the neurons to work in synchrony (Baillet et al., 2001; Nunez and Srinivasan, 2006).

Postsynaptic potentials in neuronal populations with an appropriate spatial organization can be sources of field potentials that can be measured at a distance and therefore are also sources of EEG signals (Niedermeyer and da Silva, 2005). EEG on the scalp is mainly caused by the synchrony of postsynaptic potentials and not by action potentials (Okada et al., 1997). In the case of action potentials, due to their short duration (1–2 ms), they tend to overlap and synchronize much less than postsynaptic potentials, which last longer (10–250 ms) (de Munck et al., 1992; Baillet et al., 2001; Niedermeyer and da Silva, 2005). Due to the slow synchrony of the postsynaptic activity of neurons and the difficulty in detecting the high-frequency action potentials, the electrophysiological signals in EEG are usually restricted to frequencies below 100 Hz (Baillet et al., 2001).

However, recently it has been demonstrated that it is possible to record high-frequency EEG (responses produced by spiking activity; Curio et al. (1994)). High-frequency EEG, about 600 Hz, had been recorded only invasively (miscroscopic recordings), but recently, it has been possible to record high-frequency EEG noninvasively (macroscopic recordings) in healthy humans (Fedele et al., 2012, 2015). Interestingly, the high-frequency EEG has been recorded at about 1 kHz, exceeding microscopic recordings

previously performed.

In EEG, the neuronal activation can be modelled as follows. The total current density $\mathbf{J}(\mathbf{r})$ at a position $\mathbf{r}$ can be divided in two flows of current: a primary or source current $\mathbf{J}^p(\mathbf{r})$, which is originated by the neuronal activity inside or in the vicinity of a cell, and a secondary or volume current $\mathbf{J}^v(\mathbf{r})$ due to the distribution of charges produced by the primary current.

The volume current is given by the the Law of Ohm:

$$\mathbf{J}^v(\mathbf{r}) = \sigma(\mathbf{r})\mathbf{E}(\mathbf{r}) , \qquad\qquad (2.4)$$

where $\sigma(\mathbf{r})$ is the conductivity of the head tissues and $\mathbf{E}(\mathbf{r})$ is generated by the distribution of charges produced by the primary current and given by $\mathbf{E} = -\nabla V$ (see section 2.2.1). $\mathbf{J}^v(\mathbf{r})$ flows passively everywhere in the medium. The recorded EEG represents the difference of potential V between two electrodes, the potential can be obtained from the measurement points associated with $\mathbf{E} = -\nabla V$, yielding the potential recorded by EEG. A magnetic field $\mathbf{B}$ arises from the total current $\mathbf{J}(\mathbf{r}) = \mathbf{J}^p(\mathbf{r}) + \mathbf{J}^v(\mathbf{r})$; $\mathbf{B}$ is measured in magnetoencephalography (MEG).

2.5 TMS combined with EEG

The use of TMS combined with a variety of different neuroimaging techniques has greatly increased in the past few years (see Siebner et al. (2009) for a review). TMS can be combined with other techniques either online (when TMS is applied while neuroimaging is being performed) or offline (when TMS is applied before or after neuroimaging). It is more challenging to perform studies online and the degree of difficulty depends on the neuroimaging technique. TMS has been combined with structural magnetic resonance imaging (MRI) (Niskanen et al., 2011), functional magnetic resonance imaging (fMRI) (Bestmann et al., 2005; Fox et al., 2012; de Lara et al., 2014), positron emission tomography (PET) (Paus et al., 1997), near infrared spectroscopy (NIRS) (Näsi et al., 2011; Thomson et al., 2011), MEG (Fuggetta et al., 2005; Raij et al., 2008), and EEG (Ilmoniemi and Kičić, 2010).

TMS can be combined with EEG both online and offline. However, it is more beneficial to perform studies online (Ilmoniemi and Kičić, 2010). TMS combined with EEG has become a powerful technique which allows one to perform both basic and clinical research. TMS–EEG has been used to non-invasively investigate functional and effective connectivity (Borto-

letto et al., 2015), cortico–cortico connectivity (Komssi et al., 2002; Massimini et al., 2005), cortico–subcortical connectivity (Ferreri et al., 2011), cortical excitability (Nikulin et al., 2003; Ilmoniemi and Kičić, 2010), cortical facilitation and inhibition (Nakamura et al., 1997; Farzan et al., 2013), the state of the cortex/brain dynamic (Miniussi and Thut, 2010; Stamoulis et al., 2011; Mutanen et al., 2013; Kawasaki et al., 2014), brain oscillations (Thut and Miniussi, 2009; Thut et al., 2011), cortical plasticity (Siebner and Rothwell, 2003; Huber et al., 2008), and has also been used as a tool for diagnostics (Rotenberg, 2010). The first successful study on TMS–EEG was performed in 1996 (Ilmoniemi et al., 1997).

Nevertheless, to combine TMS with simultaneous EEG is challenging, the main problem coming from the strong magnetic field since it induces currents in the electrode leads, which may produce saturation of the amplifiers and artifacts (Ilmoniemi and Kičić, 2010). This problem can be addressed by using gain-control and sample-and-hold circuits to block the artifacts induced by TMS in the leads (Virtanen et al., 1999). Besides that, during the application of the TMS pulse, some current can pass through the electrode–electrolyte interface, causing polarization, which produces an EEG baseline shift that can last for hundreds of milliseconds. Overheating of the electrodes is another problem that may occur, particularly when long trains of pulses are delivered. Those problems can be effectively solved by using special electrodes, such as small Ag/AgCl electrodes (Virtanen et al., 1999; Ives et al., 2006).

TMS–EEG has successfully been used for studying brain areas where the evoked EEG signals are not affected by large artifacts, *i.e.*, motor, sensory, and visual areas (Komssi et al., 2002; Kähkönen et al., 2004, 2005; Silvanto and Cattaneo, 2010). However, if TMS is applied over facial nerves, or lateral areas close to cranial muscles, large muscle artifacts lasting for tens of milliseconds are activated by the magnetic stimulus (Mutanen et al., 2013; Hernandez-Pavon et al., 2014) (Fig. 2.3). Therefore, these large artifacts mask the evoked EEG signals, restricting the study of lateral areas with TMS–EEG. Several off-line methods based on independent component analysis (Rogasch et al., 2014), principal component analysis (Litvak et al., 2007) and signal-space projection (Mäki and Ilmoniemi, 2011) have been proposed to remove the artifacts from TMS-evoked EEG data. However, the methods to some extent have not been efficient in removing the strong muscle artifacts. For instance, the TMS–EEG study of language areas has been restricted since these areas are
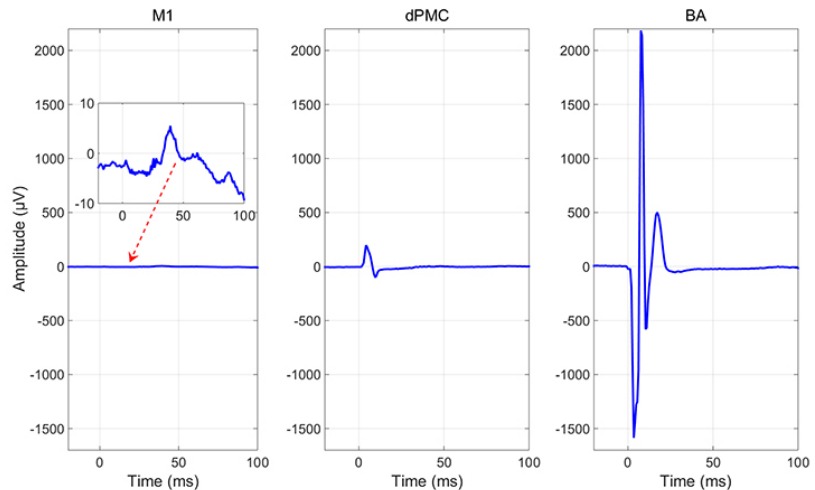
Figure 2.3 Typical waveforms after stimulating the motor cortex (M1), dorsal premotor cortex (dPMC), and Broca's area (BA) in a representative subject. The artifacts in both dPMC and BA are much larger than the brain signal, which is much weaker than the artifacts, see M1 response. Modified from (Hernandez-Pavon et al., 2014).

close to cranial muscles (see Publications I and II). Despite great advances in neuroimaging techniques, there are many open questions regarding the mechanisms involved in the language process. There is evidence that the motor area is also involved in the processing of meaningful information about language and action (Pulvermüller, 2005; Pulvermüller et al., 2005). Therefore, being able to study those areas with TMS–EEG might provide important information for basic research and in clinical applications.

2.6 Navigated TMS

MRI-guided navigated TMS systems have become state-of-the-art in performing TMS studies (Siebner et al., 2009; Ruohonen and Karhu, 2010). A navigated TMS system is composed of several elements that make the stimulation very accurate and reproducible (Fig. 2.4). The stimulation coil has trackers attached to it and the subject wears a head tracker system. The tracking system applies infrared light to measure the 3D position of the reflective passive markers attached to the trackers. This enables the recording of the relative position between the head of the subject and the TMS coil in real-time (see Ruohonen and Karhu (2010), for details). The induced electric field in the brain is also computed by the nTMS system.
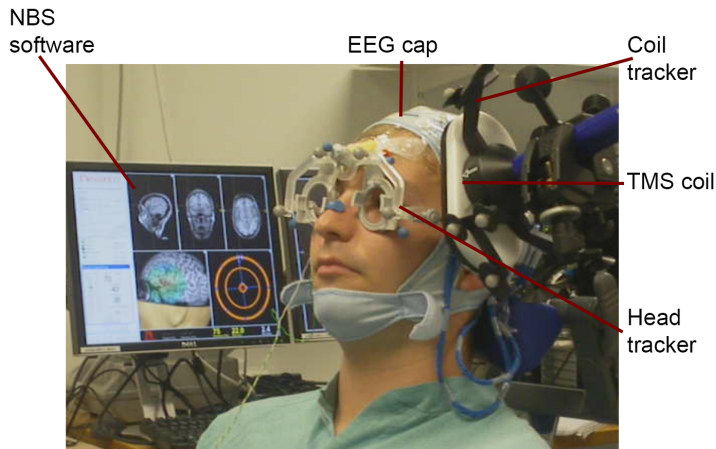
Figure 2.4 TMS combined with EEG. Different elements of the NBS TMS system.

In nTMS, the stimulated cortical target can be defined anatomically from the individual's brain MRI. In addition, the coil position can be monitored, the orientation and strength of the induced electric field can also be estimated in real-time, which are the main and most important features for reproducibility (Lioumis et al., 2009; Casarotto et al., 2010). nTMS can be combined with electromyography (EMG) and EEG. The EMG measures the motor response elicited by the magnetic stimulus. The system used in all the Publications presented in this Thesis was a navigated brain stimulation (NBS) TMS system (Nexstim., Helsinki, Finland).

2.6.1 Use of repetitive nTMS for speech mapping

The use of neuroimaging techniques for brain mapping has extensively increased in the past few years (Archip et al., 2007). Navigated TMS has shown its potential in mapping the primary motor cortex in comparison to fMRI (Weiss et al., 2013). However, the main difference between TMS and other non-invasive neuroimaging techniques is the causality, *i.e.*, when TMS is used a physiological response is evoked by stimulating a cortical area; therefore, that specific cortical area is causally related to the response. Other neuroimaging techniques only detect and map a brain area that is involved in a task or reaction (Ruohonen and Karhu, 2010). Techniques such as fMRI, DTI, and MEG are used for preoperative mapping (Archip et al., 2007; Mäkelä et al., 2006; Bello et al., 2008; Stufflebeam, 2011). nTMS has also been used in preoperative localization of the motor cortex (Picht et al., 2009; Vitikainen et al., 2009). The infor-

mation provided by nTMS is useful for surgical planning; this information can be transferred into the operating theater via surgical neuronavigation systems. It has been reported that nTMS localizes the cortical representations of hand muscles as accurately as direct cortical stimulation (DCS, the gold standard technique for brain mapping) (Picht et al., 2011; Krieg et al., 2012) and more accurately than fMRI (Forster et al., 2011; Krieg et al., 2012). rTMS has also shown to be useful for studying the functional localization of speech in healthy subjects; however, the early results were variable (Pascual-Leone et al., 1991; Epstein et al., 1999; Devlin and Watkins, 2007).

Recently, the use of repetitive nTMS and object naming for preoperative localization of speech-related brain areas has been introduced (Lioumis et al., 2012), Fig 2.5. This approach has been compared to DCS during awake craniotomy (Picht et al., 2013; Tarapore et al., 2013). The results imply that repetitive nTMS is remarkably sensitive but relatively non-specific in detecting the sites producing speech disturbance in DCS. Pre-operative speech mapping by repetitive nTMS can give important a priori information to the neurosurgeons. In addition, it may aid in objective pre-operative risk-benefit balancing of the planned surgery, in particular of eloquent areas. It might also help in more targeted and smaller craniotomies, faster and safer intraoperative mapping, and safer surgeries for patients who cannot undergo awake craniotomy (Picht et al., 2013). Therefore, a better understanding of the effects of rTMS during naming tasks may have an impact on surgery planning and provide also information about the cortical organization of speech in general.

2.7 Independent component analysis (ICA)

Independent component analysis (ICA) is a method for finding underlying random variables or components from multivariate (multidimensional) statistical data. ICA looks for components that are both statistically independent and nongaussian (Hyvärinen, 1999; Hyvärinen and Oja, 2000; Hyvärinen et al., 2001). ICA was originally proposed to solve the blind source separation (BSS) problem, to recover independent sources (for instance, different voices, music, or noise sources) after they have been linearly mixed. A simple way to understand the BSS problem is to imagine that there are several people speaking at the same time in a room containing as many or more microphones. In this case, the output of each
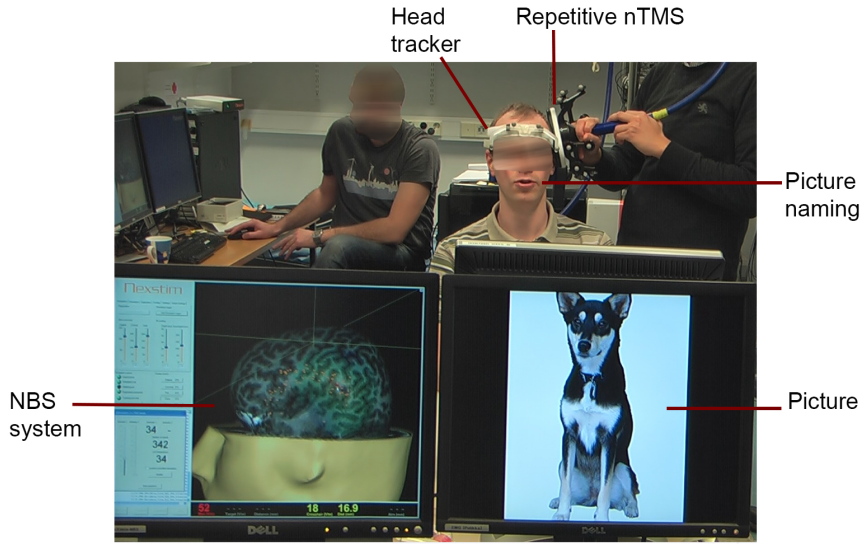
Figure 2.5 Experimental setup to perform speech mapping.

microphone is a mixture of several voice signals. Given these mixed signals, ICA, in principle, can recover the original voices or source signals of each single speaker (Fig. 2.6 A). The same problem arises in EEG and MEG. In EEG and MEG the sensors record a mix of electric and magnetic responses, respectively, from neuronal sources in the brain. In principle, ICA can separate the mixed responses into the original components or sources (Fig. 2.6 B).

2.7.1 Formulation of ICA

The starting point for modelling ICA in EEG is as follows. Let

$$\mathbf{Y} = \mathbf{AS} \ , \tag{2.5}$$

where the recorded data $\mathbf{Y}$ is denoted by an $M \times T$ matrix, where M is the number of channels and T the number of time points (for simplicity, the noise is not considered here). The element $\mathbf{Y}(m,t)$ represents the signal in channel m at time t, $m = 1, \ldots, M$; $t = 1, \ldots, T$. $\mathbf{A}$ is the $M \times n$ mixing matrix, with $\mathrm{rank}(\mathbf{A}) = n$, and $\mathbf{S}$ is the $n \times T$ time-course matrix of the independent components (ICs) so that $\mathbf{S}(j,t)$, $t = 1, \ldots, T$, is the time-course or waveform of the jth independent source and the vectors $\mathbf{S}(:,t)$, $t = 1, \ldots, T$, are thought to be random samples of a random vector $\mathbf{s} = [s_1, \ldots, s_m]^{\text{T}}$ whose components $\mathbf{s}_i$ are statistically independent with unit
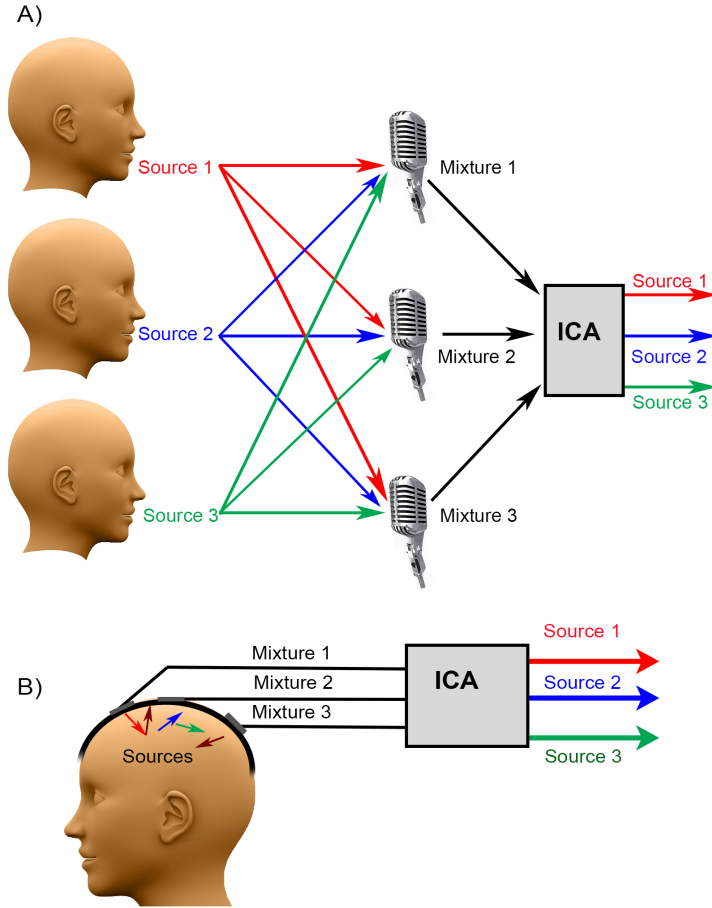
Figure 2.6 ICA model. A) ICA can separate the mixed sources recorded by three microphones when three people speak simultaneously (this example can be extended to several people). B) ICA model in EEG.

variance. Consequently, $\mathbf{S}$ is normalized so that the *covariance matrix*

$$\mathrm{Cov}(\mathbf{S}) = \frac{1}{T}\mathbf{S}\mathbf{S}^\mathrm{T} = \mathbf{I}\,, \tag{2.6}$$

where $\mathbf{I}$ is the $n \times n$ identity matrix. The task of an ICA algorithm is to find the estimates for $\mathbf{A}$ and $\mathbf{S}$, respectively. Every column of the mixing matrix $\mathbf{A}(:,j)$ is also called the topography of the underlying source.

2.7.2 Preprocessing and the FastICA algorithm

Preprocessing is a crucial step that should be carried out before applying any ICA algorithm. Publications I and II describe in detail the different preprocessing steps. After removing bad channels and bad trials, and setting the reference potential, the matrix $\mathbf{Y}$ should be preprocessed before

applying ICA (Hyvärinen and Oja, 2000), in particular the means of the signals should be removed. Whitening simplifies the analysis; it could be understood as a rescaling process. It transforms the data so that its covariance matrix is equal to the identity matrix. The whitened data matrix $\mathbf{Y}_{\text{white}}$ can be obtained as follows:

$$\mathbf{Y}_{\text{white}} = \mathbf{BAS} = \mathbf{WS} \, , \tag{2.7}$$

where $\mathbf{B}$ is the *whitening matrix* and $\mathbf{W} = \mathbf{BA}$ is the orthogonal $n \times n$ *weight matrix*. The matrix $\mathbf{B}$ is obtained by the singular value decomposition $\mathbf{Y} = \mathbf{UDV}^{\text{T}}$ as $\mathbf{B} = \mathbf{D}^{-1}\mathbf{U}^{\text{T}}$.

In general, any ICA algorithm should be applied to $\mathbf{Y}_{\text{white}}$, given by eq. (2.7), to find the weight matrix $\mathbf{W}$ (the whitened mixing matrix), when the algorithm yields an orthogonal matrix $\widehat{\mathbf{W}}$ as an *estimate* for $\mathbf{W}$. An estimate $\widehat{\mathbf{S}}$ for $\mathbf{S}$ is then obtained with (2.7) as

$$\widehat{\mathbf{S}} = \widehat{\mathbf{W}}^{\text{T}}\mathbf{Y}_{\text{white}} \, , \tag{2.8}$$

with $\frac{1}{T}\widehat{\mathbf{S}}\widehat{\mathbf{S}}^{\text{T}} = \mathbf{I}$. Then an estimate $\widehat{\mathbf{A}}$ for $\mathbf{A}$ is obtained by multiplying equation $\mathbf{Y} = \widehat{\mathbf{A}}\widehat{\mathbf{S}}$ by $\frac{1}{T}\widehat{\mathbf{S}}^{\text{T}}$ from the right which yields

$$\widehat{\mathbf{A}} = \frac{1}{T}\mathbf{Y}\widehat{\mathbf{S}}^{\text{T}} \, . \tag{2.9}$$

Figure 2.7 depicts graphically the steps carried out in ICA. Several algorithms have been developed for ICA, such as Infomax, CUBICA, etc., (for a review see (Klemm et al., 2009)). In Publications I and II, the FastICA algorithm is used (Hyvärinen, 1999; Hyvärinen and Oja, 2000; Hyvärinen et al., 2001). FastICA searches for the orthonormal weight vectors $\mathbf{w}_1, \ldots, \mathbf{w}_n$, *i.e.*, the columns of $\mathbf{W}$, as the local maxima of the *negentropy function* (Hyvärinen and Oja, 2000),

$$J_G(\mathbf{w}^{\text{T}}\mathbf{Y}_{\text{white}}) = \left[\frac{1}{N} \sum_{j=1}^{N} G(\mathbf{w}^{\text{T}}\mathbf{Y}_{\text{white}}(:,j)) - c \right]^2 \, , \tag{2.10}$$

where G is the *contrast function* and c is the mean of $G(u)$, u being a scalar Gaussian random variable with zero mean and unit variance. The algorithm starts from random initial orthonormal vectors $\mathbf{w}_1, \ldots, \mathbf{w}_n$ and upgrades them, step by step, by a fast fixed-point algorithm (Hyvärinen, 1999), retaining the orthonormality and trying to push each $\mathbf{w}_j$ as close to one of the local maxima of (2.10) as possible. After no changes in the upgrading have happened up to a given tolerance, the algorithm stops. Thereafter, having formed the estimate $\widehat{\mathbf{W}} = [\mathbf{w}_1, \ldots, \mathbf{w}_n]$ for $\mathbf{W}$, the algorithm sets the estimates for $\mathbf{S}$ and $\mathbf{A}$ to be as in (2.8) and (2.9), respectively. FastICA returns $\widehat{\mathbf{W}}$ and $\widehat{\mathbf{S}}$ with slightly varying values from one
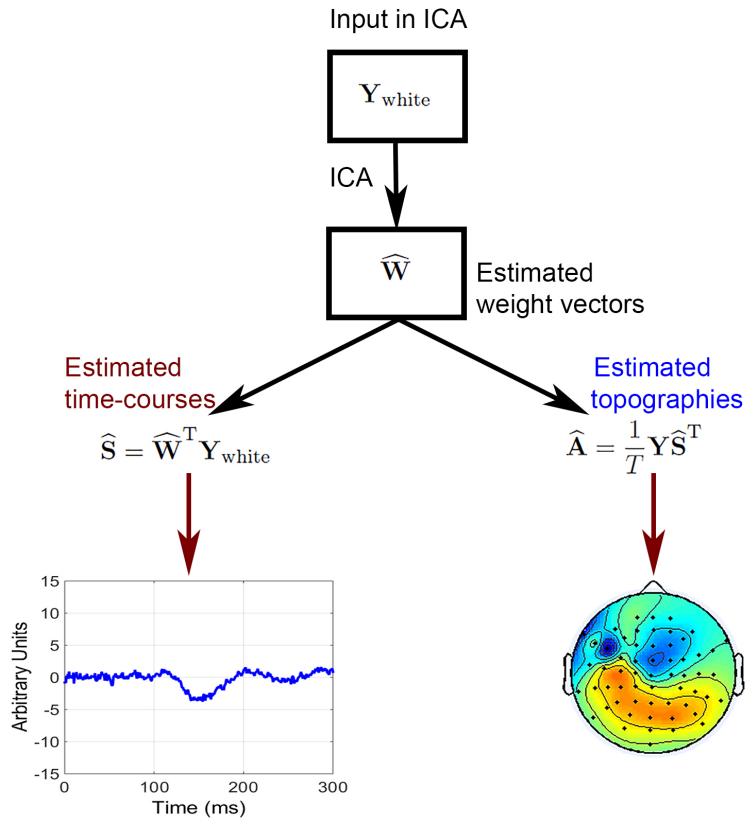
Input in ICA

$$\mathbf{Y}_{white}$$

ICA

$$\widehat{\mathbf{W}}$$

Estimated
weight vectors

Estimated
time-courses

$$\widehat{\mathbf{S}} = \widehat{\mathbf{W}}^{\mathrm{T}} \mathbf{Y}_{white}$$

Estimated
topographies

$$\widehat{\mathbf{A}} = \frac{1}{T} \mathbf{Y} \widehat{\mathbf{S}}^{\mathrm{T}}$$

Figure 2.7 Steps carried out in ICA. The outputs are estimated time-courses and topographies of the independent components.

run of the algorithm to another because of the random initial $\mathbf{W}$. The FastICA algorithm is also described in detail in Publications I and II.

2.8 Beamformer

Spatial filters are linear operators or estimators applied to EEG and MEG data to estimate the strength of neuronal activity at a particular spatial location within the brain (Sekihara and Nagarajan, 2008). Spatial filters estimate the source activity at points of interest, by passing the signal from desirable locations while blocking signals from other locations. The spatial filters can be divided in non-adaptive and adaptive. *Non-adaptive spatial filters* are those where the filters only depend on the geometry or lead-field matrix of the measurement data, whereas the *adaptive spatial filters* depend on the geometry of the measurement and on the data co-variance matrix (Sekihara and Nagarajan, 2008).

Among the non-adaptive spatial filters one can lists minimum norm estimate (MNE) (Hämäläinen and Ilmoniemi, 1984, 1994), low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994) and standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui et al., 2002). Among the adaptive spatial filters one can mentions, for instance multiple signal classification (MUSIC) (Schmidt, 1986; Mosher et al., 1992) and recursively applied and projected MUSIC (RAP-MUSIC) (Mosher and Leahy, 1999). Those methods make use of the lead-field matrix of the measurement data and dominant subspaces spanned by the vector structure of the data. In RAP, one projects out the topographies of the found dipoles from the data in an iterative manner. In RAP each source is found iteratively as the global maximum of a function.

Adaptive spatial filters are also called beamformers, a beamformer can be interpreted as a set or an array of spatial filters with the special quality that there is a single filter with each location. The most widely used is the linearly constrained minimum-variance (LCMV) beamformer (Van Veen et al., 1997). Beamformers have the best spatial resolution in comparison to other tomographic methods (Darvas et al., 2004; Sekihara et al., 2005; Sekihara and Nagarajan, 2008), are very robust in the presence of noise and can also tolerate slightly correlated time-courses (Sekihara et al., 2005). Beamformers are based on two assumptions, first the sources should be dipolar and secondly the time-courses of the sources should be orthogonal to each other, *i.e.*, temporally uncorrelated (Sekihara et al., 2002; Brookes et al., 2007). Therefore, the main disadvantage of beamformers is that highly temporally correlated time-courses distort the outcome of beamformer (Sekihara et al., 2002; Dalal et al., 2006; Quraan and Cheyne, 2010). In addition, the correlation might make some time-courses linearly dependent, or almost dependent, which turns the corresponding dipoles invisible for the beamformer.

3. Summary of Publications

This Chapter summarizes the four studies constituting this Thesis. More details on the methods and data analysis can be found in Publications I–IV.

3.1 Publication I: "Removal of large muscle artifacts from transcranial magnetic stimulation-evoked EEG by independent component analysis"

In this study, two methods based on ICA were introduced to remove very large muscle artifacts from TMS-evoked EEG data after stimulation of Broca's area and dorsal premotor cortex. The first method, so-called enhanced deflation method (EDM), is novel and semiautomatic; in particular, it was designed to select the independent components with the highest negentropy to be the artifacts to be removed. The second method, called manual method (MAM), makes use of the symmetric mode of FastICA; the user selects the artifactual components visually by looking at the topographies, waveforms, and amplitudes of the components. The results showed that both methods are effective in removing the large artifacts (Fig. 3.1). However, EDM is more robust, faster and less subjective than MAM. This is the first study where ICA is used to remove large muscle artifacts in EEG evoked by TMS of lateral areas (Broca's area and dorsal premotor cortex). These methods open new possibilities to study artifactual areas of the brain with TMS–EEG.
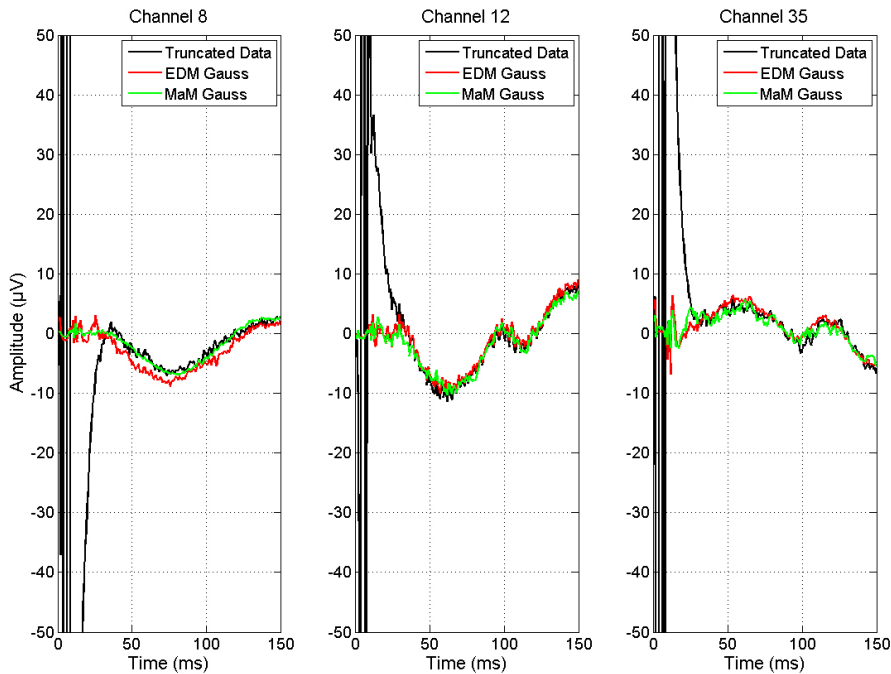
Figure 3.1 TMS-evoked EEG data from Broca's area. The responses in electrodes 8 (F5), 12 (F6) and 35 (TP7) are presented. EDM and MAM were able to remove the large artifacts. The shape of the original signal was reached at about 40 ms after applying the methods. See Publication I for more details.

3.2   Publication II: "Uncovering neural independent components from highly artifactual TMS-evoked EEG data"

This Publication is complementary to the previous one. Here, TMS-evoked EEG data from Broca's area were studied. The main goal was to determine how badly the large artifacts affect the ICA separation, and whether the distortion can be avoided without fully removing the artifacts. It was found that the large artifacts do not much distort the time-courses of the independent components; however, they may greatly distort the topographies. Three suppression methods based on principal component analysis (PCA), wavelet analysis, and whitening of the measurement data were developed. The methods, instead of removing the artifacts, rescale the data so that the artifacts are suppressed to about the same size as the neuronal signals. The suppression was chosen so that the neural EEG signals are suppressed much less than the artifacts; therefore, the neural information is retained well enough for the ICA separation, while the suppressed size of the artifacts does not degrade the numerical performance of the ICA

algorithm. The techniques were tested in measured and simulated data and were combined with source localization (single-dipole search). The results showed that the neural EEG signals are suppressed much less than the artifactual ones, and that the artifact suppression improves significantly the source localization (Fig. 3.2). In conclusion, the theoretical and experimental results suggest that is possible to study the neuronal independent components found by ICA, even in the case of highly artifactual TMS-evoked EEG data, such as data from Broca's area.
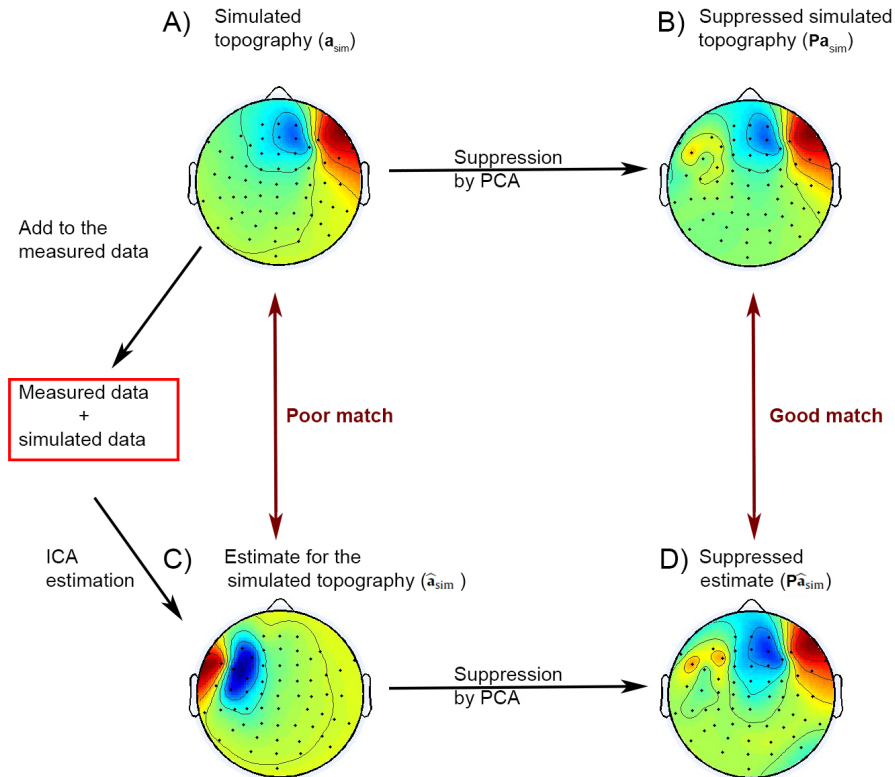
A) Simulated topography ($\mathbf{a}_{sim}$)

B) Suppressed simulated topography ($\mathbf{Pa}_{sim}$)

Suppression by PCA

Add to the measured data

Poor match

Good match

Measured data + simulated data

ICA estimation

C) Estimate for the simulated topography ($\widehat{\mathbf{a}}_{sim}$)

D) Suppressed estimate ($\mathbf{P}\widehat{\mathbf{a}}_{sim}$)

Suppression by PCA

Figure 3.2 Example of the topography estimation with principal component analysis (PCA) suppression. A) A simulated dipole (neuronal topography) was placed in the right hemisphere corresponding to Broca's area. B) The simulated topography can be suppressed by PCA suppression and it is only slightly affected because there is no presence of artifacts in it. C) The simulated dipolar EEG data, containing the topography (A), were added to the measured data with large artifacts producing the combined data. ICA estimation was then used on the combined data to find the estimate for the simulated topography. The measurement data contain large artifacts mainly in the left channels; the estimate is badly distorted toward that direction. Due to the strong artifacts, the simulated topography (A) and the estimate for the simulated topography (C) have poor resemblance with each other. D) The PCA suppression is applied to the estimate topography by ICA. Because the artifacts are suppressed by PCA suppression, the suppressed simulated (B) and suppressed estimated (D) topographies have now strong resemblance with each other. See Publication II for more details, note that in Fig. 3.2 of this Thesis a principal component suppression is presented, while in Fig. 7 of Publication II a similar example with wavelet analysis is shown.

3.3 Publication III: "Effects of navigated TMS on object and action naming"

In this study, the sensitivity and distribution of object and action naming tasks to repetitive nTMS were studied in eight subjects. Repetitive nTMS

at 5 Hz was delivered to the left hemisphere while the subjects named pictures of objects and actions. Naming during repetitive nTMS was compared with the picture-naming baseline performance. nTMS induced no-response errors, and phonological and semantic paraphasias. The errors were categorized by location. The results showed that object naming was significantly more disturbed by nTMS than action naming. No-response errors were the most common in both tasks; however, no-response errors were significantly more frequent in object naming than action naming. In addition, the postcentral gyrus was significantly more sensitive to object naming than action naming, no statistical differences were observed in other gyri (Fig. 3.3). Semantic and phonetic paraphasias did not shown statistical differences during both tasks. This study suggests that the efficacy of repetitive nTMS in inducing naming errors can be modulated by the task, i.e., if a higher sensitivity is required, object naming can be used; if a sparse amount of errors is required, then action naming is preferred. Furthermore, the findings do not allow conclusions on cortical areas essential for processing of object-related or action-related words. In contrast, they support the network nature of language processing. In conclusion, here it was demonstrated how repetitive nTMS affects both object and action naming, which provides information for presurgical planning and also about the cortical organization of speech in general.
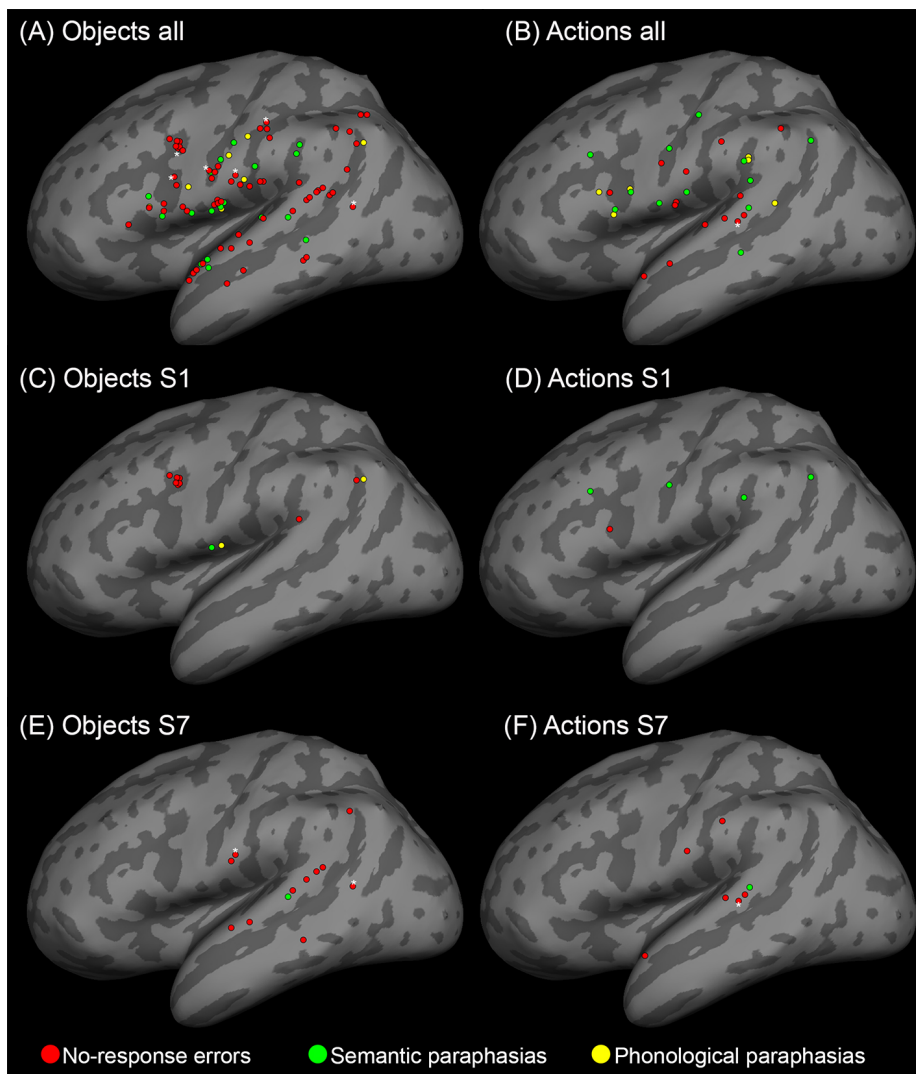
Figure 3.3 Visualization on an inflated brain of the cortical sites for both object and action naming errors. Red spheres: no-response errors; green spheres: semantic paraphasias; yellow spheres: phonological paraphasias. (A, B) All cortical sites that elicited naming errors during nTMS in all subjects. (C, D) Individual data from subject S1. (E, F) Individual data from subject S7. The number, type and location of the naming errors vary between subjects. The white asterisks indicate the sites of repeated errors at the same location. See Publication III for details.

3.4 Publication IV: "Beamformer with temporally correlated sources and iterative search in EEG"

In this Publication, the goal was to develop a new technique to improve the traditional beamformer and to enhance the source localization when the sources are temporally correlated. Two key points are introduced in

this study. 1) A closed-form formula for beamformer is derived, which exactly describes the outcome of beamformer for both uncorrelated and temporally correlated sources. 2) Beamformer is combined with the iterative RAP technique, resulting in so-called RAP beamformer, for improving the search of the dipole locations of correlated and even linearly dependent time-courses. Three types of beamformer were used and called according to the source dipole orientation as follows: scalar beamformer (when the dipole orientation was predetermined), optimal orientation beamformer (when the dipole orientations were unknown but an optimal orientation was assigned to every dipole), and vector beamformer (when the dipole orientations were unknown and the dipoles had free orientations). Several EEG simulations were carried out with the three beamfomers for data contaminated with either white or colored noise. The methods were tested in both spherical and realistically shaped head models. The results obtained from the simulations suggest that the closed-form formula, proposed in this study, shows the real outcome of beamformer even when the sources are highly correlated. The combination of RAP beamformer and adding extra white noise to the measurement data greatly improves the dipole locations property of beamformer with correlated sources, making even invisible sources visible (Fig. 3.4). In summary, this study shows that RAP beamformer is an ideal technique to study correlated sources and to make invisible sources visible. This is the first study where beamformer is combined with RAP. This study opens big possibilities for source localization of temporally correlated sources in EEG and TMS-evoked EEG data.
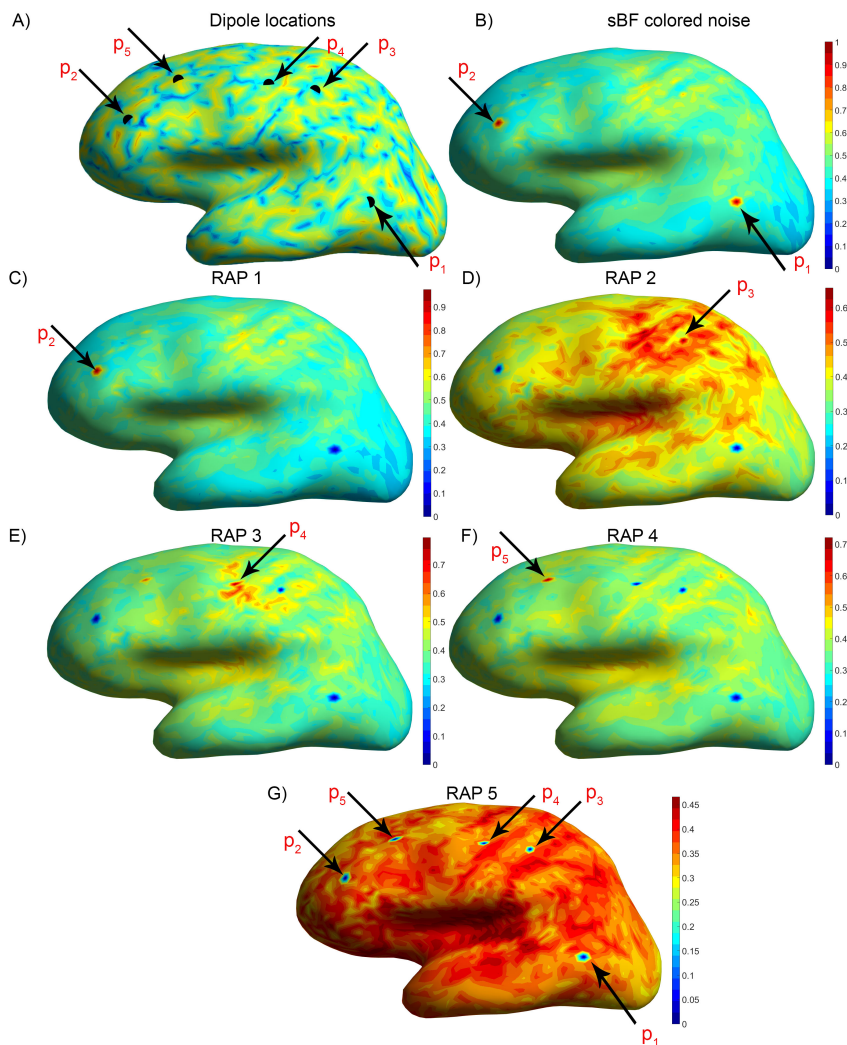
Figure 3.4 Scanning by scalar beamformer (sBF) and RAP sBF for five dipoles and five simulated time-courses. Time-courses (S1, S2, S4, S5) were with 20% of correlation and S3, S4, S5) linearly dependent with S3= S4+ S5. The data were contaminated with 20% of colored noise and 5% of extra white noise was added to improve the search. A) Locations of the simulated dipoles. B) sBF shows two active dipoles (p1 and p2), however, three dipoles are invisible to beamformer due to the linear dependence (p3, p4 and p5). C) Dipole p1 is projected out by RAP technique preserving the four remaining ones by only p2 is visible. D) Dipole p2 is projected out making dipole p3 visible. E) Projection of dipole p3 out makes dipole p4 visible. F) Dipole p4 is projected out making dipole p5 visible. G) Projection of dipole p5 out leaves the scanning pattern chaotic showing no clear further "hill-tops" as potential locations of active dipoles. The true sources (p1, p2, p3, p4 and p5) are marked by blue spots. See Publication IV for more details.

4.   Discussion and conclusion

This Thesis has presented the combination of TMS with EEG to study lateral areas of the brain. TMS–EEG is a powerful combination for studying cortical excitability and connectivity (Ilmoniemi et al., 1997), but TMS of lateral areas induces strong artifacts in EEG. Here, the nature of those artifacts has been described and several methods were introduced to deal with them. In particular, in this Thesis, two approaches were presented to remove and to suppress the large muscle artifacts. The methods are based on ICA and PCA. Methods based on ICA have been used before in artifact reduction from TMS-evoked EEG data; however, there, the artifacts were only of moderate size (Iwahashi et al., 2008; Hamidi et al., 2010). The studies in this Thesis have gone further and ICA was introduced for the first time to remove very large muscle artifacts from TMS-evoked EEG data arising from brain areas close to cranial muscles. The results are promising, allowing one to study speech-related areas with TMS–EEG. In addition, these methods have allowed us to perform studies of areas not previously studied with TMS–EEG, for instance, dorsolateral prefrontal cortex (Rogasch et al., 2014, 2015), which has a potential clinical application in depression.

TMS has proven to have many clinical applications (Wassermann and Zimmermann, 2012). In particular, nTMS has been shown to have a big impact on brain mapping (Weiss et al., 2013) and presurgical planning (Picht et al., 2009; Vitikainen et al., 2009; Picht et al., 2011; Krieg et al., 2012). The use of repetitive nTMS combined with picture naming has been shown to be very successful on language mapping (Picht et al., 2013; Tarapore et al., 2013). In this Thesis, we have compared the impact of repetitive nTMS on object and action naming, providing new evidence of the effect of repetitive nTMS for language mapping. Hence, this research can be extended to presurgical planning and may help improve our un-

derstanding of the speech organization at cortical level. Thus, repetitive nTMS can be combined with EEG and protocols of picture naming to study language in the near future.

An extra problem in TMS–EEG analysis, despite the artifacts, is source localization. In the general 3-D inverse problem, there is no unique solution and many constrained source localization methods are very sensitive to noise, temporal correlation or other parameters which make the search difficult. Here, the beamformer technique was improved by combining it with iterative RAP technique (see Section 2.8) in order to find correlated sources and make invisible sources visible.

In the introduction, it was already mentioned that this Thesis came from the idea of studying functional connectivity between language areas, *i.e.*, Broca's and Wernicke's areas. The methods presented here open possibilities for applying TMS–EEG to study different sites of the brain, where the stimulation evokes not only muscle artifacts, but also other kinds of artifacts that distort EEG responses. Thus, these methods combined with source localization are promising for studying functional connectivity with TMS–EEG.

In summary, in this Thesis TMS, nTMS and TMS–EEG were used for basic research. Specifically, different methods were introduced for analyzing TMS-evoked EEG data, for removing and for suppressing muscle artifacts, and for studying source localization. Also a study for speech mapping was performed, with implications on both basic and clinical purposes. Overall, this Thesis has covered several aspects which are fundamental to carrying out further research; the impact of all these studies can be reflected at both scientific and clinical levels as follows:

I) TMS evokes large artifacts from lateral areas. The methods presented here can solve that problem, allowing one to study areas of the brain not explored before or restricted because of the artifacts. Therefore, studies of brain connectivity can be carried out, for instance, to improve our understanding of the connections between cortical language areas in the brain. Such knowledge could be applied to patients with aphasia, stroke, Parkinson's, and Alzheimer's diseases.

II) Repetitive nTMS can be combined with object and action naming to perform brain mapping of language areas. This approach can bring many benefits to cognitive neuroscience for understanding the language net-

work and in clinical practice such as presurgical planning.

III) Beamformer combined with RAP technique is a good tool for studying correlated sources in EEG and TMS-evoked EEG data. This has many potential applications to improve the knowledge of brain excitability and connectivity induced by TMS.

IV) The impact of all these techniques and methods can be summarized in the following paradigm. Repetitive nTMS could be used to functionally localize speech sites, and then TMS–EEG could be applied specifically to those sites. TMS of speech areas would induce strong artifacts produced by the activation of the lateral muscle (speech areas being lateral). The methods presented here could remove or sufficiently suppress the artifacts. Therefore, the EEG signals would be useful and the RAP beamformer technique could provide information of source localization. This paradigm would not only give cognitive information, but also could be useful in clinical practice; as consequence many, patients would benefit from it. The combination of these studies can be utilized as diagnostics and therapeutical tools.

Finally, all the tools presented in this Thesis can be used to carry out new studies with TMS–EEG in order to understand more about brain connectivity and excitability of language areas, as well as to perform basic research and clinical applications of TMS–EEG of other lateral areas of the brain.

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