Biosystems & Biorobotics

Christoph Guger
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E.C. Leuthardt *Editors*

Brain-Computer Interface Research

A State-of-the-Art Summary -2

Springer

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Aims & Scope

Biosystems & Biorobotics publishes the latest research developments in three main areas: 1) understanding biological systems from a bioengineering point of view, i.e. the study of biosystems by exploiting engineering methods and tools to unveil their functioning principles and unrivalled performance; 2) design and development of biologically inspired machines and systems to be used for different purposes and in a variety of application contexts. The series welcomes contributions on novel design approaches, methods and tools as well as case studies on specific bioinspired systems; 3) design and developments of nano-, micro-, macro- devices and systems for biomedical applications, i.e. technologies that can improve modern healthcare and welfare by enabling novel solutions for prevention, diagnosis, surgery, prosthetics, rehabilitation and independent living.

On one side, the series focuses on recent methods and technologies which allow multi-scale, multi-physics, high-resolution analysis and modeling of biological systems. A special emphasis on this side is given to the use of mechatronic and robotic systems as a tool for basic research in biology. On the other side, the series authoritatively reports on current theoretical and experimental challenges and developments related to the "biomechatronic" design of novel biorobotic machines. A special emphasis on this side is given to human-machine interaction and interfacing, and also to the ethical and social implications of this emerging research area, as key challenges for the acceptability and sustainability of biorobotics technology.

The main target of the series are engineers interested in biology and medicine, and specifically bioengineers and bioroboticists. Volume published in the series comprise monographs, edited volumes, lecture notes, as well as selected conference proceedings and PhD theses. The series also publishes books purposely devoted to support education in bioengineering, biomedical engineering, biomechatronics and biorobotics at graduate and post-graduate levels.

About the Cover

The cover of the book series Biosystems & Biorobotics features a robotic hand prosthesis. This looks like a natural hand and is ready to be implanted on a human amputee to help them recover their physical capabilities. This picture was chosen to represent a variety of concepts and disciplines: from the understanding of biological systems to biomechatronics, bioinspiration and biomimetics; and from the concept of human-robot and human-machine interaction to the use of robots and, more generally, of engineering techniques for biological research and in healthcare. The picture also points to the social impact of bioengineering research and to its potential for improving human health and the quality of life of all individuals, including those with special needs. The picture was taken during the LIFEHAND experimental trials run at Università Campus Bio-Medico of Rome (Italy) in 2008. The LIFEHAND project tested the ability of an amputee patient to control the Cyberhand, a robotic prosthesis developed at Scuola Superiore Sant'Anna in Pisa (Italy), using the tf-LIFE electrodes developed at the Fraunhofer Institute for Biomedical Engineering (IBMT, Germany), which were implanted in the patient's arm. The implanted tf-LIFE electrodes were shown to enable bidirectional communication (from brain to hand and vice versa) between the brain and the Cyberhand. As a result, the patient was able to control complex movements of the prosthesis, while receiving sensory feedback in the form of direct neurostimulation. For more information please visit http://www.biorobotics.it or contact the Series Editor.

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Editors

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Acknowledgment

The editors wish to dedicate this book to our many colleagues in BCI research. The work in this book represents only a small fraction of the BCI research worldwide. We are grateful to our many hardworking colleagues for advancing the field and helping a growing variety of different patients.

Contents

Recent Advances in Brain-Computer Interface Research - Projects Nominated for the BCI Award 2012

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1 Introduction

Brain-Computer Interfaces (BCIs) are devices that translate a user's brain activity into messages or commands (Wolpaw et al., 2002; Pfurtscheller et al., 2010; Wolpaw and Wolpaw, 2012). BCIs have four components: a signal acquisition system that records the user's brain activity; a signal processing module that finds meaningful patterns within this brain activity that reflect a user's intent; an output device such as a monitor, wheelchair or robotic arm; and an operating protocol that controls the interaction among these different modules and people such as the user or an operator. Signal acquisition may involve sensors placed on or in the brain (through neurosurgery), or noninvasive methods such as scalp-mounted electrode caps or functional MRI.

BCI research has been active for almost half a century. Although BCIs were first presented publicly about 50 years ago, and published about ten years later, the field saw relatively little progress until recently (Graimann et al., 2010; Wolpaw and Wolpaw, 2012). Figure 1 below presents two figures that show increasing interest in BCI research. The left panel shows the participation in major international conferences, and the right panel shows peer-reviewed research articles.

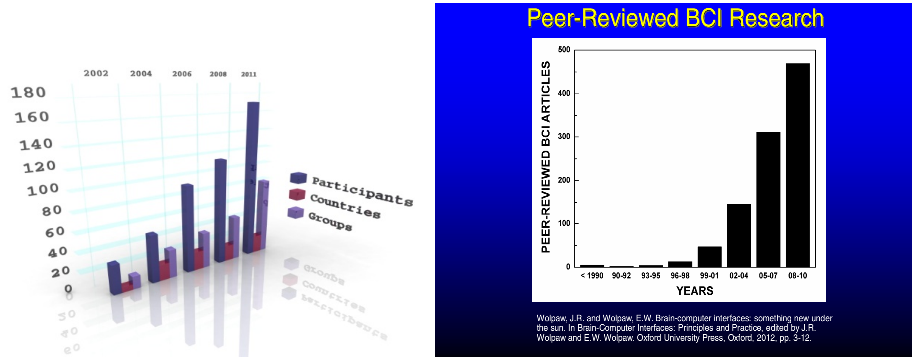

Fig. 1. Two different measures of activity in the BCI research community: conference participation and peer-reviewed articles. The left panel is from the Future BNCI roadmap, and the right panel is from Wolpaw and Wolpaw (2012).

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This surge of BCI research has opened new directions to help new patients and other user groups. Until recently, most BCI research efforts on providing communication for severely disabled users. Although BCIs were slow, unreliable, and inconvenient, they could sometimes be the only means of communication possible for very limited groups of patients. However, new BCIs have aimed to assess damage and recovery in stroke patients, reduce symptoms of autism or attentional disorders, help blind people see, help people control new prosthetics or devices, and improve our understanding of the brain networks involved in movement, speech, attention, and other functions (Schalk and Leuthardt, 2011; Ortner et al., 2011, 2012; Birbaumer et al., 2012; Pineda et al., 2012; Mattia et al., 2013). These and other new directions are making BCIs useful to far more people than before, while other developments such as dry electrodes, improved invasive sensors, and diminishing costs are making BCIs more practical (Schalk and Leuthardt, 2011; Guger et al., 2012; Allison et al., 2013).

Hence, it seems likely that BCIs will become much more common tools over the next several years. As BCI research further accelerates, there will be a growing number of noteworthy and even exceptional progress, and a growing need to highlight the top developments in our research field. This is why the BCI Award was created in 2010, and has been an annual event since then.

2 The BCI Award

The annual BCI Award is sponsored by g.tec, a company that has long been active in BCI research and development. The prize includes a certificate, trophy, and 3,000 USD. The competition is open to any group, regardless of location or affiliation, and has typically drawn projects from around the world. Most submissions and nominations have involved groups in the USA, Europe, and Asia, reflecting global BCI research trends. Submissions may describe any type of hardware or software.

Each year, a renowned research laboratory is asked to assemble a jury, help judge the submitted projects and award the prize. This year, the jury was recruited by its chair, Dr. Eric Leuthardt of the Washington University in St. Louis, USA. The jury consisted of some of the most respected and accomplished experts in the BCI community: Leigh Hochberg, Gert Pfurtscheller, Gerwin Schalk, Moritz Grosse-Wentrup and Junichi Ushiba. The jury selects and announces ten nominees and then the winner. The 2012 jury members were an international group that spanned the research spectrum of signal modality and research approaches. Leveraging their combined experience, which reflects the diverse and exciting field, the jury members converged on a winner that best represented the year's most innovative project. The jury based their decision on the following **Award Criteria**:

- Does the project include a novel application of the BCI?
- Is there any new methodological approach used compared to earlier projects?
- Is there any new benefit for potential users of a BCI?
- Is there any improvement in terms of speed of the system (e.g., bits/min)?
- Is there any improvement in system accuracy?

- Does the project include any results obtained from real patients or other potential users?
- Is the used approach working online/in real-time?
- Is there any improvement in terms of usability?
- Does the project include any novel hardware or software developments?

Each year, the winner is announced at a public ceremony attached to a major conference. The 2010 BCI Award was presented at the BCI Meeting 2010 in Asilomar, California, and the 2011 BCI Award was presented at a gala dinner during the Fifth International BCI Conference in Graz, Austria. The 2012 Award was presented at the Society for Neuroscience in New Orleans, Louisiana.

3 The Ten Nominees in 2012

We received a total of 68 high quality submissions in 2012. Out of these submissions, the jury nominated the 10 nominees for the BCI Research Award in August 2012. Being nominated for the BCI Award is a major honor. Prof. Dr. Gert Pfurtscheller, Chairman of the 2011 Jury, said, “The BCI Award is outstanding because the whole world competes and only one project can win.” Each nominee receives a certificate at the public ceremony, an invitation to summarize their work in a chapter in this book, and a mark of distinction on their resume or curriculum vita. Figure 1 presents the nominees receiving their certificates.

Fig. 2. This picture presents the nominees, jury members and organizers

The authors, affiliations and project titles of the 10 nominated projects are:

- *A.B. Ajiboye, D. Bacher, L. Barefoot, E. Berhanu, M.J. Black, D. Blana, S.S. Cash, K. Centrella, E.K. Chadwick, A. Cornwell, J. P. Donoghue, E. Eskandar, J. M. Feldman, G. M. Friehs, E. Gallivan, B. Jarosiewicz, S. Haddadin, L. R. Hochberg, M. Homer, P.-S. Kim, B. King, R. F. Kirsch, J. Liu, W. Q. Malik, N. Y. Masse, J. A. Perge, D. M. Rosler, A. Sarma, N. Schmansky, J. D. Simeral, P. van der Smagt, S. Stavisky, B. Travers, K. Tringale, W. Truccolo, J. Vogel (BrainGate Research Team, School of Engineering, Brown University, Deutsches Zentrum für Lift- und Raumfahrt, Institut für Robotik und Mechatronik)*

  Intracortical Control of Assistive Devices by Individuals with Tetraplegia.

- *C.A. Domingues Teixeira[a], B. Direito[a], M. Bandarabadi[a], H. Feldwisch-Drentrup[b,c,d,f], A. Witton[g], C. Alvarado[g], M. Le Van Quyen[g], B. Schelter[b,f,h], G. Favaro[i], A. Dourado[a]*

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  Brainatic: A System for Real-time Epileptic Seizure Prediction.

- *L. George[a], M. Marchal[b], L. Glondu[c], A. Lécuyer[d] ([a] INRIA, Rennes, France [b]INSA, Rennes, France [c]ENS Cachan, Bruz, France [d]IRISA, Rennes, France)*

  Combining Brain-Computer Interfaces and Haptics: Detecting Mental Workload to Adapt Haptic Assistance.

- *T. Z. Lauritzen[a], J. Harris[a,b], J. A. Sahel[c], J. D. Dorn[a], K. McClure[a], R. J. Greenberg[a]*

  ([a]Second Sight Medical Products, Sylmar, CA, USA. [b]Brigham Young University – Idaho, Rexburg, ID, USA.[c]UMR-S 968, Institut de la Vision, Paris, France; and CIC INSERM DHOS 503, National Ophtalmology Hospital, Paris, France.)

  Reading Visual Braille with a Retinal Prosthesis.

- *D. Looney[a], P. Kidmose[b], D.P. Mandic[a]*

  ([a]Imperial College London, UK [b]Aarhus University, Denmark)

Ear-EEG: User-Centered, Wearable & 24/7 BCI.

- *N. Mrachacz-Kersting[a], N. Jiang[b], K. Dremstrup[a], D. Farina[c]*

  ([a]Center for Sensory-Motor Interaction, Department of Health Science and Technology, Aalborg University, DK-9220 Aalborg, Denmark [b]Strategic Technology Management, Otto Bock HealthCare GmbH, Duderstadt, Germany [c]Neurorehabilitation Engineering Bernstein Center for Computational Neuroscience University Medical Center, Göttingen, Germany)

  A novel Brain-Computer Interface for Chronic Stroke Patients.

- *S. Ruiz, M. Rana, K. Sass, T. Kircher, N. Birbaumer, R. Sitaram*

  (Institute of Medical Psychology and Behavioral Neurobiology. Eberhard-Karls-University of Tübingen, Germany, Psychiatry Department, Medicine School. Pontificia Universidad Catolica de Chile, Santiago, Chile.)

  Brain Connectivity and Semantic Priming Enhancement using Brain Computer Interfaces based on Real-time fMRI Neurofeedback.

- *S. R. Soekadar[a], N. Birbaumer[b]*

  ([a]Applied Neurotechnology Lab, University Hospital Tübingen, Eberhard Karls University, Tübingen, Germany[b]Institute of Medical Psychology and Behavioral Neurobiology, Eberhard Karls University, Tübingen, Germany)

  Improving Efficacy of Ipsilesional Brain-Computer Interface Training in Neurorehabilitation of Chronic Stroke.

- *M. Takemi, Y. Masakado, M. Liu, J. Ushiba (Keio University, Japan)*

  Online Estimate of Event-related Desynchronization by Hand Motor Imagery is Associated with Corticospinal Excitability-physiological Evidence for Brain-Computer Interface Based Neurorehabilitation.

- *T. Yanagisawa[a,b], M. Hirata[a], Y. Saitoh[a,e], H. Kishima[a], K. Matsushita[a], T. Goto[a], R. Fukuma[b,c], H. Yokoi[d], Y. Kamitani[b,c], T. Yoshimine[a]*

  ([a]Department of Neurosurgery, Osaka University Medical School, Osaka [b]ATR Computational Neuroscience Laboratories, Kyoto [c]Nara Institute of Science and Technology, Nara [d]University of Tokyo Interfaculty Initiative in Information Studies Graduate School of Interdisciplinary Information Studies, Tokyo, Japan[e] Department of Neuromodulation and Neurosurgery office for University-Industry Collaboration, Osaka, Japan.)

  Electrocorticographic Control of Prosthetic Hands in Paralyzed Patients.

Nine of these ten projects are described in a separate chapter in this book. Nominees described the projects they submitted, and provided some additional background material and new developments since their submissions. These chapters also describe why the project was nominated, based on the **Award Criteria** described above. Each chapter ends with a very recent update, completed in late 2013, with new work from the nominees. In the concluding chapter, the submissions are analyzed to show key properties and trends that help identify the dominant and emerging directions of BCI research.

As noted above, the BCI Research Award provides unique opportunities to assess trends in BCI research. The ten nominees reflect the jurors' perspectives on which imaging methods, applications, user groups, research projects, and other directions are most promising based on the **Award Criteria**. Notably, recent years have seen a trend toward medical applications, and most of this year's nominees focused on helping patients, including persons with stroke, paralysis, tetraplegia, epilepsy, and visual deficits. This reflects the growing importance of helping a broader number of users with BCI technology, and presents an exciting preview of new ideas and systems that may become prevalent in the next several years.

Brainatic: A System for Real-Time Epileptic Seizure Prediction

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Abstract. A new system developed for real-time scalp EEG-based epileptic seizure prediction is presented, based on real time classification by machine learning methods, and named Brainatic. The system enables the consideration of previously trained classifiers for real-time seizure prediction. The software facilitates the computation of 22 univariate measures (features) per electrode, and classification using support vector machines (SVM), multilayer perceptron (MLP) neural networks and radial basis functions (RBF) neural networks. Brainatic was able to operate in real-time on a dual Intel® Atom™ netbook with 2GB of RAM, and was used to perform the clinical and ambulatory tests of the EU project EPILEPSIAE.

1 Introduction

Despite recent advances in anti-epileptic drugs, about 30% of the epileptic patients that suffer from epilepsy cannot be treated by available therapies, including surgical treatments [1]. Epileptic seizures can occur at any time and anywhere, severely affecting the

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patient's daily activity and increasing the risk of accidents resulting in severe injuries [2,3]. The development of a transportable medical device incorporating effective algorithms capable of raising warnings within an appropriate time-frame in advance would minimize the effect of the disease.

The first algorithms proposed in the literature were based on thresholds optimized for a given electroencephalogram (EEG) measure (feature). A variety of single channel and multiple channels features were studied for this purpose [4]. In threshold-based methods, an alarm is triggered when a determined feature crosses an absolute or adaptive value [5]. Recent studies revealed circadian dependencies in the prediction algorithms, i.e., it was determined that the specificity is worse during night times [6]. These findings suggest that different thresholds for night and day may be used to increase the accuracy of the prediction algorithms.

Some authors tried to improve seizure prediction by applying classification techniques [7-10], based on the assumption that the different features extracted over time can be separated into two or more classes corresponding to different cerebral states. Different families of supervised classifiers such as support vector machines (SVMs) [11] have been applied to address this classification problem [9,10].

This chapter presents the Brainatic, one of the first worldwide transportable devices for seizure prediction. A prototype was developed as part of the EPILEPSIAE (www.epilepsiae.eu) project and is able to test seizure prediction algorithms based on computational intelligence methods in clinics (patient in Fig. 1a) and ambulatory settings (patient in Fig. 1b). Besides its architecture and functionalities, the results from 10 patients are also presented.

a)

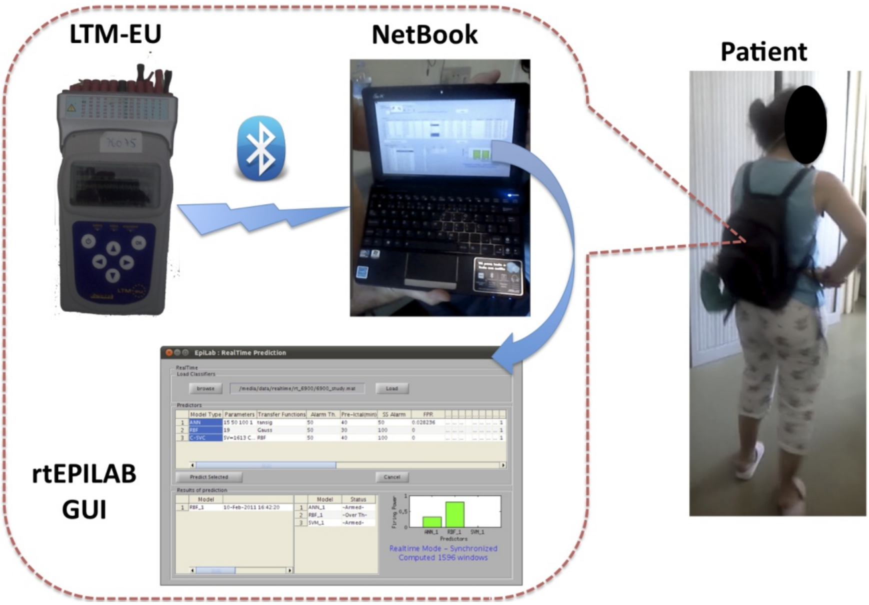
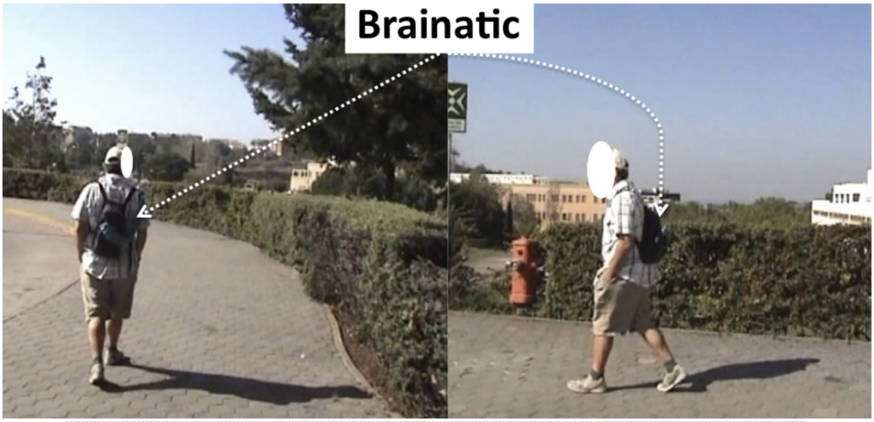


Fig. 1. (a) General overview of Brainatic, showing a patient in the hospital (Centro Hospitalar e Universitário de Coimbra-CHUC) with the Brainatic in a backpack. (b) A patient walking from the CHUC to home (ambulatory mode). (c) rtEPILAB building blocks and their relations with the other Brainatic software components.

b)



c)

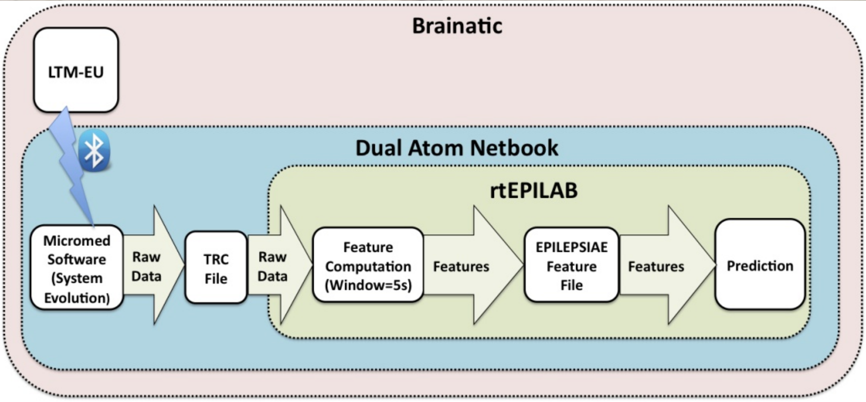


Fig. 1. (*continued*)

2 Methods

2.1 General Architecture

The Brainatic hardware is composed by an EEG acquisition system, the LTM-EU [12], and by a netbook (Dual Intel® Atom™ with 2GB of RAM), as presented in Fig. 1a. The main conceptual blocks of the Brainatic are presented in Fig. 1c.

The LTM-EU is a novel hardware developed for the EPILEPSIAE project. The acquisition system can perform long-term EEG signal acquisition with 64 channels at the maximum sampling rate of 2048 Hz per channel. One of the main challenges in the development of the EEG acquisition hardware was the low energy consumption (consumption below 0.4W and power supply based on two alkaline AA batteries).

The communication between the acquisition system and the netbook is performed via a Bluetooth connection. In the netbook, the data is stored into binary files (TRC format) through the software System Evolution (Micromed, Italy). Due to the high volume of the data, these files act as buffers.

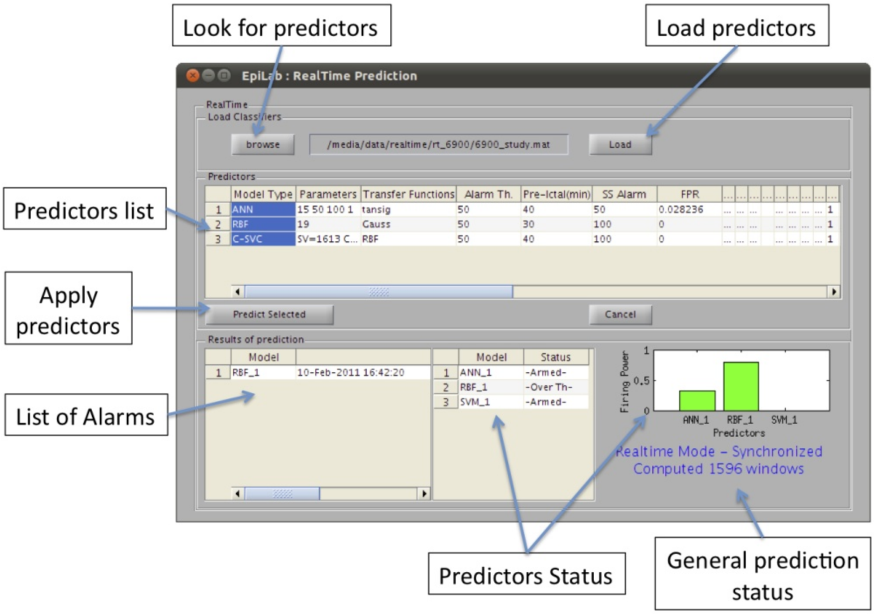


Fig. 2. rtEPILAB prediction GUI

The prediction algorithms run inside the netbook, and are referred to as rtEPILAB. The software rtEPILAB is a modified version of the Matlab™ platform EPILAB [13] with special capabilities for online data retrieval and processing. As EPILAB, rtEPILAB is an object oriented Matlab software with some extensions to C/C++ code.

The prediction algorithms are designed to process short windows of data extracted from the binary files. When the number of samples available in the buffer completes a window, a set of features is extracted and stored in another binary file, called EPILEPSIAE feature file. This file is then used as a buffer for the classification and prediction modules.

rtEPILAB considers predictors based on machine learning techniques, such as radial basis functions neural networks (RBF), support vector machines (SVM) and multilayered perceptron neural networks (MLP).

An off-line preprocessing step based on the development of the predictors is necessary. The preliminary study involves the optimization of classifiers that are subsequently loaded and available for on-line implementation. rtEPILAB provides a GUI, presented in Fig. 2, that enables the loading, selection and application of predictors. One or more predictors can be applied in parallel. The general status of the prediction, as well as specific information about the individual predictors, is presented. All the prediction parameters were saved at each processing instant in log-files for future analysis.

Table 1. EEG features extracted

Time domain	First statistical moment of EEG amplitudes (mean)
	Second statistical moment of EEG amplitudes (variance)
	Third statistical moment of EEG amplitudes (skewness)
	Fourth statistical moment of EEG amplitudes (kurtosis)
	Energy
Frequency domain	Mean-Squared error of estimated AR models
	Relative power of spectral band delta (0.1-4Hz)
	Relative power of spectral band theta (4-8Hz)
	Relative power of spectral band alpha (8 -15Hz)
	Relative power of spectral band beta (15-30Hz)
	Relative power of spectral band gamma (>30 Hz)
	Spectral edge frequency
	Spectral edge power
	Decorrelation time
	Hjorth mobility (Hjorth, 1970)
	Hjorth complexity (Hjorth, 1970)
Time and Frequency	Energy of the wavelet coefficients (Daubechies-4 (DB4) with 6 decomposition levels (Daubechies, 1992))

2.2 Algorithmic Details

EEG Features

Presently, the features computable in Brainatic are based in single channel measures, i.e., they are univariate (Table 1). As time domain features, the first four statistical moments and the energy ate calculated. The skewness is a measure of the symmetry of the signal distribution, while the kurtosis measures the relative peakness or flatness of the signal distribution. It was reported that the variance and kurtosis vary significantly in the preictal phase. More precisely, a decrease in variance and an increase in kurtosis were reported [14]. The prediction error derived from an autoregressive (AR) model of the EEG signal is reported to decrease as seizures approach, because the EEG signals are claimed to be better predictable [15]. The *decorrelation time* is the time of the first zero crossing of the autocorrelation function. If the zero-crossing time is small, the signal is itself less correlated. The extreme case is for an infinite white noise sequence that theoretically presents a decorrelation time of zero. A decrease in the power related to the lower frequencies has been reported before the seizures onset, which is characterized by a decrease in the decorrelation time [16]. The *Hjorth mobility* (HM) and *complexity* (HC) [17] provide information of the root-mean-square frequency and of the root-mean-square frequency spread, respectively. The decrease in the power of the lower frequencies prior to seizure onset results in an increase in the Hjorth Mobility and Complexity [16]. Shifts from lower to high frequencies have been observed before the seizures by computing the relative *spectral power* in different frequency bands of the EEG [16]. The *spectral edge frequency* quantifies the power distribution along the spectral range of a given signal. Usually most of the power of an EEG signal is concentrated in the range of 0-40 Hz, and the spectral edge-frequency is defined as the minimum frequency such that 50% of the total power within 0 to 40 Hz is contained in a given signal. The spectral edge-power is the corresponding half power of the signal up to 40 Hz. The successive application of the *Discrete Wavelet transform* [18] enables a multi-level decomposition of the EEG in several sub-bands. The first levels are related to the high frequency components of the signal, while the last ones contain the lower frequency contents [18,19]. By computing the energy of the signals pre-processed by the decomposition (the so called wavelet coefficients), a measure of the energy in different frequency ranges is achieved.

The seizure prediction study presented using Brainatic is based on patient-specific six electrode setup. This number of electrodes is a good compromise between signal quality and patient comfort, as other studies suggest [20,21]. Since we have considered six decomposition levels for the wavelet decomposition, the feature vector has a total of 132 measures estimated at each time epoch (22 features per channels). Then, the feature vector is fed to the seizure prediction stage.

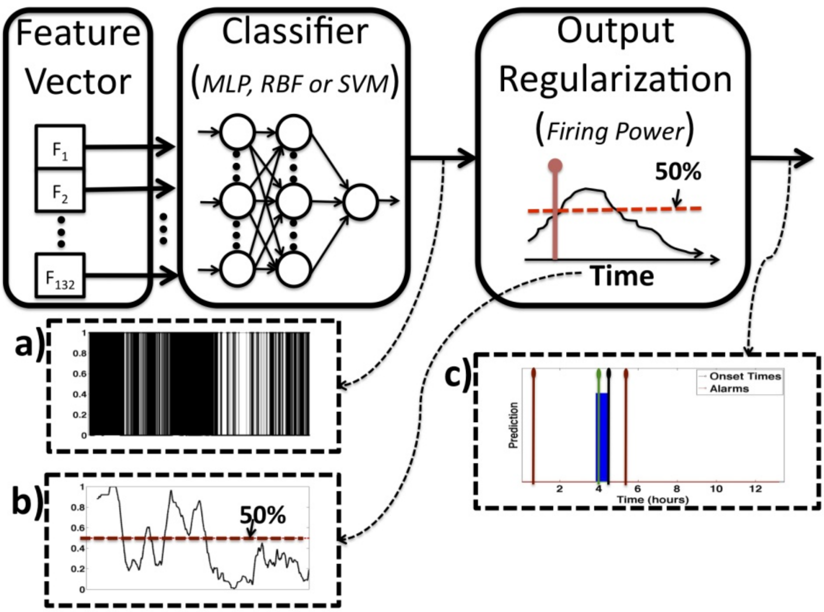


Fig. 3. Prediction strategy. a) Output of the classification stage. b) *Firing power*. c) Raised alarms. The vertical red lines represent false alarms, while the green and black lines represent a true alarm and a seizure onset, respectively. The blue area indicates the preictal time, where a raised alarm is considered as a valid prediction.

Prediction Strategy

Once the feature vector is constructed, the next step is the construction of an alarm series based on the classification output. This stage is composed by a classifier plus an alarm generation method (regularization) as presented in Fig. 3. The classifier is a MLP, RBF or SVM which was previously trained to classify the each epoch into one of four classes: interictal, preictal, ictal and postictal. Epochs classified as interictal are assumed to belong to times where the patient is far from a seizure. The epochs classified as preictal are related to the times prior to a seizure and are those of interest for seizure prediction. The ictal and postictal epochs are related to the seizure time and to the instability period after a seizure, respectively. Based on our results, the classification in four classes improved performance relative to the performance obtained by taking into account just two classes (preictal vs non-preictal).

Another variable of the model optimization was the preictal period considered. This parameter was selected individually for each patient and averaged around 30 minutes. The final step in the classification stage is the transformation of the four-class output into just two classes. The epochs classified as preictal are attributed with the label '1' while the other are labelled '0' (Fig. 3a). If the output of the classification stage is directly considered for seizure prediction, whenever the classifier considers an epoch as preictal, an alarm is raised. In practice, this behaviour is unrealistic due to the high number of incorrectly labelled interictal epochs, and consequently high number of false alarms. Thus, in Brainatic the output of the classifier is smoothed (regularized) in order to reduce the number of false alarms. The regularization method, called the *firing power*, is described in detail in [13] and consists in a sliding window with a size equal to the considered preictal time. Alarms are raised whenever the number of epochs classified as preictal in the sliding window is larger than 50% (Fig. 3b-c). Once an alarm is raised, another one can only occur after a dead-time equal to the preictal time and if the *firing power* crosses the threshold in an ascending way. This method raise less false alarms than the Kalman filter approach used by other authors [10,22]. The firing power is a normalized measure that presents values between zero and one. Zero means that no epochs were classified as to belong to the preictal class in the past preictal time frame, while one is the opposite, reflecting that all the epochs were classified to belong to the pre-seizure period (Fig. 3b). The *firing power* is displayed in real-time as green bars in the rtEPILAB GUI, while the raised alarms are displayed as a list where each entry is composed by the name of the classifier and the timestamp of the warning.

Performance Quantification

The quantification of the online prediction performance was performed, taking in account the sensitivity (SS) and false prediction rate per hour (FPR) as a measure of specificity. Sensitivity is the percentage of correctly predicted seizures. A seizure is considered correctly predicted if an alarm is raised in the preictal period preceding its onset.

The false prediction rate is defined as the number of false alarms divided by the duration during which false alarms could be triggered, which is obtained by subtracting the time under false warning (preictal time (*PT*) times the number of false alarms) from the total interictal duration. Mathematically the FPR is given by [4]:

$$FPR = \frac{\#\,False\,Alarms}{Interictal\ Duration - (\#\,False\ Alarms \times PT)} \quad (1)$$

3 Results

rtEPILAB was tested in patients in the three EPILEPSIAE participating hospitals. Table 2 presents the prediction performance obtained by using Brainatic in 10 of these patients. The raw-data sampling frequency was set to 1024Hz. As mentioned, we used a setup with six electrodes, and each epoch corresponds to a five-second window. A notch filter at 50 Hz was applied to remove artifacts related to the power line frequency.

Table 2. Prediction results in 10 patients. SS refers to the sensitivity, i.e. the percentage of predicted seizures. FPR stands for false prediction rate, i.e. the rate of false prediction per hour

Pat	Operation Time(h)	Nº Seizures	Pred. Type	SS (%)	FPR (1/h)
1	45	8	RBF	75	0.22
2	63	21	RBF	43	0.27
3	63	3	RBF	0	0.12
4	29	0	SVM	-	0.10
5	60	0	SVM	-	0
6	163	3	RBF	33	0.19
7	10	2	SVM	100	0.25
8	22	0	SVM	-	0.1
9	9	1	SVM	0	0
10	100	2	RBF	100	1.5

The operation time for these patients ranged from 9 hours to 163 hours (approx. 7 days). During operation, the predictions were performed in real-time, and only stopped for changing the LTM-EU's batteries and correcting the electrode impedances. Real-time here means that the Brainatic was able to acquire data at a sampling rate of 1024Hz, compute 132 EEG features and perform a prediction based on computational intelligence methods in a time frame of less than 5 sec. The patients that were allowed to go home were taught how to charge the netbook battery, and had to return to the hospital every morning and afternoon for LTM-EU battery replacement and correction of electrode impedances.

Concerning the prediction performance, for some patients, no seizure occurred during the analyzed period, and performance can only be evaluated through the false prediction rate (patients 4, 5, and 8). For two patients (7 and 10) the system was able to predict both seizures. However, a very high number of false predictions were observed for patient number 10. For patient 1, six out of eight seizures were predicted with fairly few false predictions.

4 Concluding Remarks

A transportable medical device that successfully predicts and warns the patient of upcoming epileptic seizures would represent an important increase in the quality of life of epileptic patients. To the best of our knowledge, Brainatic is the first device tested in real-time scenarios, and evaluated both in clinics and ambulatory. The system is based on computationally efficient features and computational intelligence methods, and was tested in different epilepsy centers.

The use of Brainatic in a set of 10 patients of the EPILEPSIAE database presented optimistic results. However, low specificity suggests that algorithmic improvements are needed for a generalized clinical application. Moreover, the classifiers used in the prediction algorithm, i.e. SVM and artificial neural networks, are purely data-driven techniques that do not consider any neurological or physiological knowledge. Predictors combining information from different sources will certainly improve the prediction performance.

5 Jury Selection Factors and Recent Work

This work was nominated because it scored very high based on several of the jury's Award Criteria. The work does reflect a novel application of a BCI, including novel methodologies. The work involved a major new software effort, called Brainatic, that itself involved a combination of signal analysis tools employed in a new way. The hardware implementation was also appealing, since the system employed a portable backpack system. The study was intended to benefit patients, and involved recording from ten epilepsy patients. Recording from such patients in real-world settings is very challenging, and could yield substantial new insights. Hence, there is a strong need for further such research. The system also operated in real-time, which was another Award Criterion. Although seizure prediction has been studied for decades, this work attained promising results in terms of speed and accuracy, which were two other Award Criteria.

The jury's decision to nominate this project has also been sustained by the excellent contributions that this group made since the BCI Award ceremony. They later published a database with data from 275 patients, with the goals of helping other researchers conduct further analyses and work toward standardization, as well as encouraging research regarding other disorders and basic neuroscience [23]. They also published more recent work focused more on seizure prediction and analysis [24-26]. In summary, the contributions made within the project that was nominated, as well as substantial follow-up work in the short time since the 2012 BCI Award, reflect a major contribution to seizure prediction that could help not only persons with epilepsy but other conditions as well.

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Combining Brain-Computer Interfaces and Haptics: Detecting Mental Workload to Adapt Haptic Assistance

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Abstract. In this chapter, we introduce the combined use of Brain-Computer Interfaces (BCI) and Haptic interfaces. We propose to adapt haptic guides based on the mental activity measured by a BCI system. This novel approach is illustrated within a proof-of-concept system: haptic guides are toggled during a path-following task thanks to a mental workload index provided by a BCI. The aim of this system is to provide haptic assistance only when the user's brain activity reflects a high mental workload. A user study conducted with 8 participants shows that our proof-of-concept is operational and exploitable. Results show that activation of haptic guides occurs in the most difficult part of the path-following task, and increased task performance by 53% by activating assistance only 59% of the time. Taken together, these results suggest that BCI could be used to determine when the user needs assistance during haptic interaction and to enable haptic guides accordingly.

1 Introduction

The passive BCI approach aims at using brain activity information to adapt and enhance the current application without the need for the user to voluntarily control his/her brain activity [1, 2]. For example, a passive BCI has been used to adapt virtual environments content [3]. Another interesting way to use passive BCI envisioned by researchers consists in adapting the interaction modalities according to the user mental state [4].

In this work, we introduce the use of the passive BCI approach in the haptic realm. Haptic feedback has already been used in a BCI system [5, 6]. However, to our best knowledge, BCI have never been used for adapting haptic feedback. We propose to use BCI technologies to adapt force-feedback in real-time. We introduce assistive tools, i.e. haptic guidance, which are automatically and continuously adapted to the user's mental workload measured through a passive BCI. Haptic guidance can be defined as an interaction paradigm in which the user is physically guided through an ideal motion by a haptic interface [7]. Bluteau et al. [8] have compared different types of guidance and showed that the addition of haptic information plays an important

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role in the visuo-manual tracking of new trajectories, especially when forces are used for the guidance. This chapter is organized as follows. Section 2 details our approach for haptic assistance based on BCI. Section 3 presents the proof-of-concept designed to illustrate this approach and the evaluation conducted. Section 4 discusses the results. Finally, the main conclusions are summarized in Section 5.

2 Using Mental Workload to Adapt Haptic Assistance

The concept proposed in this chapter consists in using a passive BCI to assess an index of the user's mental workload in real-time and to adapt haptic assistance accordingly. Mental workload is a generic term which can cover or apply to different and various cognitive processes and mental states. It could apply for example to a memorization task (e.g. image memorization), driving task, lecture task and cognitive task [9]. In this chapter, we use the term mental workload to qualify the modification of the user's brain activity in relation to the difficulty of a manipulation task. The mental workload index is expected to increase with the manipulation difficulty level. Several EEG markers have been identified as correlated with mental workload, task engagement or attention [10, 11, 9]. In [10], the authors proposed to use ratios of activity in a specific band-power such as alpha (8-12Hz) or theta (3-7Hz) bands to compute an index of the user task engagement. More recently, more complex approaches based on machine learning have been used to compute an index of the user's mental workload based on EEG activity [11, 9]. In this chapter, we propose to use a BCI system based on these approaches for assessing an index of the user's mental workload during a haptic interaction task.

Haptic assistance systems could benefit from the user mental workload information. Indeed, this information could determine when the user needs assistance. For example, a high mental workload could present a risk in the context of safety-critical haptic tasks. A smart assistance system that interrupts the haptic interaction or toggles specific haptic guides might improve comfort or safety of operations in such conditions. Haptic guides that would be only active when the user exhibits a high mental workload (e.g. the user is focused on a difficult precision gesture) might improve task performances and learning process.

3 Evaluation

We design and evaluate a proof-of-concept system that toggles haptic guidance during a path-following task based on the user's mental workload. The task entails following a path in a virtual 2D maze while avoiding collisions with borders. An EEG-based BCI is used to compute an online index related to the user's mental workload. If the index indicates a high (resp. low) mental workload, the haptic assistance is activated (resp. deactivated).

3.1 Objectives and Hypotheses

Our experiment has two goals: to test the operability of a system that adapts force-feedback based on mental workload measurement; and to evaluate the influence of such a system on task performance. We hypothesize that adapting haptic assistance based on mental workload index would help the user and increase task performance.

3.2 Apparatus

The experimental apparatus is shown in panel 1 of Figure 1. Participants manipulated a 2D cursor through a Virtuose 6D haptic device (Haption, Soulgé sur Ouette, France). A g.USBamp (Guger Technologies OG, Austria) was used to acquire EEG signals at a sampling rate of 512Hz.

Fig. 1. Experimental **apparatus.** 1: EEG headset, 2: EEG acquisition, 3: haptic device, 4: LCD screen where the virtual scene is displayed.

EEG data were measured at positions Fp1, Fp2, F7, F8, T7, T8, F3, F4, C3, C4, P3, P4, O1, O2, Pz and Cz according to the 10-20 international system. A reference electrode (located at FCz) and a ground electrode (located on the left ear) were also used. This electrode montage covers a large area of the scalp. Similar electrode positions were successfully used to record mental workload [9].

The Experimental task consists of following a path by moving a sphere-cursor in a maze avoiding collisions (Figure 2). The scene is divided in two parts. These two parts aim at exhibiting two different levels of difficulty. The first part is composed of numerous turns and should lead to high difficulty, whereas the second part presents less collision possibilities to present less difficulty.

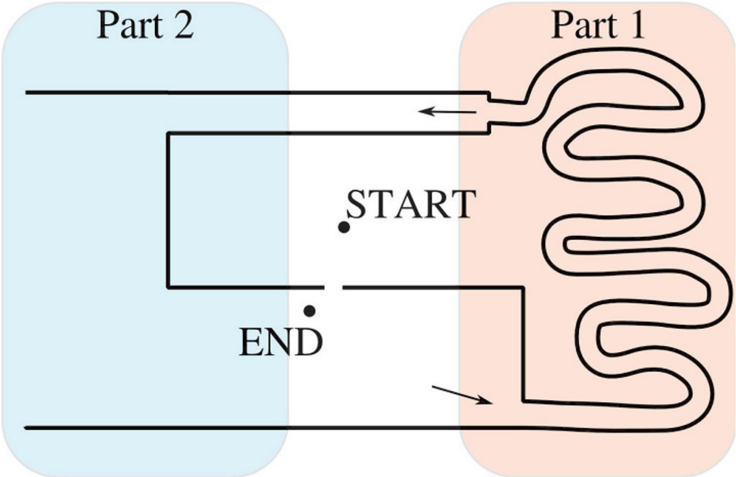


Fig. 2. Virtual **scene.** The path to follow is divided into 2 parts. Part 1 (in red) is more difficult with numerous turns. Part 2 (in blue) is less difficult with fewer turns and less borders.

The virtual environment, haptic force and collision detection are computed and simulated with the open-source physical engine Bullet. The haptic guide consists of a repulsive force inversely proportional to the distance of the 2D cursor to the nearest wall (see Figure 3). This haptic guide aims at helping the user to slide between walls avoiding collision. The cursor was colored in blue when the haptic guide was active.

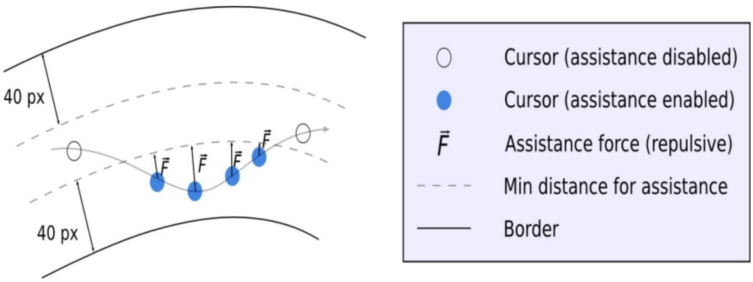


Fig. 3. Haptic **assistance.** Repulsive force inversely proportional to the distance to the nearest wall: force is null if the distance to the wall is greater than 40 pixels.

A Mental workload index is computed using OpenViBE software [12]. A technique based on [13] is used. EEG signals are passed through a bank of 4 bandwidth filters centered on all the frequencies between 5Hz and 12Hz. A Common Spatial Pattern (CSP) method [14] is then used to compute spatial filters for each of them. Minimum redundancy maximum relevance feature selection is used to select the six most relevant couples of frequency band and spatial filter [15]. A Linear Discriminant Analysis (LDA) classifier is trained on the learning data-set using a moving window of 1sec (overlap=0.9sec).

The learning data set contains 2 minutes of EEG activity. The first minute is recorded when the user is performing a simple control task, which should lead to a low mental workload: the user has to move the cursor around a rectangle without trying to avoid collisions. The second minute corresponds to a more difficult task: the user has to move the cursor inside a spiral pattern while avoiding collision.

Online values provided by the classifier (1 for high mental workload, -1 for low mental workload) are smoothed on a 1sec window. The median of the last 10 values is provided to the application at a 1Hz rate. This index is used to activate or inhibit the haptic assistance.

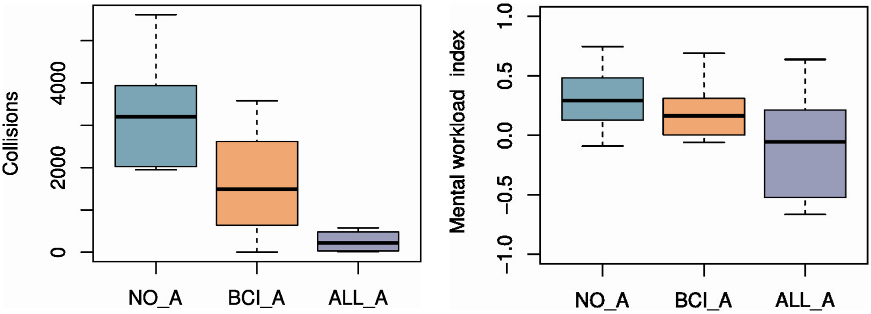
3.3 Procedure

Three conditions were evaluated: **No Haptic Assistance (NO_A)**, **Haptic Assistance based on BCI (BCI_A)** (i.e. assistance activated if the mental workload is above 0), and **Haptic Assistance activated all the time (ALL_A)**. Each participant performed the task in the three conditions and repeated it 3 times. To reduce order effects, the order of presentation was permuted across subjects. For each trial and each participant, the mental workload index, the cursor positions and the number of collisions were recorded. The mental workload index and the cursor position were recorded at 10Hz.

At the end of the experiment, participants were asked to grade the correlation between their perceived mental workload and the computed mental workload index.

4 Results

Performances (i.e. number of collisions per trial) for each condition are presented in Figure 4a. A Friedman test shows a significant effect on assistance condition (χ^2= 38.7, $p<0.001$). Post-hoc comparisons were performed using Wilcoxon signed-rank test with a threshold of 0.05 for significance. The post-hoc analysis shows a significant difference between condition NO_A and ALL_A ($p<0.001$), and between condition NO_A and BCI_A ($p<0.001$). BCI_A and ALL_A did not differ significantly from each other ($p=0.08$). Activation of assistance enables to reduce the number of collisions. The average decrease over trials is 53% for condition BCI_A and 88% for condition ALL_A.



a. Average number of collisions. b. Average mental workload index.

Fig. 4. Performance **and mental workload index in each condition** (NO_A: no haptic assistance, BCI_A: haptic assistance activated based on BCI, ALL_A: haptic assistance activated all the time). a. Boxplots of collisions. b. Boxplots of mental workload index. They are delimited by the quartile (25% quantile and 75% quantile) of the distribution of the condition over all the individuals. For each trial, the median is shown.

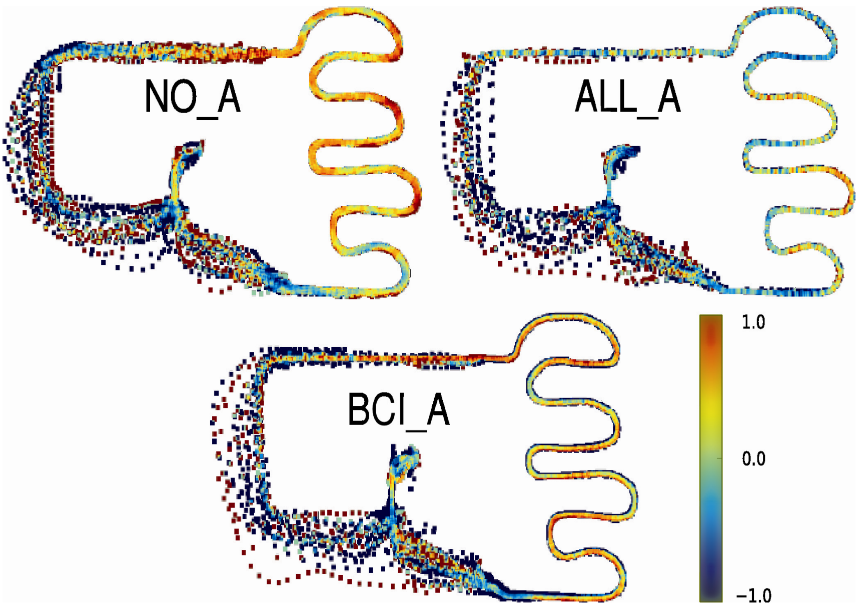


Fig. 5. Mental **workload averaged over trials and subjects for each condition** (NO_A: no assistance, BCI_A: assistance activated based on BCI, ALL_A: assistance activated all the time). Colored squares (9x9 pixels) are used to display mental workload index at each position on a 1024x768 image which represents the virtual scene. For each pixel, mental workload indexes were averaged over all the subjects and trials. A red color reflects a high mental workload index, whereas a blue color corresponds to a low workload index.

The computed mental workload index in each condition is presented in Figure 4b. A Friedman test revealed a significant effect of assistance mode on the index value (-χ^2=16.0, p<0.001). A post-hoc analysis revealed a significant difference between condition ALL_A and NO_A (p<0.001), no significant difference between condition NO_A and BCI_A (p=0.053) and no significant difference between condition BCI_A and ALL_A (p=0.21). Mental workload index was lower when the assistance was activated.

Figure 4 shows the evolution of the mental workload through the path followed by participants. During turns (part 1) we can observe a higher mental workload index than during part 2 (Mean over subjects: M=0.27 for part 1, M=0.14 for part 2). It is particularly clear on Figure 5 for condition NO_A.

Participants reported a high correlation between computed and felt mental workload (M=71%, sd=4.7). This suggests that the BCI system is able to provide a convincing measurement of the mental workload.

5 Discussion

We tested our proof-of-concept system in a path-following task. Results indicate that the proposed system works and helps the users accomplish the task. Activation of guides based on measured mental workload index can increase performance by significantly reducing the number of collisions. No significant difference was observed between condition ALL_A and BCI_A in terms of performance (p=0.08). This suggests that assistance activated based on BCI is almost as helpful as permanent assistance.

Results also suggest that this proof-of-concept system was able to measure a mental workload index that seems well correlated with the difficulty of the task. Indeed, the measured mental workload was higher when the task was more difficult (near walls) as shown in Figure 5. Moreover, the users reported a high correlation between the computed index and their perceived mental workload (above 70%).

In this study, we used binary adaptation (i.e. activating or deactivating assistance). The system could benefit from a progressive adaptation, e.g. more assistance if the workload is higher. We should note that 25% of participants asked for this feature. A future system could also use other kinds of haptic assistance. Indeed, adapting the damping level proportionally to the user's mental workload or toggling inverted damping [16] only if the user presents a high mental workload are options that should be studied. Concerning the measurements of the mental workload, a combination of EEG with other modalities such as Galvanic Skin Response in a multi-modal measurement system could increase the reliability of the mental workload index. Finally, it would also be interesting to evaluate the role of BCI-based adaptation in real applications such as medical training systems notably in terms of learning performance. Indeed, activated assistance only when user presented a high mental workload could improve the learning performance compared to assistance activated all the time.

6 Conclusion

In this work, we studied the combination of haptic interfaces and Brain-Computer Interfaces (BCI). We proposed to use BCI technology to adapt a haptic guidance system according to a mental workload index. We designed a proof-of-concept system and conducted an evaluation that revealed the feasibility and operability of such a system. High levels of mental workload could be well identified by the BCI system in the most difficult parts of a path-following scenario. Toggling haptic guides only when the user presented a high mental workload could improve task performance indicators. Taken together, our results pave the way to novel combinations of BCI and haptics. Haptic feedback could be fine-tuned according to various mental states of the user, and for various purposes. Future work will focus on the extraction of other mental states, and on real applications such as haptic-based medical simulators.

7 Jury Selection Factors and Recent Work

The preceding chapter described work involving seizure detection, which has been a major challenge for decades. The same is true of work described in this chapter. There have been extensive efforts to assess workload and develop effective feedback, but practical tools to identify workload and provide effective feedback still require substantial development. This work described a novel approach to detect workload based on the EEG and provide feedback. The project functioned in real-time with good results in terms of speed and accuracy. The jury's Award Criteria also included work with patients or other real-world users, which this work did conduct. The hybrid BCI hardware and software that combines EEG recording and haptic feedback did reflect a novel and interesting contribution to the BCI community. The Award Criteria also included usability. The haptic feedback approach described here could provide a natural and straightforward type of feedback that could lead to more adaptive, easy to use systems for workload monitoring.

Since the BCI Award, this group published work describing adaptive workload estimation that combined their haptic feedback approach with virtual reality [17]. This novel VR medical simulator can assist trained surgeons by providing visual and haptic cues based on EEG-measured workload. A 2013 book chapter also summarized this and other work [18]. As noted in that chapter, many recent efforts have focused on BCI research and VR and found that VR can also improve usability, reduce errors and training time, and yield other benefits. Hence, this group has remained active in this research direction, with major efforts to combine haptic VR and EEG, develop improved classification to improve performance, and develop novel interfaces to improve usability.

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Reading Visual Braille with a Retinal Prosthesis

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Abstract. Retinal prostheses can restore partial vision to patients blinded by outer retinal degeneration. The Argus II retinal prosthesis system, used in this study, includes a 10 x 6 electrode array implanted epiretinally, a tiny video camera mounted on a pair of glasses, and a wearable computer that processes the video and determines the stimulation current of each electrode in real time. This study investigates the possibility of using the retinal prosthesis to stimulate visual braille as a sensory substitution for reading written letters and words. Single letters were stimulated in an alternative forced choice (AFC) paradigm, and short 2-4-letter words were stimulated in an open-choice reading paradigm. The subject correctly identified 89% of single letters and 70% of all presented words. This work suggests that text can successfully be stimulated and read as visual braille in retinal prosthesis patients.

Keywords: Retina, Epiretinal Prosthesis, Sensory substitution, Retinitis Pigmentosa, Blindness, Perception, Degeneration, Sight Restoration.

1 Introduction

Retinal prostheses restore partial vision to people blinded by outer retinal degenerative diseases such as Retinitis Pigmentosa (RP) [1]. Recent results have demonstrated the ability of prosthesis users to read large letters and short words and sentences for some subjects [2-4]. But with the current spatial resolution of prosthetic vision, reading takes seconds to tens of seconds for single letters and short words, and requires letters to be ~1-20 cm high at normal (approximately 30 cm) reading distance [2-4]. While these results are by themselves impressive, and the performance is expected to improve significantly with future prosthesis development, their practical application at the current level is limited. For example, signs one might read while walking

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around have letters of a few centimeters in height, but are intended to be read from several meters distance.

An alternative is to use the prosthesis to create percepts in the form of braille letters (to be read visually rather than tactually). For example, letter recognition software could identify text, which could then be converted into braille and stimulated directly to the eye via the retinal prosthesis. This project addresses the feasibility of reading visual braille with a retinal prosthesis. The specific device used in this study is the Second Sight Argus® II System (Second Sight Medical Products Inc, Sylmar, CA).

The Argus II System consists of a surgically implanted 60-channel stimulating microelectrode array and inductive coil link used to transmit power and data to the internal portion of the implant, an external video processing unit (VPU), and a miniature camera mounted on a pair of glasses. The video camera captures a portion of the visual field and relays the information to the VPU. The VPU digitizes the signal in real time, applies a series of image processing filters, down-samples the image to a 6 by 10 pixilated grid, and creates a series of stimulus pulses customized to the individual user based on pixel gray-scale values. Currently, the Argus II System is the only commercially available retinal prosthesis.

Here, we present results showing that a subject implanted with the Argus II Retinal Prosthesis System can read visually-stimulated braille. Performance is 89% correct for individual letters at 500ms presentation, and 60-80% correct for short words, proving the feasibility of reading via visual braille.

2 Methods

2.1 Description of the Argus II Retinal Prosthesis System

The Argus® II System consists of an implantable device surgically placed on and in the eye, and an external unit worn by the user (Fig. 1). The external unit consists of a small camera and transmitter mounted on a pair of sunglasses, and a video processing unit (VPU) and battery that can be worn on a belt or shoulder strap. The implanted portion consists of a receiving and transmitting coil and a hermetically sealed electronics case, fixed to the sclera outside of the eye, and an electrode array (a 6 by 10 array of 60 electrodes, 200 µm in diameter, 525 µm between nearest neighbor center to center cardinal axes) that is secured to the surface of the retina (epiretinally) inside the eye by a retinal tack. The electrode array is connected to the electronics by a metalized polymer cable that penetrates the sclera in the pars plana. The camera captures video and sends the information to the processor, which converts the image to electronic signals that are then sent to the transmitter on the glasses. The implanted receiver wirelessly receives these data and sends the signal to the electrode array via a small bus, where electric stimulation pulses are emitted. The controlled electrical stimulation of the retina induces cellular responses in retinal ganglion cells that travel through the optic nerve to the visual cortex and results in visual percepts.

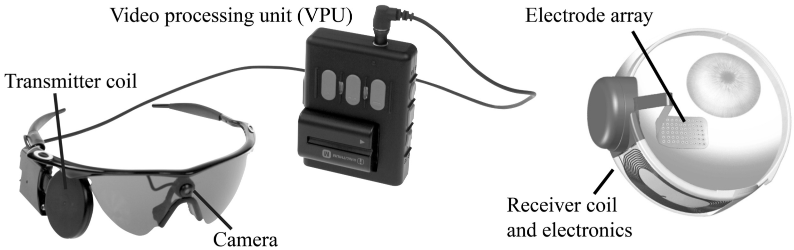

Fig. 1. Overview of Argus II System. The external portion consists of a miniature camera mounted on a pair of sunglasses, a Video Processing Unit (VPU) and a transmitter coil (left). The internal portion consists of a receiver coil and electronics case connected with a cable to a 60 electrode epiretinal array (right).

2.2 Subject Selection

30 subjects are enrolled in an ongoing clinical study of the Argus II [5]. The subjects are blinded by the degenerative retinal disease, Retinitis Pigmentosa (RP), which causes the photoreceptor cells in the retina to die. Subjects are implanted with the Argus II implant, which stimulates the surviving cells in the retina. A single subject was selected for this feasibility study on the basis on three criteria: the ability to read (tactile) braille, spatial resolution high enough to isolate responses from 6 individual electrodes arranged in 3 by 2 pattern, and availability for testing. The experiments were approved by the Institutional Review Board at the Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France, and under the principles of the Declaration of Helsinki.

2.3 Selection of Basis for Braille Stimuli

The Argus II System was used in "direct stimulation mode." The camera was by-passed and individual electrodes were stimulated, controlled by a computer. Therefore, no visual reading software was used in these experiments.

The basis for the braille alphabet is a 3 by 2 array of dots, and each letter has a specific configuration (Fig. 2). For braille stimulation, a set of 6 electrodes were picked that spanned a 3 by 2 array (Fig. 3). Only these electrodes were used in the experiments. The current amplitude of pulses was set individually for each of the 6 electrodes to be 2.5-3 times the threshold for detection of a phosphene.

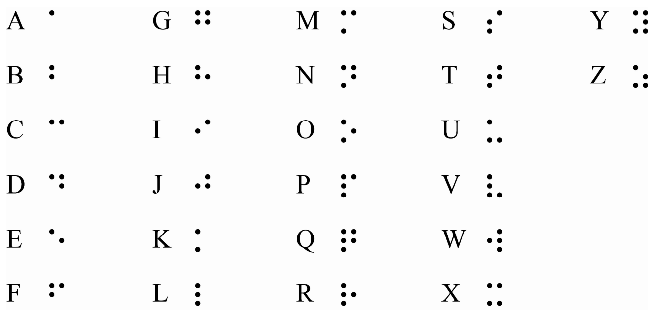

Fig. 2. The braille alphabet

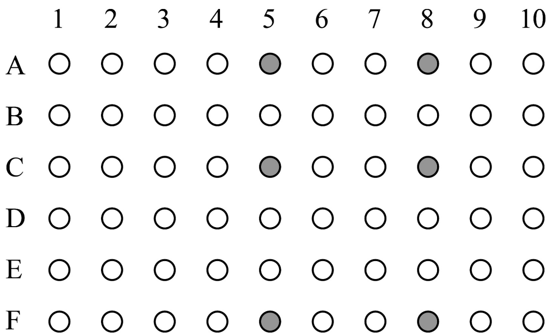

Fig. 3. Six electrodes forming the basis of the braille stimulation used in the experiment

2.4 Visual Braille Stimulation

The experiment was inspired by character recognition experiments of the Argus II subjects [2,4]. For single letter recognition experiments, the 26 letters of the alphabet were split into three sets of 8 or 9 letters: Set 1 (F, G, H, L, O, P, R, V), set 2 (A, C, D, I, K, M, S, W, Y) and set 3 (B, E, J, N, Q, T, U, X, Z). The subject was aware of which letters were contained in the current set. Selection of the letters for each set was picked randomly with the one rule that letters with dots in the same geometric structure, but a single difference in distance, would not be in the same set. Four such pairs exist, b-k, f-m, g-x, and h-u. For example, b and k are both made up of two dots in a vertical line with just a difference in spacing (Fig. 3). The letters were formed by stimulating a subset of electrodes within the selected six basis electrodes. The letters were presented in random order with 5 repeats of each letter in an 8- or 9-alternative forced-choice (AFC) paradigm. After each visual braille stimulation, the subject identified which letter was perceived, and the response was recorded by the experimenter. During the experiment, the subject could request that the letter set be repeated (i.e., he could be reminded of which letters were possible within the set). No other information was given to avoid biasing answers. A letter was presented as a 20Hz pulse train of 500ms of 1ms cathodic-anodic square pulses, i.e. 10 pulses.

To test the subject's ability to read words in visual braille, the 10 most common 2-, 3-, and 4-letter words in French (the native language of the subject, Table 1) were picked based on usage frequency [6,7]. Each word was presented with 500ms per letter and 1000ms break between letters. The subject was informed that short words would be presented, but was not aware of which words were contained in the set. The order of the words was random and each word was stimulated once. The subject was allowed to request a single repetition of a word, but a guess would be considered a final answer. Responses were recorded by the experimenter.

Table 1. List of used words (in French)

2-letter	3-letter	4-letter
de	les	dans
la	des	pour
et	que	elle
le	une	plus
il	est	mais
un	qui	nous
en	pas	avec
du	par	tout
je	sur	vous
ne	son	bien

2.5 Data Analysis

Answers were summed and significance of the proportion of correct answers was determined based on binomial distributions (correct/wrong) and chance levels, 1/8 or 1/9 depending on letter set.

3 Results

3.1 Single Letter Recognition

Single letters were stimulated in sets of 8 or 9 letters in an alternative forced choice (AFC) paradigm with five repetitions of each letter. Single letters were presented for 500ms. Letter recognition was high for all presented letters. The detection rate for the three letter sets ranged between 75-98% with a mean of 89% correct, and all were highly significantly above chance level ($p<0.001$) (Fig. 4).

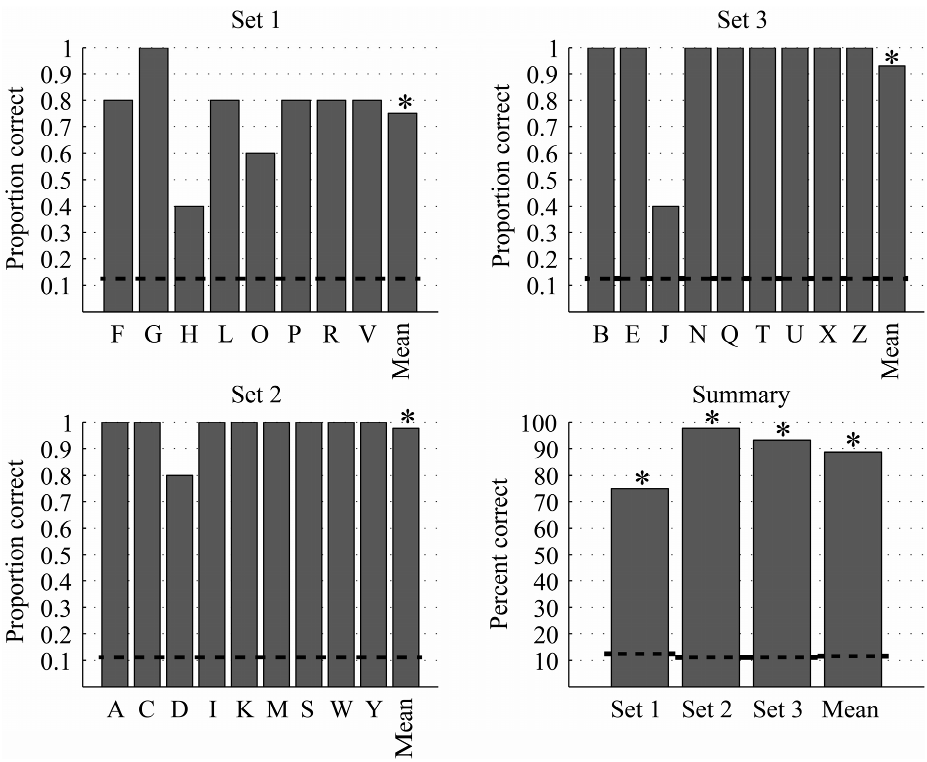

Fig. 4. Proportion correct of identification of single letters in Set 1 (8 AFC), set 2 (9AFC), and set 3 (9 AFC) and the summary percent correct. Each letter was presented 5 times in random order within its set. The dashed lines denote chance level for the respective set. * $p<0.001$ (binomial probability distribution).

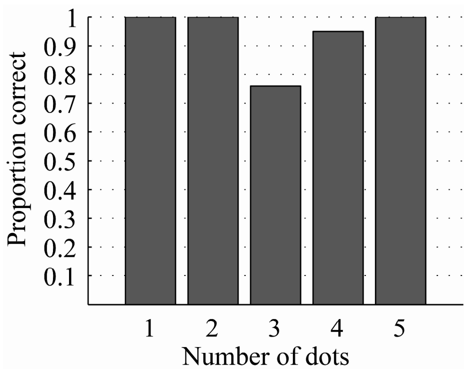

Fig. 5. Identification of single letters as a function of letter complexity, measured as the number of dots forming a letter

While the complexity of letters varies, there is no indication that performance depended on the complexity of letters, measured as the number of dots in a letter (Fig. 5).

3.2 Word Recognition

The subject was presented ten 2-, 3- and 4-letter words and correctly identified eight, six and seven words respectively (Fig. 6). The proportion of word recognition was highly significant based on random letter presentation. (For example, since the whole alphabet was available, chance of a 2-letter word is $1/26^2 = 0.0015$). The proportion of correct word recognition is not significantly different from what would be predicted by the single letter recognition proportion ($0.89^{[\text{word length}]}$), with 0.89 being the average proportion correct from the single letter experiments. It is reasonable to expect the number would be similar in a 26 AFC task (ignoring the use-frequency of individual letters in regular text).

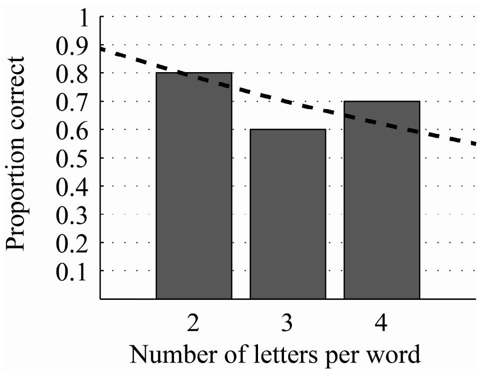

Fig. 6. Proportion correct identification of 2-, 3-, and 4-letter words. Dashed line represents the expected proportion correct given a proportion of single letter identification rate of 89%.

4 Discussion

This work shows that an Argus II user can read both single letters and short words in visually stimulated braille. The subject recognized 89% of presented letters. The subject also identified eight of 2-, six of 3-, and seven of 4-letter words of a total of ten presented words of each length. It is reasonable to expect the performance will improve with training. The subject is an experienced braille reader. While we did not test it specifically in this study, it is safe to assume a 100% identification rate for tactile braille. Thus the discrepancy is due to visual stimulus comprehension and not braille comprehension. This opens the possibility for the Argus II users to read text by making a sensory substitution to visual braille.

4.1 Considerations on Braille Reading Performance

In this experiment, single letter performance was 89% correct, and performance of reading of short words aligned well with expectation based on single letter performance (Fig. 6). While the single letter performance is high, and should improve with training, a simple multiplication of probabilities would increase the error rate for just slightly longer words. But this is alleviated by the increased structure of longer words and context of sentences [7,8]. For example, missing a letter in ‘brain-computer interface’ does not alter it to something unrecognizable.

4.2 Comparison to other Visual Prostheses

Dobelle et al. [9] stimulated visual braille with a cortical visual prosthesis. Presenting randomized single letters for 500 ms to a subject, these authors reported 73-85% correct responses, depending on the exact experimental paradigm. These results are similar to the results presented here.

Other retinal prostheses have the ability to function in a ‘direct stimulation’ mode [3,10]. To the best of our knowledge, these groups have not experimented with visual braille in direct stimulation. Real world use of visual braille for reading requires visual processing filters, such as character recognition software, to allow for translating text into braille. The Argus II system is the only currently available system able to apply such visual processing filters for stimulation in real world use.

4.3 Considerations on Braille Reading Speed

The stimulation time used in these experiments (500 ms per letter and 1000 ms between letters) is significantly faster than the current reading speed reported with retinal prostheses (seconds to tens of seconds per letter; [2-4]). The current study did not explore details on how stimulation time affects perception. In a short experiment, we did set the stimulation time to 250ms in a run of letter set 1, and found that the subject perceived 77.5% of the letters correctly. This is not significantly different from the 75% correct at 500 ms (Fig. 4). This indicates that it is possible to perceive visual braille at very short presentation times of down to, at least, 250 ms.

While shortening the presentation time of individual letters may increase word reading speed, we expect a limiting factor to be the timing between letters and words. Recent experiments with direct stimulation in retinal prostheses indicate that the persistence of a phosphene is 150-200 ms [11,12]. Similarly, Dobelle et al. [9] reported that “at frames faster than $4s^{-1}$, presentations tend to blur” indicating that phosphenes generated by direct cortical stimulation have a persistence of close to, but below, 250 ms. These findings indicate that a theoretical lower limit for the interval for visual braille reading is around 250 ms. If letter (and word-space) presentations are also around 250 ms, i.e. around 500 ms per letter plus space, a realistic goal for reading speed is around 120 letters per minute. This is an adequate speed for reading signs and shorter messages.

4.4 Considerations for Prosthetic Applications

Implementing a visual braille function in prosthetic vision requires implementing optical character recognition software for reading text in the VPU. Such software is common use and Open Source codes are available [13]. Reading identified text is only part of the problem. Identifying text in the environment is also critical. Different groups have published algorithms for detecting and reading text in natural scenes [14,15]. In particular, Chen and Yuille [14] report a success rate of detecting and reading text of more than 90% (detecting 97.2% of all text in natural images, and reading 93% of the detected text). Algorithms like this are only expected to improve in the future.

Further, the user would need to be able to read visual braille. The subject in this study reads braille, but only about 10% of blind people read braille [16]. Interestingly, the subject in the Dobelle et al. [9] study did not know (tactile) braille at the onset of the study. During the study, they tested both tactile and visual braille, and the subject only got 28% correct letter identification using tactile braille as opposed to 73-85% letter identification using visual braille. This validates the notion that visual braille is a different modality than tactile braille. While knowledge of tactile braille is useful, it is not necessary to successfully read visual braille.

Alternative methods, of course, exist to convey text to visually impaired people. An obvious example would be to convert text to an auditory signal, which the person can hear via an earphone. The whole purpose of developing visual prosthetics is to provide useful vision to blind people, and many patients express the wish to keep their hearing free.

5 Conclusion

In summary, stimulation of visual braille is feasible for conveying text to visual prosthesis users, and the technology needed can readily be implemented. It is a requirement that the user is able to read braille, but this can be learned with limited effort if the user does not already have this ability.

6 Jury Selection Factors and Recent Work

This work described a novel combination of hardware and software, and a novel approach and methodology. All of these were significant factors in the jury's decision. The system was tested with 30 real-world patients, which is another Award Criterion. The group attained promising results in terms of speed and accuracy, which were also Award Criteria. The system did function in real-time, and could clearly provide an improvement in usability. Overall, the jury felt that this work could make a major contribution to helping persons with visual deficits.

After the BCI Award, the group published work that further described and extended their Argus II system and yielded 89% accuracy when detecting single letters [16]. Other work published after the 2012 Award focused on retinal connectomes, which could facilitate future applied research as well as fundamental issues in retinal function and vision [17, 18]. Therefore, this group's ongoing work could lead to both direct and indirect benefits to persons with visual disabilities, and improve our understanding of the visual system and how it differs in persons who have trouble seeing.

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Ear-EEG: User-Centered and Wearable BCI

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Abstract. We present a radically new solution for EEG-based brain computer interface (BCI) where electrodes are embedded on a customized earpiece, as typically used in hearing aids (Ear-EEG). This provides a noninvasive, minimally intrusive and user-friendly EEG platform suitable for long-term use (days) in natural environments. The operation of Ear-EEG is illustrated for alpha-attenuation and responses to auditory stimuli, and its potential in BCI is evaluated on an SSVEP study. We show that Ear-EEG bitrate performances are comparable with those of on-scalp electrodes, thus promising a quantum step forward for wearable BCI.

Keywords: Ear-EEG, brain computer interface (BCI), non-medical BCI, wearable EEG, steady state visual evoked potential (SSVEP).

1 Introduction

Opportunities for EEG-based BCI are rapidly expanding beyond medical uses where the primary aim is a high-performance *communication* pathway for paralyzed patients, to numerous non-medical uses for healthy subjects wherein the goal is a continuous *measurement* of brain state [1]. Typical non-medical applications could include monitoring fatigue or stress to optimize performance in the work place, or the evaluation of emotional state to create more natural man-machine interfaces. This all requires overcoming several multi-disciplinary challenges in, e.g., machine learning and signal processing, but most crucial of all is the realisation of a robust and portable technology for continuous recording of EEG.

A demand for EEG systems capable of outpatient monitoring, aided by developments in miniature preamplifiers and continuous analog-recording technology, led to the first ambulatory EEG (AEEG) systems in the 1970's [2]. Digitization of recording platforms, coupled with the integration of computer technology, has provided even greater portability, and current recording systems can operate for 24 h with up to 32 channels. However, conventional recording systems remain bulky and cumbersome, and primarily operate in the laboratory setting (see Figure 1, left). This limits the use of EEG in operations such as BCI and highlights the need for so-called wearable systems which allow long-term recordings in natural environments [3].

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1.1 Towards Wearable EEG

The concept of wearable EEG is of particular value in non-medical BCI applications where a trade-off in performance is acceptable in order to satisfy needs of the user. One of the ways such a trade-off can be achieved is in the design of systems which can accommodate smaller batteries, thereby reducing the system size and increasing its wearability, either by reducing the number of electrodes or through advanced data compression algorithms which reduce data logging and/or the transmission costs (50% reduction in raw data using lossless compression techniques [3]).

Another key advance in wearable EEG is dry electrode technology (see Figure 1, right); standard systems require the use of conductive gel to enable an electrical connection between the electrodes and the scalp which is time consuming, can cause discomfort and limits the time that the recording system can remain functional as the gel dries out. Dry electrode technologies have been in development since the late 1960's [4, 5] and recent research illustrates that, for a standard BCI paradigm based on motor imagery, dry electrode systems can match the operation of wet electrode systems with only a 30% reduction in performance [6].

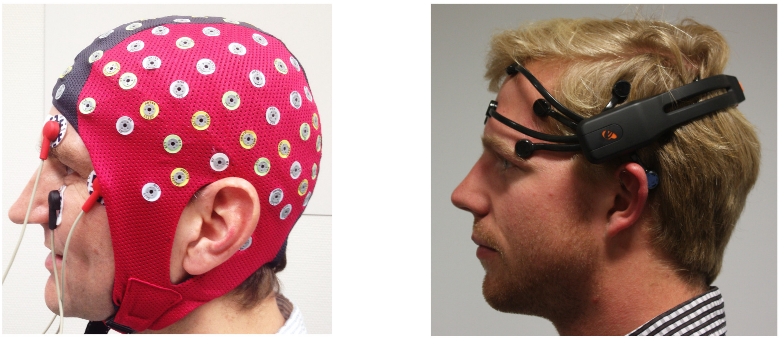

Fig. 1. [Left] A conventional 'stationary' EEG system[1] and [right] a wearable system with dry electrodes[2].

Despite such advances in wearable EEG technology, research has focused on systems which utilise on-scalp electrodes; a methodology which is fundamentally limited as it requires a means for stable attachment (cap and/or adhesive), making the recording process uncomfortable and stigmatising. In order for EEG-based BCI to be adopted more widely and to be robust for use in natural environments, the recording technology must be:

- **discreet** – not clearly visible or stigmatizing;
- **unobtrusive** – comfortable to wear and impeding the user as little as possible; and
- **user-friendly** – users should be able to attach and operate the devices themselves.

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[1] A 128-channel system by ANT Neuro.

[2] A 14-channel dry-electrode system by Emotiv (EPOC Headset).

2 Ear-EEG

To expand the use of BCI, particularly in non-medical applications where core user requirements (unobtrusive, discreet, user-friendly) are paramount over performance, we have developed the Ear-EEG concept [7-10]. The approach, as shown in Figure 2, is radically new in that EEG is recorded from within the ear canal, which is achieved by embedding electrodes on a customized earpiece (similar to earplugs used in hearing-aid applications). Both in terms of the propagation of the brain electric potentials and the recording technology, Ear-EEG uses the same principles as standard recordings obtained from on-scalp electrodes. In electrophysiological terms, bioelectrical signals from the cortex are attenuated by the cerebrospinal fluid, skull, and skin before reaching the ear canal, as is the case with conventional scalp measurements [9].

In addition to satisfying the aforementioned BCI user-requirements, crucial advantages of the Ear-EEG platform are as follows [9]:

- the earpieces are personalized, comfortable to wear, discreet, and are easy to put in place by the users themselves, facilitating everyday use;
- the tight fit between the earpiece and ear canal ensures that the electrodes are held firmly in place, thus overcoming some critical obstacles in scalp EEG – such as motion artifacts and experiment repeatability.

The current in-ear prototype (see Figure 2) comprises several electrodes, with areas of approximately 20mm^2, made of silver (Ag) epoxy glue mounted onto a plastic earpiece (see [8] for more details). The earpiece does not enter the ear by more than 10 mm and does not approach the part of the ear canal surrounded by bone. Signal acquisition is performed via an external biosignal amplifier (g.tec g.USBamp). When comparing with scalp-EEG both sets of electrodes are connected to the same amplifier, which facilitates the recording of several independent blocks of inputs, allowing a fair comparison between the two approaches.

Fig. 2. [Left] The right Ear-EEG earplug with electrodes visible and an arrow indicating the direction in which it enters the ear canal. [Right] The earplug inserted in the right ear.

The Ear-EEG approach has recently been rigorously validated [7-10] in terms of time, frequency and time-frequency signal characteristics for a range of EEG responses (see Figure 3); its robustness to common sources of artifacts has also been demonstrated (see Figure 3, upper). Comparative analysis of the alpha attenuation response (see Figure 3, centre) shows that Ear-EEG responses match those of neighbouring scalp electrodes located in the temporal region [8, 9]. In general, while signal amplitudes measured from within the ear are weaker, so too is the noise, and for certain auditory responses the signal-to-noise ratios (SNR) are similar (see Figure 3, lower) [8]. All in all, Ear-EEG offers a unique balance between key user needs and recording quality to enable long-term EEG monitoring in natural environments.

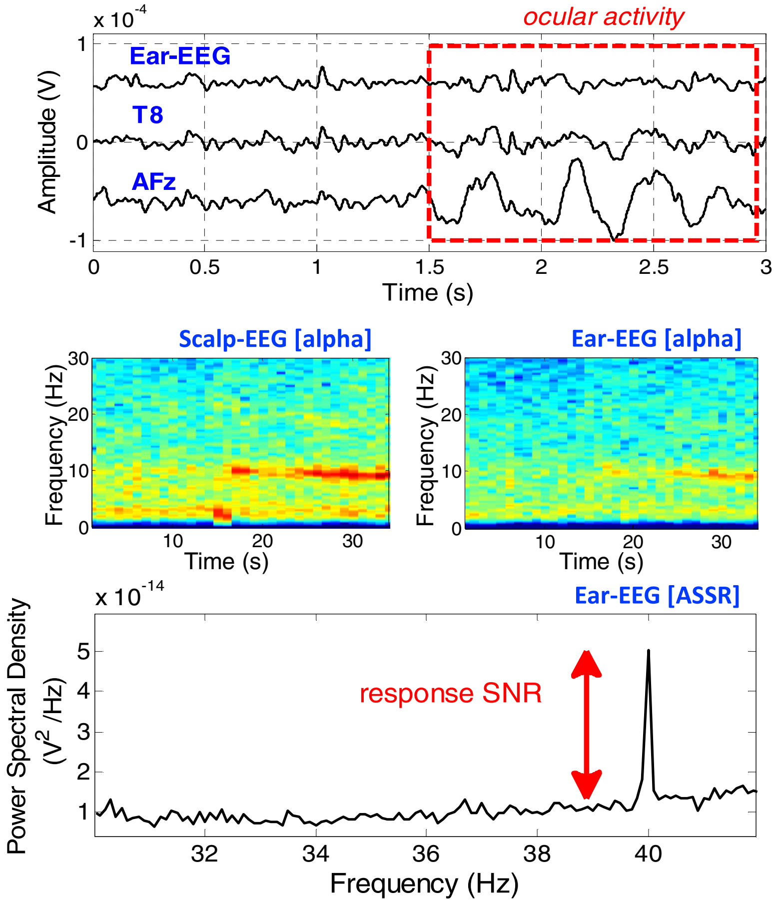

Fig. 3. [Upper] Time waveforms for scalp and Ear-EEG over 3s with consecutive eye blinking starting at 1.5s, Ear-EEG exhibits a suppression of ocular artifacts. [Centre] Time-frequency plots as subject closes eyes from 15-35s, with increased activity visible for scalp [Centre, left] and Ear-EEG [Centre, right] in the alpha range (8-12 Hz). [Lower] The auditory steady state response for Ear-EEG (40 Hz stimulus): the SNR (ratio of the response peak to background EEG) matches that of temporal scalp electrodes [8].

3 Ear-EEG: SSVEP-Based BCI

In the future, the Ear-EEG platform is likely to be of value in non-medical BCI applications. However, for rigor, we here demonstrate its BCI potential for a core paradigm typically used in medical scenarios – the steady state visual evoked potential (SSVEP). The SSVEP is induced by visual stimuli flashing at frequencies between 1 and 100 Hz and is characterized by an increased activity at the same frequency in EEG. The SSVEP-based BCI has achieved the best performance to date, allowing some subjects to reach information transfer rates (ITRs) exceeding 1 bit/sec [11].

Although the source of the SSVEP is located around the occipital region, the response is sufficiently strong that it can be robustly detected by electrodes within the ear canal. Figure 4 illustrates the SSVEP-based BCI mode-of-operation of Ear-EEG. A grid of LEDs flashing at different frequencies (13, 14, 15 and 16 Hz) was employed. The setup enables a user to convey a command, since attending a given LED induces a corresponding SSVEP; observe peaks in the spectrum in Figure 4 at the location of the attended frequencies.

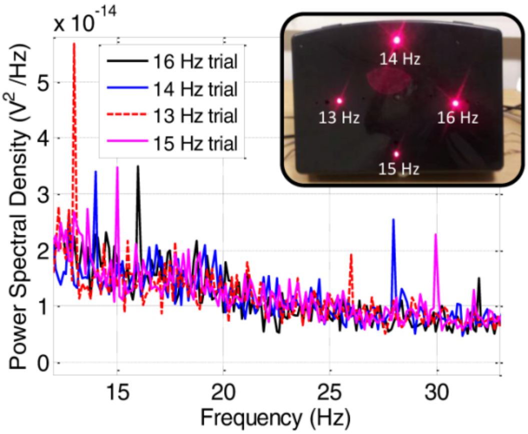

Fig. 4. The average Ear-EEG power spectral density (PSD) for four 120s trials as the user attended 13, 14, 15 and 16 Hz stimuli. [Insert: upper right] The SSVEP stimulus interface with four LEDs.

The in-ear SNR of the SSVEP was recently assessed [10] by calculating the ratio between the power spectral density (PSD) of the SSVEP response peak and the background EEG estimate at the fundamental frequency of the stimulus (see Figure 5). The study was performed via a fully in-ear approach, with reference and ground electrodes on the earpiece (see [8, 10] for more details), for several stimulus frequencies and subjects (trial length 256 s) and compared with standard on-scalp[3] EEG.

[3] All scalp electrodes were referenced to the earlobe and the ground electrode was placed at Cz (10-20 system).

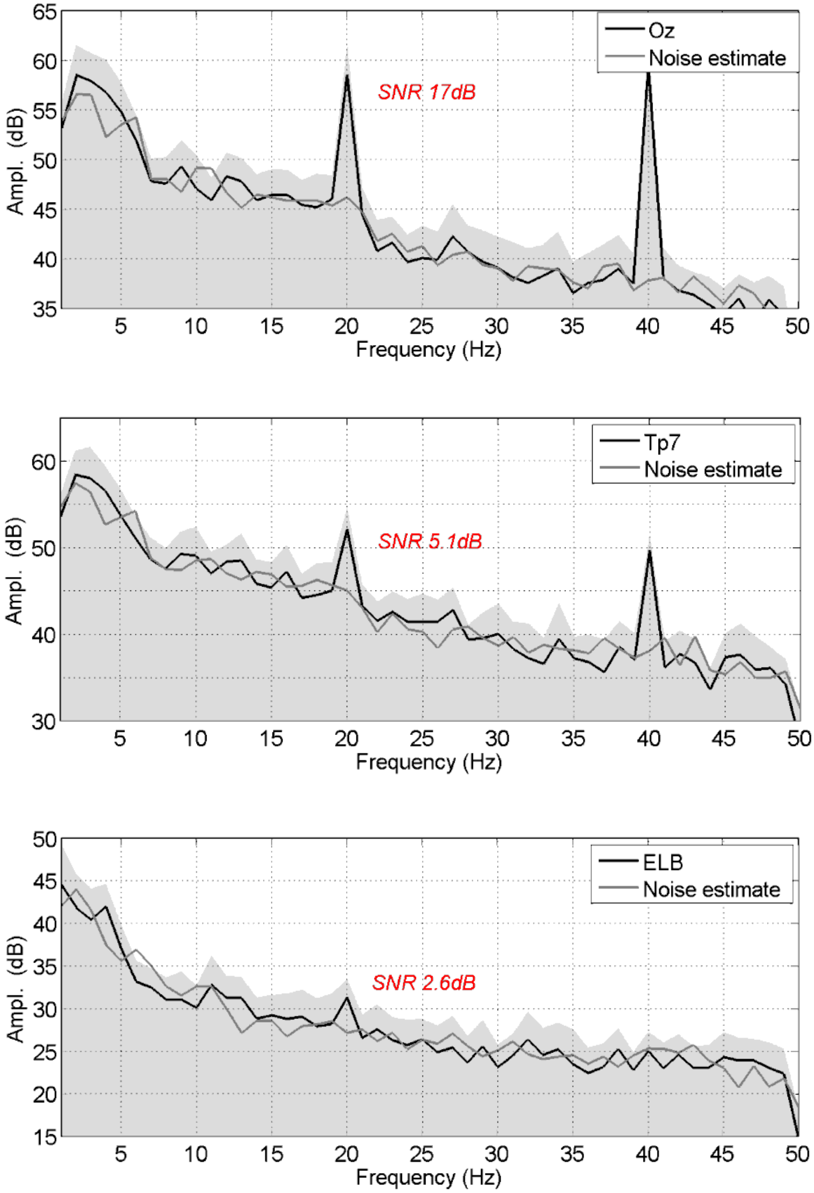

Fig. 5. The SSVEP SNR, which is the ratio between the PSD of the response peak and the background EEG, for a stimulus of frequency 20 Hz at [upper] the occipital region (electrode Oz), [centre] the left temporal region (electrode Tp7) and [lower] the left ear (electrode ELB – see [8, 10] for more details). Observe that, although the SNR is greatest at the occipital region [upper], the response can be clearly detected using Ear-EEG [lower].

3.1 BCI Performance Evaluation

For rigor we evaluated the BCI performance of Ear-EEG using a metric that is based on the estimated SSVEP SNR and independent of the stimulus presentation. This was done as stimulus design is itself a focus of research and can greatly affect the performance of a BCI system. The Shannon-Hartley theorem,

$$C = B \log_2 (1 + SNR) \tag{1}$$

where B is the bandwidth of the channel and the SNR is expressed as a linear power ratio, was used to evaluate the bitrate performances (bits/sec) for each electrode. Table 1 shows the capacity ratios for Ear-EEG, where ELB and ERB denote the left and right electrodes respectively, relative to 1) neighbouring TP7 and TP8 on-scalp electrodes (located in temporal region); and 2) the Oz on-scalp electrode, a natural choice for visual potential detection (located in occipital region).

Table 1 shows that Ear-EEG electrodes attain an average BCI bitrate capacity of 56% that of neighbouring scalp electrodes (mean ratio is 0.56). Compared to the Oz electrode, which is typically optimal for SSVEP-based BCI [11], observe that Ear-EEG exhibited a performance reduction (bits/sec) of only approximately 50%. The best results for each subject are marked in red, with the bitrate capacity ratios exceeding 0.70 for three of the four subjects, and even reaching 0.95 (see Table 1: Subject 2 denoted by S_2).

Table 1. SSVEP-BCI capacity ratios for scalp and Ear-EEG. C_{ELB} and C_{ERB} denote respectively the capacities of left and right Ear-EEG electrodes and C_{OZ}, C_{TP7} and C_{TP8} the capacities of electrodes Oz, TP7 and TP8. Subjects S_1 to S_4 attended stimuli of 15Hz and 20Hz.

	S_1 15Hz	S_1 20Hz	S_2 15Hz	S_2 20Hz	S_3 15Hz	S_3 20Hz	S_4 15Hz	S_4 20Hz	MEAN
C_{ELB}/C_{TP7}	0.44	**0.51**	0.24	0.32	0.46	0.78	**0.85**	0.71	**0.54**
C_{ELB}/C_{OZ}	0.39	0.31	0.24	0.21	0.39	**0.78**	0.80	0.44	**0.45**
C_{ERB}/C_{TP8}	0.38	0.42	0.93	0.89	0.51	0.54	0.48	0.51	**0.58**
C_{ERB}/C_{OZ}	0.23	0.38	**0.95**	0.44	0.31	0.52	0.62	0.40	**0.48**

4 Future Work

The presented results were obtained using a simple prototype system, but with further developments Ear-EEG will be a tiny battery powered brain monitoring device with gel-free electrodes that, like a hearing aid, will perform both the recording and signal processing in situ (see Figure 6). Moreover to increase the functionality of Ear-EEG in BCI applications where the user state must be evaluated (arousal, fatigue, emotion) other physiological parameters can be inferred by integrating additional non-invasive sensors onto the ear-based platform [9]:

- cardiovascular function: ear-based photoplethysmography devices available [12];
- respiratory function: respiratory sounds can be recorded within ear canal [13]; and
- movement: accelerometers are sufficiently small size and low-power for in-ear use.

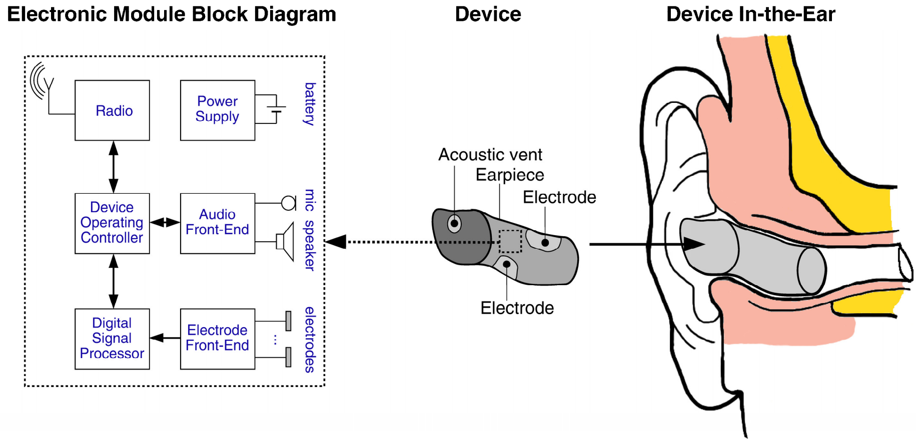

Fig. 6. A depiction of a future Ear-EEG device with an electronic module comprising instrumentation for the electrode signals, analog-to-digital conversion, a signal processing unit, a battery, and a radio module.

5 Conclusion

We have illustrated the usefulness of the Ear-EEG methodology for BCI, where all the electrodes (including reference and ground) are embedded on an earpiece. For a fair comparison, scalp and Ear-EEG electrodes have been evaluated via the same recording amplifier. Future commercial Ear-EEG earplugs will incorporate the recording and signal processing electronics, as is a standard in hearing aids. This will enable the freedom to perform wearable BCI in any environment and in real-time over long time periods (days) and to meet core user needs (robust, discreet and comfortable). The rigorous analysis against standard on-scalp electrodes has illustrated the potential of Ear-EEG in expanding the horizons of real-world BCI, while keeping the same order of magnitude of the channel capacity.

6 Jury Selection Factors and Recent Work

Three of the Award Criterion were testing with real-world users, speed, and accuracy. The work described here was tested with such users, yielding impressive speed and accuracy results. The system scored very high on the Award Criteria of usability and novelty. Ear-based electrodes could be very convenient and discreet, proving additional information to persons with hearing aids without adding embarrassing hardware or complex additional tasks for users. Ear-based electrodes are not well established in the EEG community today. This group's effort reflected novel hardware and software contributions, as well as a new concept and novel methodologies.

Since the BCI 2012 Award, this group published work that further explored steady-state and ERP activity collected by in-ear EEG electrodes and further demonstrated performance comparable to scalp-mounted electrodes [10]. The group also explored ear-EEG based on generic earpieces, which could make this technology accessible to a broader group of end users [14]. They also explored heart rate variability during music perception and its relationship to stress [15], thereby extending their work to explore other physiological signals during auditory perception. These efforts could lead to much more practical, convenient systems for persons with hearing difficulties and other conditions. As the authors noted, the work could also benefit other users by sensing heart rate variability or other physiological signals, thus providing continuous brain monitoring for many different applications.

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A Novel Brain-Computer Interface for Chronic Stroke Patients

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Abstract. We present a novel brain-computer interface for neuromodulation that leads to long lasting cortical plasticity. The system entails in recording the movement-related cortical potential (MRCP) as a subject imagines a dorsiflexion task and triggering an electrical stimulator to generate a single stimulus to the target nerve. This system has been tested on healthy subjects to demonstrate that an artificially generated signal (the peripheral afferent volley) can interact with a physiologically generated signal (the MRCP) in humans, leading to plastic changes. Further, in a group of 13 chronic stroke patients, the intervention also induced functional improvements within only three sessions. In this chapter, we outline the protocol in detail and discuss the potential for artificially inducing cortical plasticity in patients (neuromodulation). In these applications, the intention to move can be detected without a cue directly from the EEG traces. We have commenced to identify force and speed characteristics from single MRCPs, and our pilot data reveals that, if the nerve stimulation characteristics match the imagined movement, plasticity is further enhanced.

Keywords: Hebbian Plasticity, movement related cortical potentials, peripheral nerve stimulation, brain computer interface, stroke.

1 Introduction

Stroke rehabilitation therapy for motor functions aims to activate and reorganize the brain areas related to the planning and execution of voluntary movements. Numerous novel rehabilitation techniques based on non-invasive brain stimulation have been proposed and can lead to functional improvements in the chronic phase following the insult (1,2). Typically, their effects are quantified by assessing the transmission change in the corticospinal tract using transcranial magnetic stimulation (TMS). However, recent evidence suggests that those cortical areas related to movement planning, sensorimotor processing, attention and task complexity contribute to a similar extend in stroke survivors and controls (3). This indicates that they are largely left intact, though their output is not conveyed to allow appropriate functionality. While

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the non-invasive cortical stimulation approaches show improvements in performance, stimulation of the cortex with techniques such as repetitive TMS or transcranial direct current stimulation (tDCS) have limitations due to current spread to adjacent non-targeted areas. They may thus activate intact areas inappropriately (both temporally and spatially) and thus affect the rehabilitation process.

We recently developed a novel technique for inducing plasticity in the human motor cortex by combining the physiologically generated signal when a person imagines a simple dorsiflexion task with the peripheral stimulation of the nerve that innervates the muscle involved in the task (4). The subject activates the relevant brain areas via imagination and is provided with the expected afferent feedback via the single peripheral electrical stimulation to the target nerve. This protocol induced significant plasticity only when the afferent volley was timed to arrive during the peak negativity (PN) of the movement-related cortical potential (MRCP) generated in the corresponding brain area during the imagined task. The changes were specific to the target muscle, long lasting and rapidly evolving. More importantly, the changes could be induced by either cue-based or self-selected imagination (4,5). A moderate number of repetitions (for example, 50 in (4,5)) of this combined stimulation paradigm are required to have an effect that outlasts the intervention. In the next paragraphs, we discuss this intervention in more detail, starting with the MRCP as a useful tool to indicate actual or intended movement, the importance of afferent feedback arising from sensors located in the periphery and the requirement that these two signals converge with synchronous timing onto the pyramidal tract neurons.

2 Movement Related Cortical Potentials

Voluntary movements, whether executed or only imagined, are associated with slow negative cortical potentials, which can be recorded from scalp surface as a component of the electroencephalogram (EEG). This specific component type is referred to as a movement related cortical potential (MRCP). The MRCPs comprise several well defined parts which are known to be linked to specific neurophysiological mechanisms. Further, a differentiation is made between these MRCPs dependent on whether they are elicited during self-paced movement generation or due to a cue provided to the subject. In the former case, the potential is often referred to as the Bereitschaftspotential, while in the latter it is termed a contingent negative variation (CNV). Evidence suggests that, specifically during the preparation phase of the movement, the cortical generators between these two potentials are not necessarily the same (6). The Bereitschaftpotential (BP) first described by Kornuber and Deecke (7) commences 1 to 1.5 s prior to the onset of movement with a deflection termed the readiness potential (RP) (7). The RP is associated with the planning of voluntary movement and is altered in neurological disease, such as in Parkinsonian patients (8,9). The CNV has two negative deflections, one immediately following the warning stimulus and one that appears approximately 1 to 0.5 s prior to the cue to perform the movement (10) and has also been observed to be altered in neurological disease (11,12). In the CNV, it is this later deflection that is comparable to that seen in the BP, and recent evidence suggests that the generators of this CNV component are in the premotor cortex, while the BP is generated in the supplementary motor area (6).

Deecke et al (13) described a second negative deflection in Bereitschatspotential which occurs 50 to 60 ms prior to the movement onset (movement potential – MP) and is thought to be related to the execution of the movement. Conversely, in the CNV, it is the peak of the late negative deflection that is associated with the movement onset (14). Finally, following the onset of movement, a third complex waveform may be observed, termed the movement monitoring potential (MMP) in the Bereitschaftpotential, which is thought to be related to the control and precision of the movement (15). In the CNV, this later waveform has been linked to both to somatosensory feedback or alternatively to the attention level during task execution (10).

Although the exact generators of the MRCPs in both types of tasks are not known, these potentials are modulated by the way a task is executed, since their characteristics change with variations in the force and speed of the executed or imagined movement (16-20). This opens up the possibility of not only detecting movement intention but also discriminating different types of movement that the subject intends to perform or indeed imagine. If one is to use the MRCPs within a Brain-computer interface (BCI) designed for neuromodulation, this property of the MRCP is of obvious value. For example, if the subject intends to lift his/her foot to clear an obstacle or climb the stairs, the feedforward planning provides the characteristics of the amount of intended force and the speed of the movement to be performed. This is contained within the initial part of the MRCP, and can be detected and used to drive an external device such as an electrical stimulator that can then be triggered to supply an electrical stimulation with the pattern required to produce the correct amount of drive to the muscle. In this light, the detection accuracy is one important component of any such system.

In recent studies within our laboratory, we have attained detection accuracies of ~70% for imagination of simple dorsiflexion movements. This decreased slightly in chronic stroke patients (5). Moreover, the number of false positives is limited, making it possible to use online detection in a fully self-paced BCI system. Finally, the latency of detection is limited to a few hundred ms, which allows detection of the movement intention before the actual movement would be performed if it was executed. This property is fundamental for determining plasticity by causally connecting motor commands with afferent input, as will be detailed in the following.

3 Afferent Feedback During Movement

If MRCPs are to be used as part of a BCI system for neuromodulation as suggested in the introduction, it is necessary to characterize the muscle activation and the generated sensory feedback during muscle contraction. For successful plasticity induction through a BCI, two criteria thus need to be met. First, the activation of the muscle has to be physiologically appropriate in both time and frequency (orderly recruitment). Second, the corresponding feedback generated from peripheral sensors has to be appropriate as well.

Sensory feedback generated from muscle receptors generally serves two purposes. First, it contributes to the activation of the muscle itself, thus for the soleus muscle, approximately 50% of the muscle activity is due to proprioceptive feedback (21-23). Second, it is used to adjust the activity of the muscle during movement as a result of unexpected disturbances such as an obstacle or uneven ground surfaces during walking (24,25). More recently we have shown that it can also affect the function of muscles located in the opposite limb (26,27). In chronic stroke patients this type of feedback is impaired (28) and thus any novel therapy must take these different roles into account if the intervention is to be meaningful.

Proprioceptive feedback has also a role in learning or indeed relearning of a task. As a movement is being executed, the generated afferent feedback is sent back to the nervous system, where this information and the outcome of the movement is being compared to what was expected based on previous experience. It is subsequently used to adjust or fine-tune the execution of the next movement. The repeated activation of somatosensory afferents projecting onto M1 has been shown to have a pivotal role in motor skill learning in monkeys (29).

The inflow of afferent information from the periphery to the somatosensory cortex can be quantified using somatosensory potentials (SEPs). SEPs are electrical potentials that can be generated by either a physiological signal or an electrical stimulation to the respective sensory nerve axons. They can be recorded from various sites as they progress towards the somatosensory cortex. The detection of specific waveform peaks are the greatest when the recording electrodes are within close proximity to their neuronal generators (30). The amplitude of a SEP peak is considered representative of the level of activity of the neural structures responsible for generating the peak. Alterations to the peak amplitudes are therefore believed to represent alterations in the amount of activity of the same postulated neural structures. SEPs are attenuated during muscle activation (31), with some components being almost completely abolished during strong contractions. In animals it is well established that the motor cortex controls sensory input during voluntary movement (32). A proposed mechanism for the SEP attenuation may thus be that the generators of the reduced components are directly affected by the motor cortex activation (33). Whatever the cause is for the SEP attenuation during muscle contraction, this factor must be addressed when designing a BCI system for neuromodulation.

In a recent series of experiments, we have investigated the alterations in the size of the SEPs following either stimulation of the deep branch of the common peroneal nerve (dCPN) or passive dorsiflexion movements induced by a specially designed hydraulic actuator system (34). The stimulation intensity was set to 1.5 or 2 × motor threshold (MT), while the passive dorsiflexion had an amplitude of 8° and velocity of 250°/s. These values were used to mimic everyday tasks such as walking where such changes in ankle angle amplitude and velocity are easily exceeded. Figure 1 displays the SEPs recorded over Cz referenced to the ipsilateral earlobe (to avoid the phenomenon of paradoxical lateralization) for all three conditions. Eight subjects were investigated in total, and the passive movement always resulted in a larger SEP size than in dCPN stimulation (p=0.006). In passive movements, the muscles are not activated voluntarily, though they continue to provide afferent feedback from stretch of muscle spindles and activation of golgi tendon organs. Since the skin is also stretched and the joint capsule affected, afferents arising from receptors located here are likely to also contribute to the generated SEP. It was somewhat surprising that the SEP during the passive movement was so much greater than that following electrical stimulation of the dCPN. Specifically, Tinnazi et al. (33) have shown that SEP amplitudes are smaller during passive movement compared to a no movement condition. However, in their experimental paradigm the SEPs were always elicited using an electrical stimulation (in their case to the tibial nerve) and they did not investigate the SEP induced by only a passive movement.

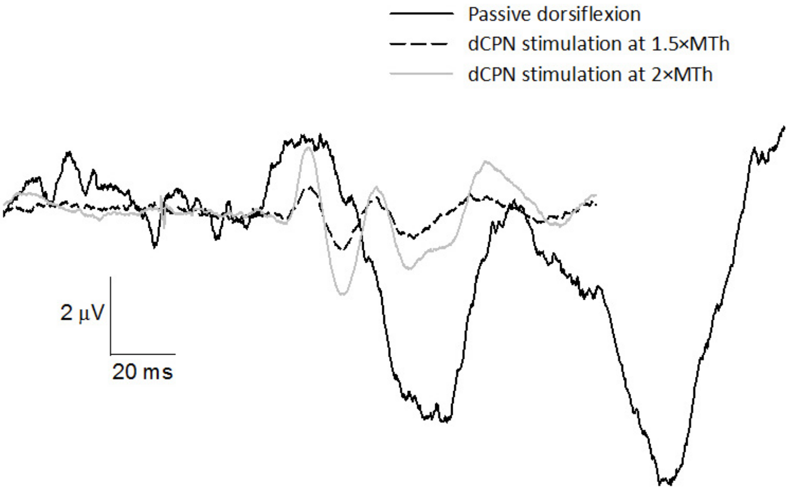

Fig. 1. Typical somatosensory evoked potential following either an imposed passive dorsiflexion (amplitude 8° and velocity 250°s^{-1}) or electrical stimulation of the deep branch of the common peroneal nerve (dCPN) at intensities of either 1.5 or 2 times the motor threshold (MTh). Data are for n=1.

Our results show that afferent feedback generated from passive movements is approximately four times greater than that due to electrical stimulation of the target nerve. Current research in our lab is targeted to use the MRCP generated during an imagined movement to trigger our hydraulic actuator to induce passive movements in line with the imagined movement within our BCI paradigm.

In a clinical setting, it may however be more advantageous to continue to use the MRCP to trigger an electrical stimulator to deliver the appropriate afferent feedback to the cortex. We have thus also continued to investigate the effect of altered stimulation parameters to the dCPN that either matches or does not match the expected muscle activation during the imagined movement. Subjects were asked to imagine either a 20 or 40% of maximal voluntary activation of the tibialis anterior muscle in response to a cue provided on a screen. Following a short training period where they were asked to produce the required level of contraction while receiving real time feedback of their produced force on a screen, they were asked to imagine this movement 50 times. The MRCP was recorded and the occurrence of the peak negativity extracted.

In the following five sessions, spaced at least 48 hours apart, they were again provided with a training period, which was followed by one of five interventions: 1. Imagination of a 20% MVC dorsiflexion where a single peripheral stimulus was applied set to an intensity of MT; 2. Imagination of a 40% MVC dorsiflexion where a single peripheral stimulus was applied set to an intensity of MT; 3. Imagination of a 20% MVC dorsiflexion where the peripheral stimulus was applied to induce a 20% MVC contraction of the TA; 4. Imagination of a 40% MVC dorsiflexion where the peripheral stimulus was applied to induce a 40% MVC contraction of the TA; and 5. Imagination of a dorsiflexion where a single peripheral stimulus was applied set to an intensity of MT. The effect of these five interventions was quantified using transcranial magnetic stimulation (TMS) of that area on the motor cortex that represents the TA muscle. TMS was applied prior to, immediately following and 30 minutes after the cessation of each intervention at intensities of 90-130% of the resting motor threshold. Preliminary results of part of this study for one subject are shown in Figure 2. These initial results suggest that if the stimulation induces a movement and thus afferent feedback that is expected, then the changes in the excitability of the cortical projections to the target muscle (as assessed by TMS) is enhanced. This has important implications for this novel technique and is currently being further developed in our laboratory.

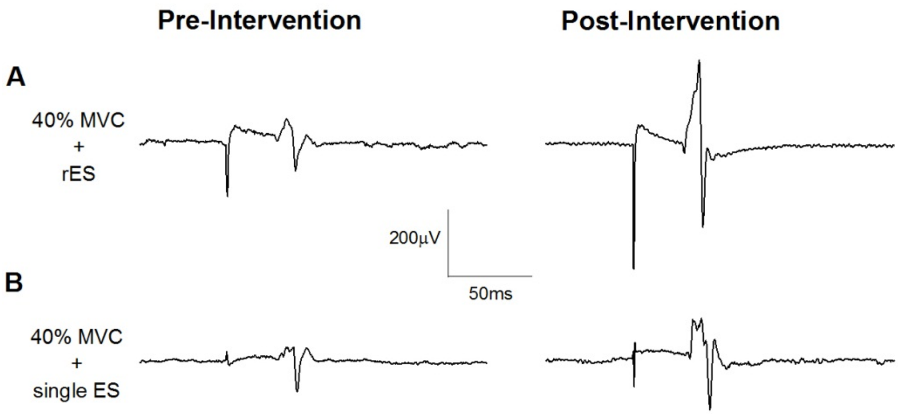

Fig. 2. Effect of the two different interventions on the size of the raw TA MEP amplitude at rest for one subject. A) TA MEP change when the subject imagined a 40% MVC and the peripheral electrical stimulation was delivered at a frequency of 20Hz and at an intensity to produce a 40% MVC. B) TA MEP change when the subject imagined a 40% MVC and the peripheral electrical stimulation was delivered as a single electrical stimulation at motor threshold as during our conventional paradigm. Data are from one subject and at least two days elapsed between each test. Data reflect and average of 10 trials.

4 Pairing of the Central Command and Afferent Feedback to Induce Plasticity

The aim of our new technique for inducing plasticity is based on Donald Olding Hebb's postulate of coincident activation. Thus, synapses that experience correlated activation of two converging inputs are strengthened, whereas those weakened by uncorrelated activity are lost (35). Hebb's theorem was subsequently substantiated by in-vitro experiments in the dentate area of the anaesthetized rabbit (36). This phenomenon, called long-term potentiation (LTP), has been one of the candidate cellular mechanisms for learning and memory storage and has been extensively investigated in the hippocampus of rats. This is particularly well suited for such studies, as the large pyramidal cells in CA1 region make synaptic connections onto those located in area CA3. Associativity – applying a weak stimulus to CA1 pyramidal cell timed with a depolarization of the CA3 pyramidal cells for a number of such pairings - led to a significant enhancement of the excitatory post synaptic potential in CA3 pyramidal cell. Importantly, the effect outlasted the stimulation period by more than 60 minutes. Stefan and colleagues applied similar principles to the intact human system (37). Their technique requires a single stimulation of the peripheral nerve that innervates the target muscle (in their case the abductor pollicic brevis – APB) followed 25 ms later by a single magnetic stimulation of that area on the motor cortex that controls the APB. The continuous pairing of these two stimuli at the appropriate interstimulus interval (ISI) of 25 ms led to a significant increase of the excitability of the cortical projections to the APB. This outlasted the stimulation period, was long lasting, specific to the target muscles and dependent on both NMDA receptors and Ca2+ channel activation. The authors thus had a technique for inducing plasticity at the systems level that exhibited many of the properties of LTP. In later publications they were able to further demonstrate that a reversal of the two stimuli (i.e. the motor cortex stimulus was provided prior to the arrival of the afferent volley induced by the peripheral nerve stimulus) could induce a depression of the signal conductance in the corticospinal tract, akin to the phenomenon of long term depression (LTD). This novel protocol is widely known as paired associative stimulation (PAS) and has since received increasing attention (38). The effects following PAS vary widely depending on many factors such as the muscle investigated, history of synaptic activity, age, attention to the task, time of day when the experiments were performed, genetics, gender and regular exercise (39).

Our novel technique is based on the findings from Stefan and colleagues. In our paradigm, the magnetic stimulus is replaced by the MRCP generated during an imagined movement. This has the advantage that the cortical structures are activated in a sequential manner as expected during voluntary movement execution. Indeed an imagined movement, a passive movement and an actual voluntary movement activate cortical structures in a similar manner (40).

As already mentioned in the introduction, we have used our protocol during imagined movements that were both cued (4) and self-paced (5). In both cases the excitability of the cortical projections to the target muscle was increased significantly. In addition and similar to the PAS paradigm, the effects were long lasting, specific to the target muscle and required the synchronous timing between the PN of the MRCP and the generated afferent volley. In a subsequent study we asked a group of chronic stroke patients to perform the same intervention, though cue based (41). In addition, we allowed them to not only imagine the task but to attempt the task if possible. The peripheral electrical stimulus was provided to the dCPN at MT as in the previous publications. The patients were 15 ± 6 months post stroke and had ceased to show any functional improvements. We assessed not only the changes in the excitability of the cortical projections to the TA but also their performance on the 10m walk test as well as a foot taping task. This latter task consisted of the patients tapping their affect foot as fast as possible within a 15 second period. Across all patients, the MEP size was significantly increased, as was their performance on all functional tasks involving the TA.

5 Long Term Perspectives

Our initial results using the novel BCI interface in healthy and chronic stroke subjects and using either a cue-based versus self-paced paradigm leave a number of open issues. First, we have shown that our intervention is successful in both a cue-based and a self-paced paradigm (4,5,41). The MRCP generated during task execution or imagination has several generators that differ depending on whether the task is cue based or self-paced. During a cue based task, the dorsal pre-motor cortex (PMd) contributes, while during a self-selected task, the supplementary motor area (SMA) shows the highest activation (6). In an ongoing study we are randomly exposing healthy subjects to either paradigm following a selective blocking of either PMd or SMA to further enhance our understanding of the generators of the MRCP. Secondly, we have shown in the past that we can differentiate between ballistic *versus* slow movements as well as between low force and high force movements (17,42), also from single trial MRCPs. The implications for the development of a brain-driven electrical stimulator that will provide the exact amount of afferent feedback necessary during an imagined movement are substantial. It will allow a more targeted approach to the rehabilitation of lost function that is tailored to the exact need of the patient. Current work aims at refining our BCI to allow this. The goal is to ask subjects to imagine a dorsiflexion consisting of different movement parameters (force and speed) and to provide the afferent feedback that would have been generated had the movement been performed rather than imagined.

6 Jury Selection and Recent Work

The work here scored high on several Award Criteria. It included the use of patients, and was strongly focused on benefiting patients. It described different novel methodologies and approaches, such as replacing a magnetic stimulus with an imagery-generated MCRP to improve cortical excitability. The work did function in real-time, and involved novel hardware and software methods and approaches. The Award Criteria of speed and accuracy could not be applied to this work.

The authors' group has conducted follow up work in related directions in 2013. The group published work in 2013 exploring MCRPs in healthy controls and ALS patients (43). This work included Niels Birbaumer, a top researcher in the field whose work was also nominated for a 2012 Award. Other recent work from the chapter authors used EEG to predict movement onset about 300 ms before movement onset, which could be useful for rehabilitation and other goals (44). Future directions such as these could improve BCIs and prosthetic systems and identify new issues in basic neuroscience research involving the brain's representation of movement details like direction, force and speed.

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Volitional Control of Neural Connectivity

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Abstract. For several decades, researchers have explored neurofeedback and related technologies to improve brain function and better understand brain plasticity. New methods to train people to improve functional connectivity or coherence could inspire new methods to treat a wide variety of brain disorders and conditions. This chapter first reviews functional connectivity and coherence, including our recent work with volitional control and MEG, then described promising new work with self-regulation via real-time fMRI. We conclude with future directions, jury selection factors, and some very new work after the 2012 Award.

Keywords: Brain-computer interfaces, BCI/BMI learning, neurorehabilitation, MEG, fMRI, real-time FMRI.

1 Introduction

Several decades have passed since the first report that suggested that humans could learn to self-regulate brain signals by neurofeedback (Kamiya, Callaway et al. 1969). Since then, non-invasive Brain Computer Interface (BCI)-neurofeedback systems have been implemented using a variety of signals from the electroencephalographic spectrum (for reviews please see: (Birbaumer 2006; Birbaumer and Cohen 2007)), leading to promising applications in neural disorders (Kotchoubey, Strehl et al. 2001; Strehl, Leins et al. 2006). With the advent of real-time functional Magnetic Resonance Imaging (rtfMRI), allowing the feedback of the activity of deep brain regions, the applications of BCI-neurofeedback have dramatically expanded (for a recent review on the topic please see: (Sulzer, Haller et al. 2013)).

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Recently, a small (but growing) number of studies have focused in an exciting variation of previous approaches by taking into account two aspects of brain functioning. In the first place, neural bases of complex cognitive process are not considered to be limited to the activation of unique, isolated brain areas. In fact, brain functioning involves the coordinated activity of several distributed networks. Secondly, several neuronal and psychiatric disorders are thought to arise from the uncoordinated activation of distributed brain regions, or from their impaired functional coupling (Friston and Frith 1995; Honey, Pomarol-Clotet et al. 2005; Just, Cherkassky et al. 2007; Wang, Liang et al. 2007; Noonan, Haist et al. 2009; Zhang, Wang et al. 2010).

In the present chapter, we summarize the studies that have shown that self-regulation of functional brain connectivity with BCI- neurofeedback is possible. In the first part, we explain the general concepts of functional connectivity from methodologies based on neuroelectric and neuromagnetic signals, and the implementation of self-regulation of neuronal coherence. In the second part, we discuss novel trends in rtfMRI- BCI research that incorporate the feedback of the direct functional connectivity of circumscribed brain regions, and that target distributed brain networks by online real–time pattern classification and feedback of mental states.

2 Volitional Control of Neuroelectric and Neuromagnetic Functional Connectivity

Functional interactivity between brain areas from electrical or magnetic signals is commonly assessed by the correlation of relative phase (phase coherence), or the correlation of their amplitude envelopes (amplitude correlation) of the signals.

In this first section, we briefly explain the above two terms, describe their significant roles in brain function, and present results from a new class of BCIs that are devised to train individuals to modulate neural coherence or synchrony between selected brain regions.

2.1 Phase Coherence and Amplitude Modulation

That the synchronization of neural activity in distributed brain regions might have an important role in brain function was first proposed in the 1980s by von der Malsburg (von der Malsburg 1981) and was later formally hypothesized by Singer and Gray (Singer and Gray 1995). Since then, many studies have provided evidence for this hypothesis and have contributed to the understanding of neural interaction using new signal acquisition and analysis tools. In this section, we focus on electrophysiological studies that have characterized functional connectivity in the brain in terms of neural coherence and synchrony by the spectral analysis of electroencephalography (EEG), magnetoencephalography (MEG) and invasive multielectrode recordings.

Phase coherence quantifies the consistency of the relative phase between two simultaneous signals that the same frequency (Siegel, Donner et al. 2012). Signals can also be in phase coherence when the two signals have a constant relative phase shift. Amplitude correlation is the correlation of the envelopes of two simultaneous oscillatory signals even when the underlying frequencies are different. Amplitudes of the two signals could be positively or negatively correlated.

2.2 Functional Roles of Large-Scale Interactions

What might be the functional roles of neuronal phase coherence and amplitude correlation? Phase coherence and amplitude correlation may enhance functional connectivity between cortical regions. Phase coherence may help in communication between different brain regions by synchronizing presynaptic spikes within regions that are sending information by exerting influence on the activity of postsynaptic spikes in the receiving regions (Engel, Fries et al. 2001; Salinas and Sejnowski 2001). On the other hand, while the precise role of amplitude correlation is not clear, one hypothesis proposed is that it may represent the phase changes across brain regions brought about by neuromodulatory systems on a slower time scale (Leopold, Murayama et al. 2003). Amplitude correlations have been closely linked with co-modulation of spontaneous fMRI signals in distant brain regions (Shmuel and Leopold 2008). Phase coherence and amplitude correlations could, however, occur independent of each other (Siegel, Donner et al. 2012): two signals may correlate in amplitude even when they phases do not cohere.

Evidence for large-scale interactions in the form of phase coherence and amplitude correlations has come from studies on sensorimotor integration and decision-making, and top-down attention. Studies in monkeys (Schall 2001) and humans (Donner, Siegel et al. 2009) have characterized how the sensory information about the outside environment is transformed into motor plans along feedforward pathways. Amplitude correlation in the beta-band between brain regions during decision formation indicates the interaction between sensory and motor areas (Brovelli, Ding et al. 2004). Other studies have looked at the cortical long-range interaction in the form of phase coherence that underlie top-down attention. A study in humans using MEG showed that attention selectively modulates the phase coherence in the cortex (Siegel, Donner et al. 2008). It has been suggested that phase coherence and amplitude correlations may represent the directionality of information flow and the rhythmicity of cognitive processes (Siegel, Donner et al. 2012).

2.3 Volitional Control of Neuronal Coherence

Traditionally, research on brain phase coherence and amplitude correlations is carried out by presenting stimuli or instructing subjects to perform a task, and then by performing functional connectivity or effective connectivity analysis on the simultaneously acquired brain signals. However, BCI enables a reverse yet complementary approach by modulating phase coherence or amplitude correlations and then observing the cognitive and behavioral changes that ensue. This represents a novel approach to investigating the direct causal link between brain activity and behavior.

To our knowledge, so far no study had demonstrated volitional control of brain coherence. However, we recently (Sacchet, Mellinger et al. 2012) explored whether coherence between bilateral MEG sensors could be controlled both an increasing and decreasing manner. The first stage of our experiment involved parameter selection in which participants were asked to perform a digit extension-contraction task to identify the magnetic field sensors that were most associated with the modulation of sensorimotor mu rhythm (Mellinger, Schalk et al. 2007). Five different behaviors were compared: left index finger tapping, right index finger tapping, bimanual synchronous index finger tapping, bimanual alternative index finger tapping, and rest. Subsequently, BCI feedback training runs were conducted during which online feedback was provided based on the current level of coherence using the sensors, frequencies, and behaviors previously identified. During these sessions, participants were instructed to perform two behaviors to move a cursor toward a target on a screen by controlling coherence in the increasing or decreasing direction. Offline analyses were carried out to ensure that no signal confounds, such as whole-head movement, single-source signal propagation, muscle artifacts, artifacts from single-trial analysis, power domination of the coherence signals, influenced brain regulation. The sensory motor rhythm (SMR) was selected as the signal of interest because it occurs with a characteristic spatial distribution over bilateral sensorimotor cortex (Kuhlman 1978). We measured coherence between neural signals by computing the correlation between time-series of discrete Fourier coefficients computed over a moving window with a length of 208 ms, and an overlap of 50%. For computation of online feedback, an FIR-based method was used to estimate coherence at individual frequencies.

Each feedback run consisted of 20 trials. In each trial, a target appeared at the right half of the vertical length of the screen, either on the top-right or bottom-right side. This target cued the participant to either increase or decrease coherence, when the target was in the upper portion of the screen and lower portion of the screen, respectively. The location of the target indicated to the participants which behavior to conduct from the two behaviors previously identified; the behavior was to be performed when the target appeared. After two seconds, a cursor appeared on the left side of the screen. Three seconds later, the cursor moved toward the right side of the screen at a constant velocity in the x direction, and a velocity in the y direction that was dependent on the value of coherence being measured. Fig.1 shows the BCI feedback trial.

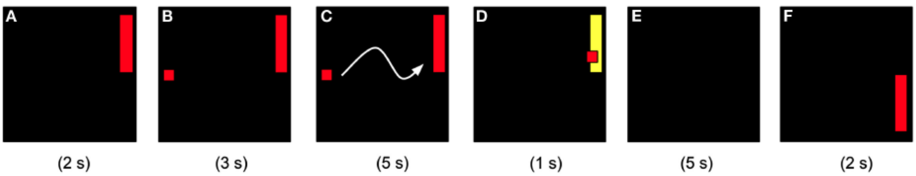

Fig. 1. Schematic of feedback trial timing. (A) Target appears for 2s (indicating goal of current trial); (B) cursor appears for 3s while real-time coherence is calculated; (C) for 5s, the cursor moves in the x direction at a constant speed while y velocity is determined by comparison against the average of the last three trials of each type (6 trials total); (D) if hit, the target changes to yellow for 1s; if missed, the target remains red; (E) inter-trial interval of 5s; (F) a new trial begins. (Reproduced with permission from Sacchet et al. (Sacchet, Mellinger et al. 2012)).

Two healthy individuals participated in our experiments involving parameter identification, and subsequent online testing of volitional control of coherence, and each showed significant control over the coherence signals. Off-line analyses to assess for confounds did not reveal evidence that the BCI control was caused by muscle artifacts, and that the coherence effects were stable across runs. Both subjects learned to significantly increase and decrease coherence of the SMR in the motor cortical MEG sensors (see Fig.2) by different types of finger tapping. Future work could investigate experimental paradigms that do not rely on finger tapping or other movements (e.g., motor or sensory imagery, or other cognitive activity), but instead rely on mental imagery guided by the feedback itself, and the brain's intrinsic ability to learn by instrumental conditioning and utilizing oscillations other than the SMR rhythm (e.g., signals from prefrontal cortex).

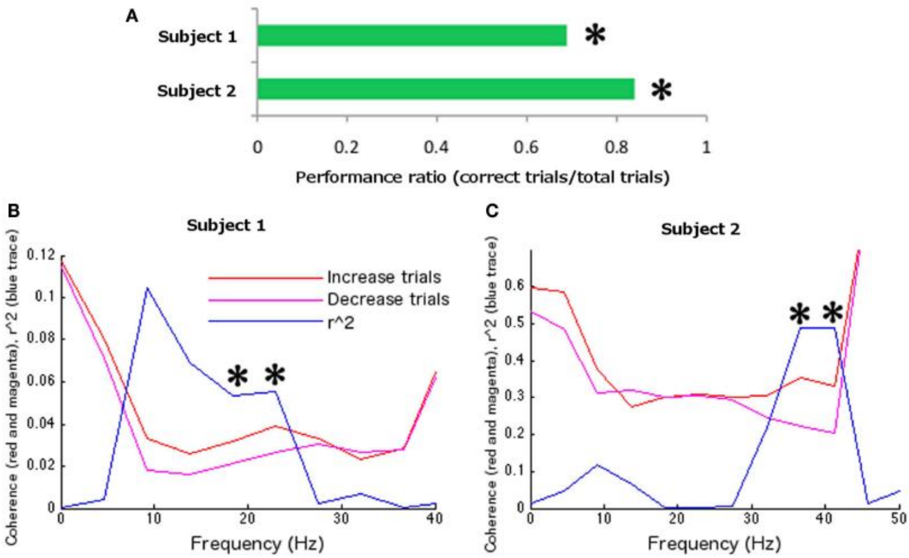

Fig. 2. Results of feedback training. (A) Overall feedback performance. Both participants were able to control neural coherence. (B) Subject 1's and (C) Subject 2's coherence and corresponding determination coefficients during feedback testing between behavioral conditions across frequency. Asterisks indicate statistical significance at frequencies of interest, nearest to the feedback frequency. (Reproduced with permission from Sacchet et al. (Sacchet, Mellinger et al. 2012)).

Vast literature has shown evidence for the hypothesis that pathological changes in long-range coherence and synchrony are central to many psychiatric and neurological disorders, including schizophrenia (Uhlhaas and Singer 2010), unipolar major depressive disorder (Knott, Mahoney et al. 2001), autism (Murias, Webb et al. 2007; Barttfeld, Wicker et al. 2011), and attention-deficit and hyperactivity disorder (Barry, Clarke et al. 2011). Disruption of coherent neural oscillations has also been observed in movement disorders such as Parkinson's disease (Stoffers, Bosboom et al. 2008) and neurodegenerative pathologies including Alzheimer's disease (Yener and Basar 2010). BCI training of brain coherence may promote the prevention, rehabilitation, and control of symptomatology in these brain malfunctions.

3 Brain Connectivity Modulation Using Functional Neuroimaging

A decade has passed since the first successful applications of fMRI-BCI. As a rapidly developing field, several studies have demonstrated the application of this methodology for the modulation of localized brain activity to induce behavioral modifications and for the potential use in neurological and psychiatric disorders (for reviews see (Sitaram, Wiskopf et al. 2008; Sitaram, Caria et al. 2009; Sulzer, Haller et al. 2013)).

However, hemodynamic/metabolic–based functional brain imaging methodologies can also reveal information about how components of neural systems are functionally coupled together during a specific task or resting state. Several statistical approaches exist for the evaluation of neural coupling with fMRI signals. A practical distinction can be made between methods that measure "functional" and "effective" connectivity. Functional connectivity is based on calculation of the correlation of BOLD signals, a methodology that has high sensitivity estimating the presence of network connections (Smith, Miller et al. 2011). Effective connectivity on its part includes the analysis of the causation and direction of the influence between brain regions, and include mapping based on psychophysiological interactions (PPI), Granger causal mapping, structural equation modelling, and multivariate autoregressive modelling (for reviews on the topic, please see (Rogers, Morgan et al. 2007; Li, Guo et al. 2009).

3.1 Volitional Control of Brain Functional Connectivity with rtfMRI-BCI

A few experiments using rtfMRI- BCI have shown that *off-line* changes in brain connectivity occur following successful self-regulation of circumscribe brain areas both in healthy subjects (Hamilton, Glover et al. 2011; Lee, Ruiz et al. 2011; Zotev, Krueger et al. 2011; Veit, Singh et al. 2012) and patients (Ruiz, Lee et al. 2013a) (see Fig.3).

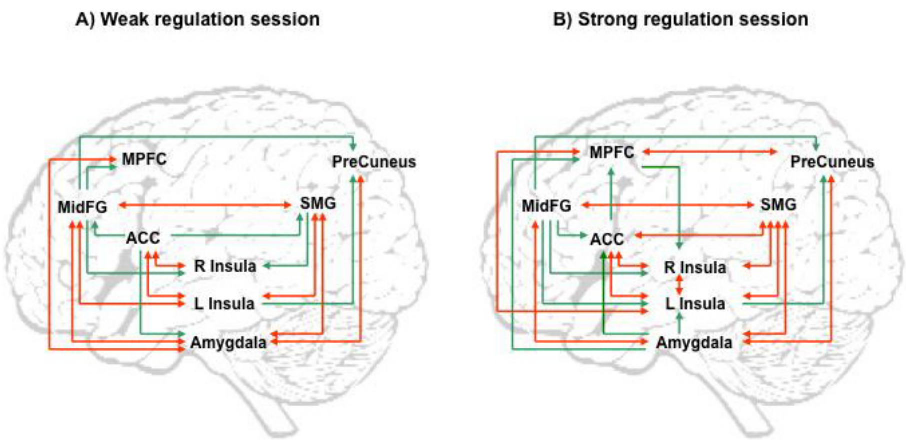

Fig. 3. Brian connectivity changes through rtfMRI-BCI training. The figure shows changes in brain connectivity in nine schizophrenia patients trained to self-regulate anterior insula cortex. The analysis was performed off-line using Granger causality modeling (GCM), methodology that examines effective connectivity by analyzing temporal information in one or more time-series of signals from a certain brain region to predict signal time courses in another (Seth 2005; Abler, Roebroeck et al. 2006; Seth 2009). After learned self-regulation, the effective connectivity of the emotional network was enhanced: new connections can be seen in the strongest session of regulation (of the last day of training) (A) compared with the weakest session of regulation (of the first day of training) (B). Red arrows indicate bidirectional influences. (Reproduced with permission from Ruiz et al. (Ruiz, Lee et al. 2013a)).

However, none of these studies explored direct feedback of brain connectivity.

Ruiz et al. (Ruiz, Rana et al. 2011) performed the first study that aimed to "directly" train subjects to achieve self-control of the functional connectivity of two brain areas with rtfMRI –BCI. Healthy participants were trained to self-regulate neural functional connectivity areas during few scanning sessions of rtfMRI, by contingent visual feedback of the correlation coefficient between inferior frontal gyrus (IFG) and superior temporal gyrus (STG). The feedback was computed including the correlation coefficient derived from the BOLD time-series in these two regions extracted from a sliding window of current and past time points.

Results of this experiment showed that participants trained with contingent feedback were able to learn self-regulation of the connectivity between IFG and STG after a few sessions of training. Furthermore, a behavioral modulation was associated with learned self-regulation: an enhancement of the semantic priming effect (Sass, Krach et al. 2009; Sass, Sachs et al. 2009)) was observed after training.

3.2 Volitional Control of Distributed Brain Networks with rtfMRI

Brain regulation of the coupling of two brain areas is an exciting advance in rtfMRI – BCI research. However, it is limited in terms of its ability to enable modulation of the entire neural circuitry involved in brain functioning. New methodologies based on brain pattern recognition could address this problem.

Applied to fMRI data, several pattern recognition techniques have been implemented including linear discriminant analysis (LaConte, Anderson et al. 2003), naïve Bayes (Pereira, Mitchell et al. 2009), neural networks (Hanson, Matsuka et al. 2004), canonical variates analysis (Mourao-Miranda, Reynaud et al. 2006), fisher linear discriminant (Shaw, Strother et al. 2003), and support vector machine (SVM) (LaConte, Strother et al. 2005). These techniques have demonstrated great sensitivity decoding brain activity as they include the analysis of the activity of spatially distributed regions of the brain and their temporal variations (in contrast to "classic" univariate analysis), and have increased our knowledge of neural patterns of different brain functions like memory recall, motor intentions, emotion perception, sleep stages, etc. (Davatzikos, Ruparel et al. 2005; Polyn, Natu et al. 2005; Haynes, Sakai et al. 2007; Bode, He et al. 2011; Lages and Jaworska 2012; Xu, Jiang et al. 2012). Pattern classification techniques could offer a more "physiological" variation of fMRI BCI-neurofeedback incorporating distributed brain areas and not only isolated brain regions. Furthermore, they have the advantage of not requiring prior assumptions about functional brain localizations (LaConte, Peltier et al. 2007).

LaConte and colleagues demonstrated for the first time the use of pattern classification of brain states for fMRI-BCI (LaConte, Peltier et al. 2007). Their study demonstrated binary decoding and feedback of motor and cognitive states of the brain.

Sitaram and colleagues (Sitaram, Lee et al. 2011) examined whether pattern recognition techniques can be used to feedback brain pattern activation of emotional states. It was shown for the first time that an online support vector machine (SVM) can be built to classify multiple discrete emotional states (happiness, sadness and disgust) from fMRI signals and for real-time feedback in healthy subjects. Furthermore, it was shown that this system could be used to enhance the functional network of emotion regulation, which is a finding of importance for potential clinical applications in emotional disorders.

Shibata et al. (Shibata, Watanabe et al. 2011) implemented an online decoder to identify voxels in early visual cortex corresponding to three distinct Gabor patch gratings differing by 60° orientation from each other. The feedback was computed representing the likelihood of these voxels predicting the perception of one of the patches. Interestingly, through BCI training, participants were not instructed about what the feedback signal represented and were rewarded to self-induce the target spatial distribution. The results showed that perceptual sensitivity was enhanced to the target grating to the exception of the other two gratings following neurofeedback training. This was a remarkable example of how real-time fMRI pattern classification can be used to address controversial questions in neuroscience, i.e. whether adult early visual cortex is sufficiently plastic to allow visual perceptual learning.

4 Conclusions

Volitional control of brain connectivity is a novel and exciting advance in BCI neurofeedback research. It offers new possibilities for exploring causal links between dynamic intracortical connectivity and perception, cognition, and/or behavior.

It could become a radically new methodology to modulate abnormally activated networks, potentially offering a non-invasive approach for neuro-rehabilitation of affected mental functions. As an incipient methodology, new studies are needed to confirm its value as a research tool in cognitive neuroscience and as a therapeutic option, that include larger samples, control groups, and that explore long-term effects of BCI training both in brain remodeling and behavior.

Future studies will explore which of the several possibilities for estimating brain connectivity has the largest impact in BCI research, and how these different methodologies can complement each other.

5 Jury Selection and Recent Work

Subjects learned to self-regulate coherence and connectivity through MEG and fMRI, which are novel real-time accomplishments. The jury appreciated the novel application of these imaging methods, which have been used in other BCI studies, but not in this fashion. The jury also noted the real-time nature of the technology and the major potential to benefit patients. The hardware and software, particularly in combination, were also novel. The work described is usable in that it requires simple mental activities, although MEG and fMRI are neither portable nor affordable.

This group has remained extremely active since the 2012 Award, with numerous results that extend the research presented here. Other work with rt-fMRI BCIs further discussed regulation of brain metabolism in the context of skill learning (Birbaumer et al., 2013). The authors also showed that subjects can self-regulate the substantial nigra and ventral tegmentum through rt-fMRI (Sulzer et al., 2013b). The group extended rt-fMRI technology to help persons with schizophrenia (Ruiz et al., 2013a). The authors contributed to a new review article, based on the first international conference on rt-fMRI neurofeedback, that assesses a variety of issues and applications from different groups (Sulzer et al., 2013a). The authors also published a separate review article, showing the rapidly developing nature of this research direction (Ruiz et al., 2013b).

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Improving the Efficacy of Ipsilesional Brain-Computer Interface Training in Neurorehabilitation of Chronic Stroke

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Abstract. Several clinical trials indicate that ipsilesional brain-computer or brain-machine interface (BCI/BMI) training coupled with behavioral physiotherapy can facilitate motor recovery after severe stroke. However, improvements are heterogeneous across stroke patients. Thus, it is important to identify biomarkers that predict BCI training-related motor recovery and to find novel approaches to enhance training efficacy. Based on our most recent results providing evidence that daily ipsilesional BCI training-related upper limb motor recovery depends on the integrity of the ipsilesional cortico-spinal system, and data indicating that non-invasive brain stimulation, e.g. transcranial direct current stimulation (tDCS), can improve BCI learning and retention, we suggest a novel BCI-based rehabilitation regime that specifically trains perilesional motor-related brain areas showing sufficient connection to the cortico-spinal tract and combining such training with real-time non-invasive brain stimulation of these specific areas. Such a novel methodological approach based on real-time integration of area-specific brain training and stimulation promises significant benefit for patients with severe paralysis and can broaden the use of BCI technology in clinical environments.

Keywords: Brain-computer interfaces, BCI/BMI learning, neurorehabilitation, brain stimulation, stroke.

1 Introduction

Injuries of the cortico-spinal system, e.g. due to stroke, are among the leading causes of long-term disability [1]. Each year approximately 15 million people suffer a stroke worldwide. Two thirds survive, but 50% of these remain severely handicapped and depend on assistance in daily life [2-4]. While motor function can significantly improve in the first months after stroke, further recovery is often slow or non-existent [5].

The last years yielded the development and clinical assessment of various neurorehabilitation approaches, some of them proven to be highly efficient, e.g. constrained induced movement therapy (CIMT) [6,7], but these rehabilitation strategies require sufficient residual motor function often not present in more severely-impaired stroke

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patients (e.g. who are unable to open their hand). For these patients, there is no standardized or accepted treatment strategy [8].

However, recent studies suggest that the application of brain-computer or brain-machine interface (BCI/BMI) systems might contribute to the development of treatment options for patients with severe paralysis. Based on the concept of neurofeedback, Birbaumer & Cohen suggested that contingent reward of ipsilesional motor related brain activity, e.g. mu-rhythms (8-15Hz), might facilitate motor recovery, even in chronic stroke patients [9,10].

The rationale of this idea was derived from previous studies that showed that modulation of ipsilesional mu-rhythm during movement intentions in the first few months after stroke correlated with long-term clinical motor outcomes, irrespective of the degree of previous motor paralysis [11]. This finding is consistent with neurophysiologic and neuroimaging data suggesting an association of ipsilesional brain activity and functional motor recovery while increased contralesional activation was associated with poor recovery [12].

2 Brain-Computer and Brain-Machine Interfaces (BCI/BMI) in Stroke Rehabilitation

A first pilot study conducted at the National Institute of Neurological Disorders and Stroke (NINDS) showed that chronic stroke patients unable to grasp can learn to control an orthotic device that opened and closed their hands and fingers through purposeful modulation of mu-rhythms [13]. However, there was no indication of a clinical improvement in those patients who used this BCI system over a period of several weeks. The ability to open and close their hand in the lab did not generalize to their daily life environment, where their brain activity was not linked to the motions of an exoskeleton.

Thus, subsequent efforts focused on two major challenges in the application of BCI/BMI in neurorehabilitation: 1. Generalization of the learned behavior from the lab to daily life and 2. Optimization of the BCI system's design to increase contingency between task-related changes of brain activity and motions of an exoskeleton, as well as augmentation of such activity in the lesioned hemisphere of stroke patients.

The latter is important as the chosen mathematical algorithms that translate brain activity into machine output can result in different responses and adaptations of brain physiology along the course of BCI control [14]. Given the non-stationary nature of brain activity, implementation of different adaptive methods - for example, [15-17] -may result in a BCI setup that is optimized for the detection of a specific brain state (e.g. discrimination of a task-free state vs. task-related state), while others might result in increasing distinguishability between those states along BCI control. Depending on the purpose of the BCI system, high performance rates without the necessity of extensive training might be favorable (e.g. in the context of assistive BCI technology), while a BCI system designed to augment specific physiologic signatures of neural activity would be associated with lower performance rates and long training periods, which would allow the "brain to adapt to the machine". Such processes resulting in successive improvements of the brain's control over the machine can be quantified as BCI/BMI learning.

The mechanisms underlying such learning, e.g. through daily BCI/BMI training, are similar if not the same as those underlying normal skill learning, e.g. based on operant conditioning. The factors identified by Thorndike (1905) [18] and Skinner

(1938) [19] for operant conditioning of overt behavior seem equally valid for abstract learning [20]. That is, controlling brain oscillations similarly depends on immediacy, contingency and relevance of the consequence (associated with activation of the reward system). While immediacy and contingency mainly relate to the quality of feedback (accuracy and time contingency between neural activity and translation into behavior, e.g. motions of an exoskeleton), an aspect that is necessary but not sufficient for learning, the relevance of the consequence is the decisive factor for any form of (instrumental) learning, e.g. in the context of (BMI-related) neurorehabilitation.

This factor, however, is often neglected in rehabilitation [21] as it introduces a dimension difficult to control, particularly in patients with potential dysfunctions of the reward system. Nevertheless, it needs special attention and consideration, particularly when developing novel concepts, machines or devices for disadvantaged persons.

For a stroke patient, the relevance of moving a hand that was completely paralyzed for several years is obvious. The patient's delight and joy often radiates to the surrounding witnesses and rewards everyone who is in the same room. However, such skill becomes meaningless if it cannot be performed in a daily life context and frustration is predetermined if there is no form of generalization to daily use.

Thus, we investigated whether behavioral therapy could facilitate generalization of the learned behavior from the lab to the individual patient's everyday life. Goal-directed or behavioral physiotherapy aims to transfer the simple arm and hand motions driven by the exoskeleton or rehabilitation robot during BCI/BMI training into daily life situations, e.g. grasping a toothpaste tube or using a fork. After a thorough behavioral analysis evaluating the capacity for motor behavior in different situations, individual reward plans, including tangible and intangible sensory and social rewards, become defined in tight interaction with the patient. Behavioral physiotherapy follows a standardized treatment manual [22,23]. Before each movement, the physiotherapist gives verbal information about the desired motion and stimulates the somatosensory system by touching the relevant muscles and moving the fingers passively. Such preceding somatosensory stimulation to the paretic hand has been shown to improve motor function in the paretic limb [24], possibly by normalizing activity-dependent modulation of inhibitory interhemispheric interactions [25]. Any purposeful visible motion or muscle contraction becomes immediately rewarded verbally by touching the patient's arm or hand. Based on the individual's capabilities, a homework-training plan is compiled to foster inclusion of the new skills into the patient's daily life. Every exercise and its success have to be written into a diary. We found that daily BCI/BMI training coupled with such goal-directed, behavioral physiotherapy results in significant recovery in individual patients [26].

This finding suggests that translation of motor-related brain activity accompanying the attempt to perform a lost function, e.g. to grasp, might induce use-dependent sensori-motor plasticity that facilitates restoration of normal motor control following behavioral physiotherapy. The mechanisms underlying such effect, e.g. rewiring and synaptic strengthening of weakened or previously inhibited ipsilesional and contralesional motor networks are yet not fully understood, though.

A larger clinical study performed at the University of Tübingen provided further evidence that such a regime that couples daily BMI training with behavioral physiotherapy can improve motor function of chronic stroke patients with severe motor deficits [27]. However, individual improvements varied substantially.

3 Biomarkers Related to Motor Recovery in Chronic Stroke

This heterogeneity of clinical outcome across study participants underlined that identifying biomarkers correlating with motor recovery would be of great importance. We used transcranial magnetic stimulation (TMS), a well-tolerated and safe technique to elicit motor evoked potentials (MEP) that reflect excitability and integrity of the corticospinal system, to investigate whether BCI/BMI related motor recovery relates to upper limb MEPs. 32 chronic stroke patients with complete finger paralysis underwent either BCI/BMI training where mu-rhythm desynchronization resulted in grasping motions of the paralyzed hand (group I) or the paralyzed hand was moved randomly (group II). We found that the ipsilesional corticospinal system's integrity, reflected by presence of an upper-limb MEP (MEP+), was associated with better motor improvement (as measured by the Fugl-Meyer Assessment) in group I (contingent motions) as compared to patients with MEP+ of group II (random motions). Across groups, patients with MEP+ improved, while patients with MEP- did not. Furthermore, only patients with MEP+ showed a trend for improvement in hand and finger function [28]. While BMI training coupled with goal-directed, behavioral physiotherapy resulted in motor function recovery [27], we concluded that cortico-spinal system integrity predicts clinical outcome, and thus may be a useful bio-marker for BMI-related motor restoration in chronic stroke patients with complete finger paralysis.

4 Brain Stimulation and BCI/BMI Learning

In a second study we tested whether transcranial direct current stimulation (tDCS), a safe and well-tolerated technique in which one applies electric currents to the brain and which has been shown to have polarity dependent effects on brain excitability [29], cognition [30] and behavior [31], can improve mu-rhythm-related BCI/BMI learning and retention. 30 healthy participants received one of three types of stimulation (anodal, cathodal or sham) applied over the primary motor cortex in association with daily BCI/BMI training over one week. While the electric current stimulation did not result in a measurable difference of mu-rhythm control on the first days of training, we found a polarity dependent effect in the subsequent course of the BCI training. Our results indicate that anodal tDCS improved mu-rhythm-BCI/BMI learning across several days and improved retention of such skills when tested one month after the end of the training [32].

Based on this finding, we investigated possibilities to further enhance effects and practicability of combined BCI/BMI and brain stimulation. Several previous tDCS studies indicated that simultaneous brain stimulation during acquisition of a new task is more efficient than sequential application of electric currents preceding training [33]. Thus, we worked on EEG- or MEG-based BCI/BMI setups that allow simultaneous application of tDCS. While EEG does not permit electric stimulation above or underneath EEG electrodes, in such experiments, tDCS can be simultaneously applied to brain areas neighboring those used for BCI control. In a first set of experiments, we showed that tDCS over pre-motor areas during mu-rhythm-based EEG-BCI control is feasible and might be a useful tool to enhance BCI/BMI-related brain training and usability in clinical environments [34].

However, when aiming at selecting a specific brain area's activity for BCI control while this brain area is undergoing transcranial electric stimulation, this can only be achieved if the area's corresponding brain signals can pass through the stimulation electrode. In theory, neuromagnetic brain activity has this feature, but immense electromagnetic noise generated by the DC stimulator hinders assessment of neuromagnetic brain activity (ranging at 15-100 femtotesla, fT, 10^{-15}T). While the use of custom-made radiotranslucent, non-ferrous stimulation electrodes solves the problem of probing brain oscillations from underneath the stimulator electrode (Fig.1), extensive testing of various signal processing algorithms and filters did not result in a satisfying localization and reconstruction of ongoing brain activity that would allow implementation of an online BCI/BMI system. Likewise, further hardware improvements of the DC stimulator (in collaboration with NeuroConn GmbH, Germany) resulted in a significant reduction of the stimulator noise, but did not solve the core of the problem: online (realtime) translation of brain oscillations from brain areas undergoing transcranially applied electric currents. With the help of our friend and colleague Stephen E. Robinson from the National Institutes of Mental Health (NIMH), we found that the appropriate mathematics to solve our problem were described as early as 1823 by Carl Friedrich Gauss. In his "Theoria combinationis observationum erroribus minimus obnoxiae" [35], he built the ground for the mathematics of beamforming, a technique that is the basis of sonar technology, cellular phones and hands-free speaking systems. Implementation of the proper mathematics using synthetic aperture magnetometry (SAM) enabled us for the first time to assess the effects of electric currents (0.5-2mA DC, 10-25V) on human neuromagnetic brain oscillatory activity with high fidelity [36] (Fig. 2). While an enigma for many decades, this novel strategy promises a better understanding of the direct effects of transcranially applied electric currents on millisecond-by-millisecond brain activity, and thus have a major impact on basic neuroscience and clinical applications of non-invasive brain stimulation.

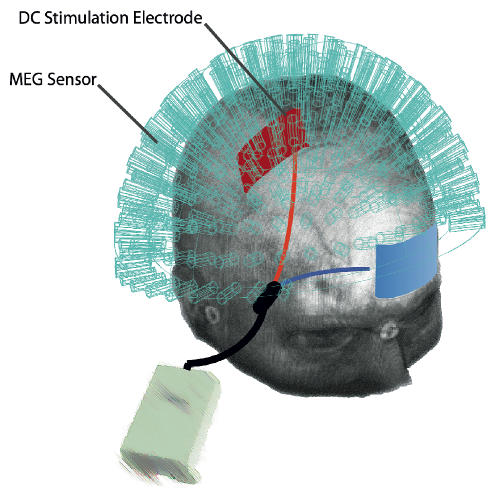

Fig. 1. Schematic illustration of simultaneous electric brain stimulation during magnetoencephalographic (MEG) recordings with a whole-head 275-sensor array. Neuromagnetic activity can pass radiotranslucent, non-ferrous stimulation electrodes allowing reconstruction of brain oscillatory activity of cortical areas undergoing electric stimulation.

In a second step, we implemented this approach in a BCI/BMI system controlled by brain oscillations derived from areas that were undergoing transcranial electric current stimulation. In a first pilot study, a stroke patient with complete finger paralysis used volitional modulation of mu-rhythm reconstructed from perilesional brain areas while these areas underwent simultaneous anodal transcranial direct current stimulation (tDCS) [37]. Future work will focus on different stimulation protocols to modulate brain oscillatory activity used for BCI/BMI control, and their relevance in the treatment of patients with neurological and psychiatric brain disorders.

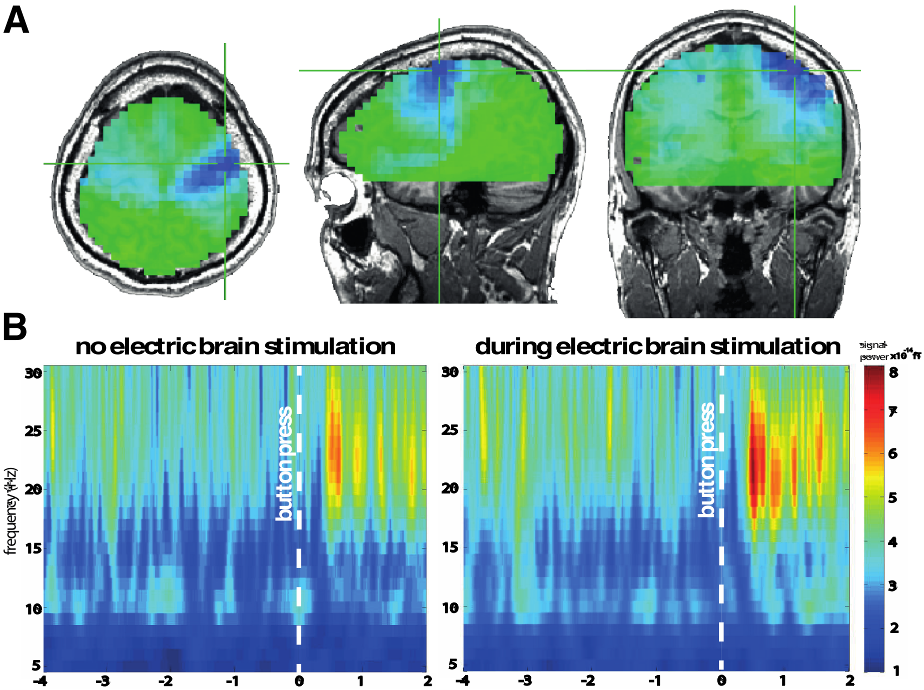

Fig. 2. A: Task-related changes of brain activity during imagined movements of the left fingers were reliably located on the right hemisphere. B: A time-frequency analysis of reconstructed brain activity showed high coherence in absence of (left) and during electric brain stimulation (right).

5 Future Directions

In the case of BMI-related stroke neurorehabilitation, the described studies and methodological advances suggest that integration of a real-time beamforming BCI/BMI with area-specific brain stimulation should be embedded in a step-wise rehabilitation regime. Such regime might substantially improve the efficacy of BCI/BMI-based brain training in neurorehabilitation of chronic stroke patients and comprises five steps: 1. thorough evaluation of the brain lesion and integrity of the cortico-spinal tract; 2. identification of the optimal brain region for BCI/BMI training;

3. MEG-based online BCI/BMI brain training during simultaneous anodal stimulation of the brain region selected for BCI control, with training that is followed by a goal-directed, behavioral physiotherapy to facilitate generalization of the learned skill to a daily-life environment; 4. after an intensive training block over 4-weeks, the training is continued with an EEG-based BCI/BMI system that can be combined if necessary with further non-invasive brain stimulation in an ambulatory setting; and 5. the patient continues the training at home using a daily-life compatible BCI/BMI system to sustain brain activity while starting rehabilitation measures that build on regained motor function, e.g. constraint induced motor training (CIMT) or auditory cued bilateral arm training (BATRAC) [38,39].

This approach employs a novel application of BCI/BMI that complements the existing (assistive BCI) systems by adding the concept of biofeedback-BCI to facilitate motor recovery in chronic stroke, and combines it with non-invasive brain stimulation, promising significant benefits for patients with severe paralysis for whom no other therapy presently exists. It incorporates the latest methodological advancements allowing real-time area specific electric brain stimulation during EEG- and MEG-based BCI training through implementation of many innovative hardware and software improvements, and it provides the potential to substantially broaden BCI use in clinical environments.

6 Jury Selection Factors and Recent Work

As the authors noted, the chapter introduced a novel application of a BCI and includes novel concepts and methods, including novel software and hardware improvements. The chapter also described a potential benefit to users, and presented work in which the novel applications were tested with real stroke patients, who were potential target users. Finally, the system could be used online, which was another consideration for the 2012 Award. Therefore, the work scored high on seven of the jury's selection criteria. The work could not be evaluated in terms of other factors such as bits/min or accuracy, since the goal was not to improve communication but rather to facilitate stroke rehabilitation.

The group recently published the aforementioned work on combined non-invasive transcranial electric current stimulation during *in vivo* assessment of human brain oscillations through the prestigious journal Nature Communications [40]. Data on the combination of this approach with an online beamformer BCI in stroke neurorehabilitation was recently presented at the 21st World Congress of Neurology in Vienna [37]. Related work from this group showed that BCI based stroke training yielded a significant improvement over conventional stroke training. Within about three weeks of training, patients who included BCIs in their therapy regimens showed some improvement of hand movement ability [27]. Thus, the work described above has remained very promising and impactful, and may influence new technologies and regimens to help people recover from movement disorders resulting from stroke and perhaps other conditions.

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Event-Related Desynchronization by Hand Motor Imagery Is Associated with Corticospinal Excitability: Physiological Evidence for BCI Based Neurorehabilitation

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Abstract. The purpose of this study was to assess the association between the magnitude of event-related desynchronization (ERD) of electroencephalogram, which is believed to represent increased activation of the sensorimotor cortex, and the excitability of primary motor cortex (M1) and spinal motoneurons. M1 excitability was tested by motor evoked potentials (MEPs), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) using transcranial magnetic stimulation, and spinal motoneuronal excitability was tested by F-waves using peripheral nerve stimulation. Results showed that MEP amplitude was significantly increased during motor imagery and large ERD during motor imagery was associated with significantly reduced SICI and increased F-wave persistence, but no significant changes in ICF and the response average of F-wave amplitudes. Our findings suggest that ERD magnitude during motor imagery reflects the instantaneous excitability of both M1 and spinal motoneurons.

Keywords: Electroencephalogram, Transcranial magnetic stimulation, Motor evoked potential, Short-interval intracortical inhibition, F-wave.

1 Introduction

There is an increasing interest in the electroencephalogram (EEG)-based brain-computer interface (BCI) as a possible tool for rehabilitation of upper limb motor functions in hemiplegic stroke patients [1]-[6]. This type of BCI often exploits the oscillations in the EEG occurring in the mu and beta bands recorded over the sensorimotor areas (SM1). Their amplitude typically decreases during movement and similarly during motor intention or motor imagery [7]-[9], and has been referred to as event-related desynchronization (ERD). Some studies revealed that movement or motor imagery-induced ERD and blood-oxygen-level-dependent (BOLD) signal in

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functional MRI changes co-localize at the SM1, and that the magnitude of ERD and BOLD co-vary [8][9]. Therefore ERD following motor imagery is believed to represent increased activation of the SM1.

However, it remains unclear whether the excitabilities at the cortical and spinal level in the motor system are actually correlated with ERD over durations ranging from several hundred milliseconds to seconds. The BOLD signal used in the previous studies [8][9] is inferior in time resolution (2-3 s) compared to mu and beta bands in EEG (of the order of 100 ms). Further, the BOLD signal indicates hemodynamic cortical activity, but not necessarily electric corticospinal excitability. Identification of a relationship between instantaneous ERD magnitude and corticospinal excitability could provide a physiological basis for BCI-based neurorehabilitation to promote motor recovery.

The purpose of this study was to assess the association between the magnitude of ERD and the excitability of primary motor cortex (M1) and spinal motor neurons during hand motor imagery. We sought to identify such a relationship using simultaneous acquisition of ERD magnitude, which was calculated from EEG online, and transcranial magnetic stimulation (TMS) or peripheral nerve stimulation (PNS), which was contingent on the instantaneous ERD magnitude. Motor evoked potential (MEP) induced by single pulse TMS and short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) induced by paired-pulse TMS are widely accepted as measures for assessing cortical excitability non-invasively [10][11]. F-wave induced by peripheral nerve stimulation is used for assessing spinal motoneuronal excitability non-invasively [12].

2 Methods

The purpose and experimental procedure were explained to the participants, and written informed consent was obtained. The study was approved by the institutional ethics review board and performed in accordance with the Declaration of Helsinki.

2.1 Experiment 1: ERD and Cortical Excitability

Ten healthy participants were recruited. MEP was recorded from the right extensor carpi radialis (ECR) muscle. TMS was applied to the left hemisphere over the optimal site for eliciting responses in the ECR muscle. Single pulse TMS was applied at an intensity of 120% of the individual resting motor threshold. Paired-pulse TMS was used to investigate SICI and ICF. A subthreshold conditioning stimulus was set at 80% of the resting motor threshold, and was delivered through the same magnetic coil at 2, 3, 10 or 15 ms prior to the suprathreshold test stimulus adjusted to 120% of the resting motor threshold. Each participant participated in a series of three experimental conditions. In the first condition, we applied single and paired-pulse TMS during rest, and collected 50 MEPs. In the second condition, participants performed 7 s of rest followed by 5 s of motor imagery of right wrist extension, and received real-time visual feedback of the ERD magnitude of the right hand SM1 while they performed a motor imagery task. We applied either single or paired-pulse TMS immediately after the ERD exceeded 5% during motor imagery, and collected 30 MEPs. The online algorithm to calculate ERD is described below (*2.3 BCI experimental system*). The third condition was performed using the same conditions as the second except that TMS was applied immediately after ERD exceeded 15% during motor imagery. MEP amplitude was measured peak-to-peak. SICI and ICF were expressed as a percentage of the ratio between the conditioned MEPs and the unconditioned MEPs (mean conditioned MEP / mean unconditioned MEP × 100%).

2.2 Experiment 2: ERD and Spinal Motoneuronal Excitability

Ten healthy participants were recruited. F-waves were recorded from the right abductor pollicis brevis (APB) muscle. To elicit F-waves, we first determined the maximal stimulus by delivering 0.2 ms square-wave pulses of increasing intensity to elicit the largest compound muscle action potentials (CMAPs). Supramaximal shocks, adjusted up to the value of 20% higher than the maximal stimulus, were applied to the right median nerve at the wrist level. Each participant participated in a series of three experimental conditions. In the first condition, we applied PNS during rest, and collected 50 CMAPs. In the following conditions, we used the same BCI experimental system as Experiment 1. The participants performed 7 s of rest followed by 5 s of motor imagery of right thumb abduction. We applied PNS immediately after the ERD exceeded 5% or 15% during motor imagery, and collected 50 CMAPs in both conditions. The trials produced F-wave were defined as a deflection of at least 50 μV occurring from 24 ms to 36 ms after PNS with baseline subtraction. F-wave measurements consisted of persistence, which is the number of definable F-waves per 50 stimuli, and baseline to peak amplitude averaged in two ways: (1) counting all trials (50) including absent responses as 0 μV (trial average) and (2) counting only those trials with detectable responses (response average).

2.3 BCI Experimental System

EEG signals were recorded over right hand SM1 (C3 and its four neighbors) with Ag/AgCl electrodes (φ = 10 mm) sampled at 512 Hz using an EEG amplifier (Guger Technologies, Graz, Austria). The signal from C3 was re-referenced using a four neighbor Laplacian spatial filter. The EEG data was segmented into successive 512-point (1,000 ms) windows with 480-point overlapping, and a fast Fourier transformation was applied in each segment. ERD was defined as the decrease in spectral power relative to 3 s reference intervals during the resting period in each trial. ERD was calculated at each segment (time resolution of 62.5 ms) with a frequency resolution of 1 Hz, according to the following calculations:

$$ERD(f,t) = \frac{R(f) - A(f,t)}{R(f)} \times 100\% \tag{1}$$

where A is the power spectrum density of the EEG at time t [s] with the onset of motor imagery and frequency f [Hz], and R is the mean power spectrum [μV^2/Hz] of the reference intervals. Feedback was provided as the length of a bar displayed on a screen placed 60 cm in front of the participant's eyes that continuously moved in accordance with the ERD magnitudes while the participant performed the motor imagery task. TMS or PNS was triggered online by the BCI experimental system (Fig. 1) when ERD magnitude reached the predetermined threshold during the motor imagery task.

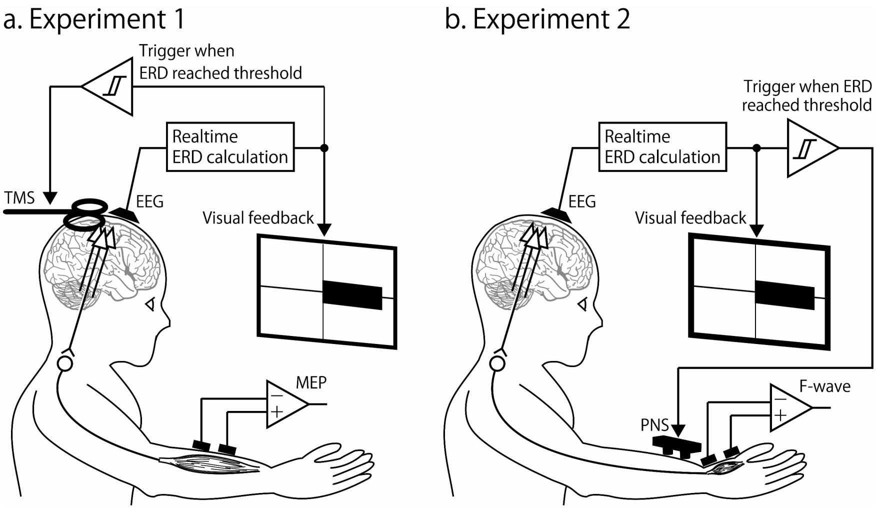

Fig. 1. BCI experimental system

3 Results

3.1 Experiment 1: ERD and Cortical Excitability

Figure 2 represents the ERD topographic maps during the condition of rest (Fig. 2a) and motor imagery of right wrist extension at ERD 5% (Fig. 2b) and at ERD 15% (Fig. 2c). ERD magnitude at C3, i.e. at right hand sensorimotor area, is largest compared to all the other EEG channels in both ERD 5% and 15% conditions (27.2% and 6.9%, respectively). In addition, ERD magnitude at Cz was the second largest in the experimental condition of ERD 15%, while ERD magnitude at P3 was the second largest in the experimental condition of ERD 5% (16.9% and 4.8%, respectively). These data suggest that the observed ERD during right wrist imagery originated from the contralateral sensorimotor area in this experimental procedure. Unfortunately, we only recorded whole-head EEG from a few participants for the purpose of checking the experimental system.

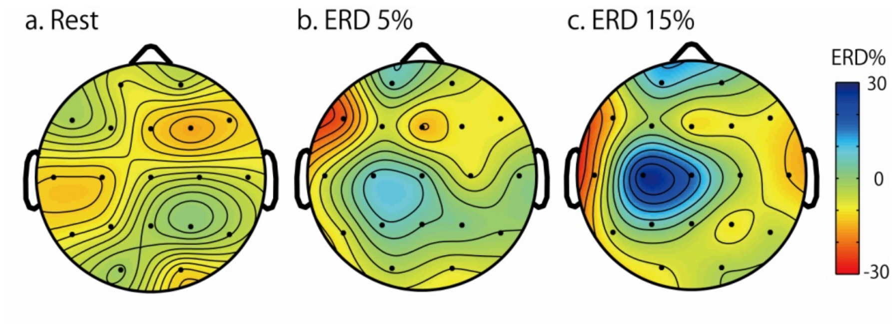

Fig. 2. A subject's ERD topographies across three conditions: rest (a); hand motor imagery at ERD 5% (b) and ERD 15% (c) from 19-channel EEG data. Electrode positions are shown by dots. Positive values (blue colors) indicate strong ERD. Adapted from Takemi *et al.* (2013a) [25].

Figure 3 presents individual results of MEP amplitudes induced by the single pulse TMS, SICI and ICF in the resting condition and during motor imagery of right wrist extension at ERD 5% and ERD 15% from 10 healthy participants. MEP amplitudes induced by single pulse TMS (mean ± S.D.) increased from 0.87 ± 0.25 mV in the resting condition to 1.33 ± 0.38 mV in the ERD 5% condition and 1.45 ± 0.48 mV in the ERD 15% condition. SICI reduced from 42.4 ± 17.7% in the resting condition to 56.6 ± 17.2% in the ERD 5% condition and 77.7 ± 13.8% in the ERD 15% condition. SICI monotonically declined with ERD magnitude in 9 out of 10 participants. However, ICF reduced from the resting condition (141.6 ± 34.8%) to the ERD 5% (condition 126.0 ± 24.1%), but not from the resting condition to ERD 15% condition (141.6 ± 30.2%). One-way ANOVA showed that the effect of ERD Condition for MEP amplitudes ($F = 6.44$, $P = .005$) and SICI ($F = 11.8$, $P < .001$) were statistically significant, but not for ICF ($F = 0.90$, $P = .42$). Post-hoc analysis by Bonferroni correction revealed that MEP amplitudes were significantly larger in the ERD 5% ($P = .016$) and ERD 15% ($P = .009$) conditions compared to the resting condition. SICI at ERD 15% was significantly smaller than at ERD 5% ($P = .022$) and at rest ($P < .001$).

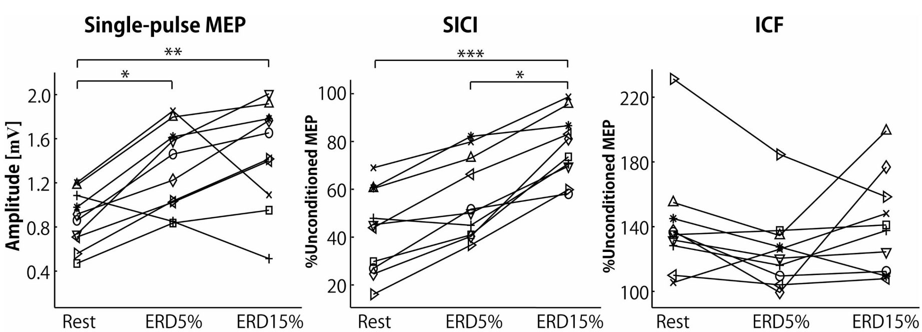

Fig. 3. Individual of MEP amplitudes induced by the single pulse TMS, SICI and ICF in 10 healthy participants. ** $P < 0.01$, ** $P < 0.01$, *** $P < 0.001$. Adapted from Takemi *et al.* (2013a) [25].

3.2 Experiment 2: ERD and Spinal Motoneuronal Excitability

Figure 5 represents individual results of F-wave persistence, trial average and response average of F-wave amplitude in the resting condition and during motor imagery of right wrist extension in the ERD 5% and ERD 15% conditions from 10 healthy participants. F-wave persistence increased from 38.4 ± 16.4% in the resting condition to 49.0 ± 15.2% in the ERD 5% condition and 60.0 ± 16.9% in the ERD 15% condition. F-wave persistence monotonically increased with ERD magnitude in 7 out of 10 participants. Trial averages of F-wave amplitudes also increased from 60.5 ± 42.5 μV in the resting condition to 101.4 ± 61.8 μV in the ERD 5% condition and 114.8 ± 56.3 μV in the ERD 15% condition. However, response averages of F-wave amplitudes were statistically unchanged, from 145.0 ± 46.6 μV in the resting condition to 204.4 ± 99.4 μV in the ERD 5% condition and 189.7 ± 85.3 μV in the ERD 15% condition. One-way ANOVA showed that the effect of ERD Condition for F-wave persistence (F = 4.46, P = .02) was statistically significant, but not for trial average of F-wave amplitudes (F = 2.73, P = .08) and response average of F-wave amplitudes (F = 1.48, P = .24). Post-hoc analysis by Bonferroni correction revealed that F-wave persistence at ERD 15% was greater than at rest (P = .03).

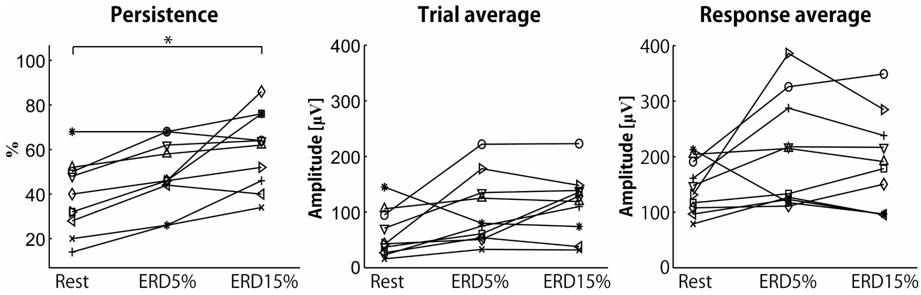

Fig. 4. Individual of F-wave persistence and trial and response averages of amplitude in 10 healthy participants. * $P < 0.05$.

4 Discussion

Numerous studies have examined the changes of corticospinal excitability during motor imagery by using single pulse TMS [13]-[16], and have reported that motor imagery significantly increases corticospinal excitability. Furthermore, Pattuzo et al. (2003) showed that SICI was significantly reduced during hand motor imagery, but not ICF [13]. Our results are in agreement with those studies. We showed that single-pulse MEP size was larger during motor imagery. In addition, and most importantly, we found that the reduction of SICI was related to the increase of ERD magnitude. While MEP amplitude induced by single pulse TMS is thought to be related to contralateral corticospinal tract excitability, SICI and ICF seem to reflect the excitability of distinct inhibitory and excitatory interneuronal circuits within M1 [11]. As it was reported that $GABA_A$ agonists enhance SICI [17] and N-methyl-D-aspartate antagonists abolish ICF [18], we suggest that ERD magnitude during motor imagery is associated with an increase in contralateral M1 excitability, which is mediated by a down-regulation of GABAergic activity.

Our results are comparable to previous reports investigating changes in cortical excitability during human voluntary movement. MEPs in response to single pulse TMS were strongly augmented in a period of 90–100 ms before the onset of voluntary EMG activity [19]. In addition, whereas ICF augmentation was small, SICI decreased gradually and disappeared 60 ms before voluntary EMG [19]. Reynolds and Ashby (1999) reported that the increase of MEP in response to single pulse TMS and the decrease of SICI were significant before the onset of voluntary movement, while the decrease of SICI appeared before the increase of MEP by single pulse TMS [20]. Alegre et al. (2003) also demonstrated that a decrease in beta band EEG activity began contralaterally approximately 1.5 s prior to the onset of movement, and that the decrease began in the alpha band at 1 s before the movement [21]. Thus, overall, these results suggest that ERD during motor imagery may induce changes in cortical excitability, which is similar to the changes accompanying actual movements and their anticipation.

We also found that the magnitude of ERD during hand motor imagery was associated with a significant increase in F-wave persistence, but no significant changes were found in the trial average and response average of F-wave amplitude. Rivner (2008) reported that the increase in response average of F-wave amplitudes, disregarding absent responses, would indicate a shift in the motor neurons recruited from smaller ones to larger ones [22]. In contrast, persistence or the number of F-wave per 50 stimuli is probably the best measure of an increase in spinal motoneuronal excitability [22]. Based on the previous findings, our results indicate that the magnitude of ERD during motor imagery has an effect on the general excitability of the motoneuron pool, but not on the type of motoneuron excited. The result of Rossini et al. (1999), that motor imagery increased the excitabilities of both M1 and spinal motoneuron pool [14], has a close resemblance to the present result. In contrast, some papers reported that motor imagery significantly increased MEP amplitudes, but not in F-wave persistence [16][17]. These inconsistencies may result from two reasons. First, since a recent study showed that more than 50 stimuli are needed to adequately measure F-wave persistence [24], the previous studies, which used fewer than 50 stimuli, may not properly evaluate the excitability of spinal motoneuron pool [15][16]. The second reason is the difficulties associated with motor imagery performance due to fatigue and lapse of concentration. In the present study, since we collected fifty F-waves and monitored the state of motor imagery by ERD, these problems have been resolved.

We can only speculate on physiological mechanisms underlying ERD during hand motor imagery facilitates spinal motoneuronal excitability. A previous report showed facilitation of F-wave following subthreshold TMS timed to collide on the spinal motor neurons [24]. In the previous study, the authors emphasized the very transient nature of the spinal motoneuronal excitability change, which returned to baseline unless the subliminary cortical motor neurons drive exactly coincided with the antidromic activity for recurrent discharge. Thus, based on this previous report and our finding, we suggest that ERD by hand motor imagery induces subliminal central drives, and plays an important role in increasing the excitability of the spinal motoneurons.

Our data indicate that ERD during motor imagery increases M1 excitability by decreasing the activity of GABAergic inhibitory interneurons. In addition, we found that ERD magnitude during hand motor imagery represents the excitabilities of both the contralateral M1 and ipsilateral spinal motorneuon pool. This study provides electrophysiological evidence that ERD-based BCI, which is a promising new intervention for neurorehabilitation in stroke, may be useful as a tool to allow users to voluntarily increase or decrease corticospinal excitability based on their intention. Through this BCI framework, stroke patients may learn to increase corticospinal excitability by repeated use of the BCI, resulting in use-dependent functional recovery.

5 Jury Selection Factors and Recent Work

The project is a novel application of a BCI, and includes new methodologies that rely on new and interesting combination of equipment and ideas. This work includes not just one novel hardware or software development, but a fairly novel combination of complex tools including EEG, MEP recording, and TMS that could be promising together. Award Criteria such as speed and accuracy were not relevant, since the BCI was not intended for online communication. Although the work does not include recording with patients or other potential users – only healthy subjects – the results could certainly benefit stroke patients with upper limb hemiplegia.

Since the 2012 Award, newer research has supported the work described here. Some of the results from this chapter, and newer information, was published in the Journal of Neurophysiology in 2013 [25] and presented as the well-known international IEEE conference series [26]. Although the authors focused on stroke rehabilitation, later versions of this technology could benefit many people with other movement disorders resulting from stroke or other causes.

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Electrocorticographic Control of a Prosthetic Hand in Paralyzed Patients

ECoG Control of a Prosthetic Hand

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Abstract. Paralyzed patients would benefit from movement restoration afforded by electrocorticography (ECoG)–controlled prosthetics. However, it is unclear whether ECoG signals from chronically paralyzed patients provide sufficient motor information and, if they do, whether they can be used for prosthetic control.

We recorded ECoG signals from sensorimotor cortices of 12 patients with various degrees of sensorimotor impairment executing or attempting to execute simple hand movements. Time-frequency and decoding analyses were performed with the patients' ECoG signals.

In all patients, the high gamma power of the ECoG signals during movements clearly responded to different movement types and could be used to successfully discriminate them. However, classification accuracies were significantly lower in severely impaired patients. Finally, some patients used the method to control a prosthetic arm in real time. ECoG signals appear useful for prosthetic arm control and may provide clinically feasible motor restoration for paralyzed patients.

Keywords. Electrocorticogram, Prosthetic arm control, cortical reorganization.

1 Introduction

Paralyzed patients and amputees would benefit from cortically controlled prosthetics in the form of a brain–computer interface (BCI). Among the possible cortical signals available for such an interface, electrocorticography (ECoG) signals are among the most clinically feasible, having superior long-term stability and fewer technical difficulties compared with other invasive signals [1, 2]. Evidence from studies with non-paretic patients with epilepsy shows that some movements or movement intentions can be inferred from ECoG signals accurately enough to control external devices such as a computer cursor [3, 4]. However, it is unclear whether these findings are applicable to paralyzed patients, whose sensorimotor cortices may have undergone extensive reorganization after deefferentation and deafferentation of the paralyzed body parts.

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We examined ECoG signals of non-paralyzed patients and patients with different levels of motor dysfunctions to quantitatively address three questions: (1) Do the ECoG signals of patients with chronic motor dysfunctions show preservation of spatiotemporal patterns of activation even after reorganization? (2) How much are ECoG activation maps for different motor tasks modified in the reorganized sensorimotor cortex? (3) Can ECoG activation be used to control a prosthetic arm?

2 Patients and Methods

2.1 Patient Population

Twelve patients (four female, eight male; age range 13 to 66) with subdural electrodes participated in this study. The patients had different degrees of motor dysfunctions and sensory disturbances (Table 1). All participants or their guardians gave written informed consent to participate in the study, which was approved by the Ethics Committee of Osaka University Hospital.

Table 1. Clinical profiles

No.	Age/sex	Diagnosis	Duration of disease (y)	Paresis on affected limb (MMT)	Sensation on affected limb
N1	34/F	R intractable epilepsy	19	None	Normal
N2	14/M	R intractable epilepsy	7	None	Normal
N3	20/F	L intractable epilepsy	6	None	Normal
N4	22/F	R intractable epilepsy	10	None	Normal
N5	13/M	L intractable epilepsy	11	None	Normal
P1	49/M	R putaminal hemorrhage	2	Slightly spastic (5−)	Hypesthesia
P2	66/F	R subcortical infarction	3.3	Spastic (4)	Hypesthesia
P3	64/M	R thalamic hemorrhage	7	Spastic (4)	Hypesthesia
P4	65/M	Ruptured spinal dAVF	8	Spastic (4)	Hypesthesia
S1	31/M	L brachial plexus avulsion	5	Complete (0) *	Anesthesia
S2	49/M	L brachial plexus avulsion	6	Severe (1) *	Severe hypesthesia
S3	47/M	Amputation below L shoulder	3.3	No arm	None

Abbreviations: R, Right; L, Left; MMT, manual muscle test; M, male; F, female; dAVF, dural arteriovenous fistula; *post transplantation of intercostal nerve

2.2 Movement Tasks

Patients performed one of three possible movement tasks: (1) grasping, thumb flexion, and elbow flexion (P1, P2, S1–S3); (2) grasping, pinching, hand-opening, elbow flexion, and tongue protrusion (P3); or (3) grasping, pinching, hand-opening, elbow flexion, and elbow extension (N1–N5, P4). All patients performed grasping and elbow flexion. The patients selected and performed one of the movements within a presented task after being cued with auditory beeps (decoder training session, Fig. 1A). Patients S1–S3 were instructed to attempt the movements of their affected limbs immediately after the auditory cue. After the decoder training session, four patients repeated the same task they had performed during the session, but at self-paced intervals without external cues (free-run session, Fig. 1B).

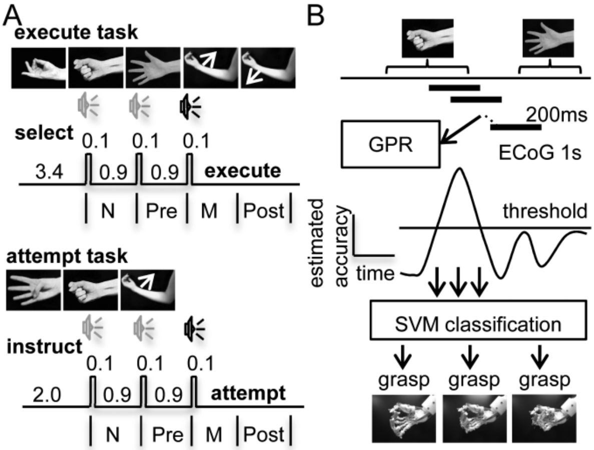

Fig. 1. Task paradigm. (A) The task paradigm during the decoder training session. In the execute task, patients selected and executed one of three (or five) movements after a sound cue. The cue consisted of three beeps 1 s apart that recurred every 5.5 s. The movements were performed with the arm contralateral to the implanted electrodes. The 1-s ECoG signals used for the decoding analysis are shown below the time line: N, used for normalization and resting state; Pre, used as the first period by the GPR decoder; M, used as the move state; and Post, as the last period by the GPR decoder. **(B)** Controlling the prosthetic hand with two decoders. The GPR decoder estimated the accuracy of the time determined to be necessary for the SVM decoder to classify the ECoG signals. The prosthetic hand was controlled incrementally according to the decoding results.

2.3 ECoG Recording and Preprocessing

For each patient, 15 to 60 planar-surface platinum grid electrodes were placed over the sensorimotor cortex and within the central sulcus (intrasulcal electrodes) [5] that covered a broad sensorimotor cortical area, including the hand motor strip. Video recording and electromyographical (EMG electrode, Nihon Koden Co., Tokyo, Japan) recordings of their hands and arms were performed solely to identify the performed movements.

ECoGs were recorded and digitized at a sampling rate of 1,000 Hz. During the decoder training session, the ECoG signals were obtained time-locked to the cue signal. In the free-run session, 1-s duration ECoG signals were recorded online at 200-ms intervals. A fast Fourier transformation (EEGLAB v5.03) was performed for each 1-s signal to obtain the power of each of the three frequency bands (2–8, 8–25, and 80–150 Hz) for each electrode. We used fast Fourier transform to complete the online decoding over the 200 ms. The three frequency bands were chosen based on our previous studies [6].

2.4 Decoding Algorithms and Prosthetic Hand Control

To infer, or decode, the movement types executed or attempted by the patients, we constructed a linear classifier trained by a linear support vector machine (the SVM decoder) [5, 7]. The trained SVM decoder was inputted with the ECoG signals to output an inferred movement type. A five-fold cross-validation was used to test how well the decoder could generalize.

To apply the SVM decoder to the free-run sessions without external cues, we developed another decoder (GPR decoder). The trained GPR decoder was also inputted with the ECoG signals to output an estimated classification accuracy of the SVM decoder. When the estimated classification accuracy exceeded a certain threshold value (Fig. 1B), the SVM decoder classified the ECoG signals to infer the intended movement [8].

The GPR decoder was trained with the classification accuracies and the three frequency band powers of three time domains (Pre, M, and Post in Fig. 1A). The trained GPR decoder estimated the classification accuracy with the three frequency band powers at a given time in a free-run session.

The commands to the prosthetic arm were updated by the host computer system every 200 ms. When the SVM decoder inferred a movement type, the posture of the prosthetic arm was partially altered to match the posture of the inferred movement. Completing a movement required two or three consecutive matched decodings.

2.5 Offline Analyses

The ECoG signals of grasping and elbow flexion were compared among patients. A Hilbert transformation (EEGLAB v5.03) was used to obtain the temporal power spectral density of each frequency band. The temporal powers were normalized by powers of the initial 1-s period (−2 to −1 s) of each trial.

The variability of the high gamma power of 0–1 s was statistically evaluated among two types of movements by the F-value obtained by one-way analysis of variance for each electrode. The classification accuracies for inferring two movements using the SVM decoder with the high gamma powers were compared among patients.

3 Results

3.1 Time-Frequency Analysis

The power spectrum of the ECoG signals showed some characteristic modulations among patients. Figure 2B illustrates examples of the power spectrum time-locked to the external cues while patients were grasping or attempting to grasp. An increase in the high gamma power and decreases in the alpha and beta powers were consistently observed for all patients with different levels of motor dysfunctions. The spatial distributions of the high gamma power during movement (0–1 s) obviously differed for each movement (Fig. 2C), and the analysis of variance F-value revealed that high gamma powers were significantly modulated between the movements. Notably, the powers around the central sulcus differed significantly ($p < 0.05$). The characteristic modulations of the high gamma power were consistently observed among all patients, although the F-values pertaining to variability were lower in patients with severe dysfunctions than in other patients.

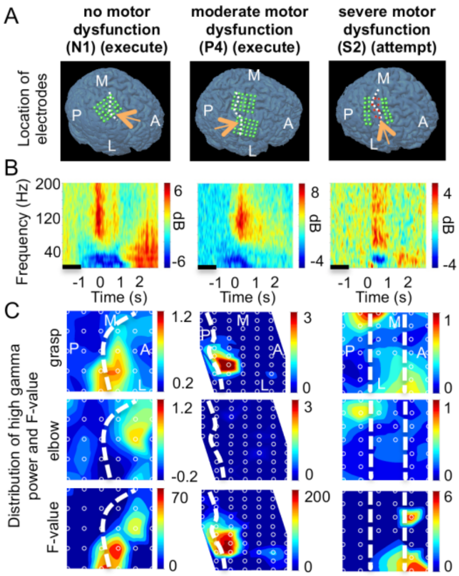

Fig. 2. Representative results of time-frequency analysis. (A) Locations of implanted electrodes for patients N1, P4, and S2 are indicated by the green (implanted on the brain surface) and red (implanted within the central sulcus) filled circles on the three-dimensional brain renderings of MRI volumes. The dashed white lines indicate the location of the central sulcus. **(B)** Power spectra of the ECoG signals recorded during grasping (execute) or attempting to grasp from the electrodes indicated by the orange arrows in **(A)**. The black horizontal bars show the 1,000-ms period used for normalization. Time 0 corresponds to the onset cue. **(C)** The high gamma power is color-coded to the location of the electrodes for grasping and elbow flexion. The direction indicators correspond to A, anterior; P, posterior; M, medial; L, lateral on the brain. The white dashed lines and the white circles indicate the locations of the central sulcus and the electrodes, respectively. For patient S2, the electrodes between the two white lines were located within the central sulcus (intrasulcal electrodes). The bottom panel for each patient shows the distribution of the F-value with statistical significance ($p < 0.05$).

3.2 Decoding Analysis

The accuracy of classifying (i.e., decoding) the movements was compared among the frequency band powers at each time. Figure 3A shows the color-coded percentage of correct movement classifications averaged over each patient group. Regardless of the level of motor dysfunction, the two movement types were best inferred by using the high gamma power around the movement onset.

The movement classifications were carried out for all patients with a high gamma power for 0–1 s. The classification accuracy of patients S1–S3 was significantly inferior to that of patients N1–N5 (Fig. 3B). However, these accuracies were still above levels that would occur by chance (50%). In contrast, the accuracies in the classifications of the resting state (−2 to −1 s) and the movement state (0 to 1 s) were not significantly different among the three patient groups (Fig. 3B).

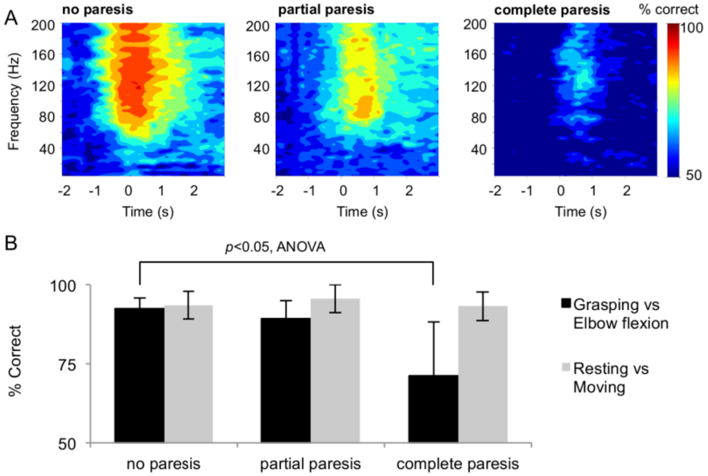

Fig. 3. Classification accuracy with frequency band power. (A) Classification accuracies at each frequency band power were averaged for the patients of each group and color-coded at the center of each frequency band and time domain. Time 0 corresponds to the sound cue for the movements. **(B)** The mean and standard error of movement classifications with a high gamma power (80–150 Hz) among three groups of patients.

3.3 Decoding in Free-Run and Real-Time Control of a Prosthetic Hand

Using the decoders trained with the high gamma power, the ECoG signals were decoded in real time while the patient voluntarily (i.e., without cue) performed the three types of movements (free-run period, Fig. 4). The prosthetic arm was controlled according to the decoding results of the SVM and GPR decoders, mimicking the hand movements of the patients. For patient P4, the prosthetic hand completed the same movement in 42 out of 48 attempts (87.5%). Each hand movement required an average of 2.2 incremental movements of 4.2 s each. Moreover, 4 days after the first experiments (second free-run), the patient was still able to perform the same free-run task (Table 2) with the decoder trained in those initial experiments. The three other participating patients (N1, N3, and N4) were also able to voluntarily control the prosthetic arm (Table 2).

Fig. 4. Prosthetic control with the ECoG signals. Representative photographs of the prosthetic arm controlled in real time by the ECoG signals of patient P4.

Table 2. Summary of the real-time control of the prosthetic hand

Patient no. and session		Hand movements (grasp, pinch, open)			
		% Correct of training	% Correct to complete (correct/trial)	% Correct of SVM decoder in free-run	Time/count to complete (s/count)
N1	1st	79.2	71.2 (37/52)	76.1	1.8/3.3
	2nd		51.2 (22/43)	67.0	1.5/3.3
N3	1st	70.0	85.7 (30/35)	80.7	1.6/3.3
	2nd		47.2 (17/36)	81.0	1.3/2.7
N4	1st	60.8	64.7 (11/17)	70.3	1.3/3.7
	2nd		—	—	—
P4	1st	80.8	87.5 (42/48)	68.8	2.2/4.2
	2nd		62.4 (63/101)	62.3	2.0/4.1
Mean ± SD		72.7 ± 9.2	77.3 ± 11.1	74.0 ± 5.5	1.7 ± 0.4/3.6 ± 0.4
			53.6 ± 7.8	70.1 ± 9.7	1.6 ± 0.4/3.6 ± 0.7

4 Discussion

We have shown that ECoG signals recorded from patients with chronic motor dysfunctions still represented motor information via high gamma power to a degree that the signals could be decoded successfully enough to control a prosthetic hand. However, the modulation of the representation for different movements may have deteriorated depending on the degree of impairment. Our quantitative evaluation of motor representations in the reorganized cortex elucidated pathological states of patients with motor dysfunctions and demonstrated the applicability of these representations for an ECoG-based BCI to improve patients' quality of life.

4.1 Preserved Features Following Cortical Reorganization

The decoding analysis showed that modulation of the high gamma power provided the most information about the movement types. This result was consistent with previous results showing that human movements can be inferred from ECoG signals [3, 4, 9]. Our results suggest that the basic features of cortical processing with high gamma powers are preserved following cortical reorganization resulting from motor dysfunctions.

4.2 Prosthetic Hand Control Applied to a Diverse Patient Population

Successful control of the prosthetic arm was demonstrated with the SVM and GPR decoders, which accurately inferred various movement types from the ECoG signals of patients with motor dysfunctions. This result suggests the feasibility of restoring purposeful movement with a BCI. Although the cortical control of some prostheses has already been demonstrated with other invasive signals [10], our success with the ECoG signals may be beneficial for clinical applications because an ECoG-based BCI exhibits signal stability and durability, which are essential for clinical applications [2]. As we demonstrated, the prosthetic hand could be controlled for several days with a single decoder trained once at the first session. This result reveals the robustness of our decoding method and the stability of the ECoG signals. Moreover, our method was demonstrated with an elderly patient who was able to naturally control the prosthetic arm without any prior training. A requisite for a clinically useful BCI system is that it be stable and easily used by a diverse population of patients in their daily lives.

5 Jury Selection and Recent Work

There are many reasons why this project scored high with the jury. Two of the Award Criteria are whether the approach could benefit patients, and whether any results were obtained from patients or potential users. The benefit to patients is clear, and the work described entailed many different patients, in clinical settings, who had a variety of sensory and motor deficits. The technology could be used by patients in real-time (another jury selection factor) without training. The jury appreciated the improvement in usability that a natural, easy to learn prosthetic hand could represent. Control of prosthetic limbs remains time consuming and inconvenient. The results for speed and accuracy presented in this chapter were impressive given the challenges inherent in the technology itself and working with ECoG patients in real-world settings. The jury also felt that the work was a novel application of BCI technology and involved new methods, including automated software to adapt to individual users' gamma activity based on ECoG activity.

Since the 2012 Award, the research directions presented here have remained promising. Later work from the chapter authors further supported the possible applications of high gamma activity for BCIs and related technologies, including not just prosthetic limb control but also surgery for epilepsy or tumors (Yanagisawa et al., 2012; Ritaccio et al., 2013). These high gamma signals cannot be precisely detected with electrodes mounted on the scalp, and so ECoG electrodes may represent an increasingly common choice when surgery is necessary.

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Recent Advances in Brain-Computer Interface Research – A Summary of the BCI Award 2012 and BCI Research Trends

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Each of the preceding chapters reviewed one of the projects nominated for a 2012 BCI Award. Many of these projects have already led to new follow-up work, and the nominees are generally still very active in the research community. This concluding chapter presents the 2012 BCI Award winner, then explores some trends that have become apparent through the BCI Award procedure. Finally, we preview future awards and directions.

1 The 2012 Winner

Since most of the 68 submissions were excellent, the jury had a very difficult time choosing the ten nominees. The jury's next task was even harder: choosing the winner of the 2012 BCI Award. In addition to the honor of being chosen, the award of $3000, and the statue, the winner was also publicly announced at the Society for Neuroscience conference in October 2012.

The winning team was Surjo R. Soekadar and Niels Birbaumer from the Applied Neurotechnology Lab, University Hospital Tübingen and Institute of Medical Psychology and Behavioral Neurobiology of the Eberhard Karls University Tübingen in Germany. The project was titled "Improving Efficacy of Ipsilesional Brain-Computer Interface Training in Neurorehabilitation of Chronic Stroke".

This work highlights a critical need to expand BCI research efforts to other clinical populations with motor disabilities. Historically, BCIs have been used in patients with motor impairments resulting from peripheral impairments, such as spinal cord injury and ALS, but with an intact brain. While these patients should certainly benefit from BCI technologies, these patient populations are relatively small given the broader epidemiologic impact of stroke. Here, Soekadar and Birbaumer highlight how their BCI methods can act not just as a component of a control system, but as a tool that can facilitate brain plasticity and rehabilitation for patients with stroke. This is an important advance that highlights a distinct and exciting new arena for BCI technology.

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Fig. 1. And **the winner is....**This picture presents the winner, as well as some jury members and organizers congratulating the winner. From left to right: Surjo R. Soekadar (holding the Award), Leigh Hochberg, Gerwin Schalk, Junichi Ushiba and Christoph Guger.

2 Directions and Trends Reflected in the Awards

One of the goals of the BCI Award is to help identify major directions in BCI Research. By analyzing the different characteristics of the projects that were nominated in 2012, we can learn more about which facets were most appealing to the jury. Table 1 summarizes the BCI Award 2012 nominees. The nominees are categorized according to the control signals that were utilized and application areas.

Table 1. Summary of the 2012 BCI Award nominees

Title	**Control Signal**						**Application**					
	ECoG	Spike	EEG	fMRI	SSVEP	MI	Robot	Stroke	Control	Connectivity	Monitoring	Vision
Intracortical control of assistive devices by individuals with tetraplegia.		X				X	X					
Brainatic: A system for real-time epileptic seizure prediction.			X								X	
Combining brain-computer interfaces and haptics: detecting mental workload to adapt haptic assistance.			X			X			X			
Reading visual Braille with a retinal prosthesis.		X										X
Ear-EEG: User-centered, wearable & 24/7 BCI.			X		X				X			

Table 1. (*continued*)

A novel brain-computer interface for chronic stroke patients.			X			X		X				
Brain connectivity and semantic priming enhancement using brain computer interfaces based on real-time fMRI neurofeedback.				X						X		
Improving efficacy of ipsilesional brain-computer interface training in neurorehabilitation of chronic stroke.			X			X		X				
Online estimate of event-related desynchronization by hand motor imagery is associated with corticospinal excitability-physiological evidence for brain-computer interface based neurorehabilitation.			X			X		X				
Electrocorticographic control of prosthetic hands in paralyzed patients.	X					X			X			

The BCI Award is also meant to show trends, such as themes that become more or less popular across different years. To more broadly explore the different facets of BCI research, we conducted another analysis that also included the 64 projects submitted to the 2011 BCI Award and the 57 projects submitted to the 2010 BCI Award. Table 2 summarizes the results.

Table 2. Properties of projects submitted to the BCI Awards in 2010, 2011, and 2012. N refers to the number of submissions for each year. The number in each cell reflects the percentage of submissions with that property.

Property	**N**	**2012 % (N=68)**	**2011 % (N=64)**	**2010% (N=57)**	**Property**	**N**	**2012 % (N=68)**	**2011 % (N=64)**	**2010% (N=57)**
Real-time BCI	64	94.1	95.3	65.2	Stroke/Neural plasticity	18	26.5	12.5	7.0
Off-line algorithms	3	4.4	3.1	17.5	Spelling	17	25.0	12.5	19.3
P300, N200	21	30.9	25	29.8	Wheelchair/Robot/Prosthetics	6	8.8	6.2	7.0
SSVEP/SSSEP	11	16.2	12.5	8.9	Internet/VR/Game	2	2.9	3.1	8.8
Motor imagery	21	30.9	29.7	40.4	Control	14	20.6	34.4	17.5
ASSR	-	-	1.6	-	Platform/Technology	11	16.2	9.4	12.3
EEG	48	70.6	70.3	75.4	Monitoring	3	4.4	1.6	-
fMRI	1	1.5	3.1	3.5	Depression	1	1.5	-	-

Table 2. (*continued*)

ECoG	9	13.3	4.7	3.5	Simulation	1	1.5	-	-
NIRS	1	1.5	4.7	1.8	Authentification/Speech /Coma	-	-	9.4	-
Spikes	7	10.3	12.5	-	Mechanical ventilation	-	-	1.6	-
Other signals	2	2.9	1.6	-	Learning	2	1.5	3.1	-
Electrodes	1	1.5	1.6	-	Vision	1	1.5	-	-
Neuromarket ing	1	1.5	-	-	Connectivity	1	1.5	-	-

The 2012 Award showed ongoing trends toward submissions that described real-time BCIs, steady-state BCIs, invasive BCIs, and stroke/neural plasticity. On the other hand, the overall prevalence of EEG-based submissions remained roughly stable, with 70.3-75.4% of total submissions in 2010, 2011, and 2012. Other non-invasive approaches such as fMRI, NIRS, MEG, or other signals were not strongly represented in the submissions across these three years. However, MEG and fMRI work was presented in two chapters (including the winner). Furthermore, three of the nominated projects (including the winner) involved transcranial stimulation, which was not characteristic of many submissions. Thus, MEG, fMRI, and transcranial methods could reflect emerging opportunities, since they scored well despite being relatively uncommon.

3 Conclusion and Future Directions

Overall, the BCI Awards have helped to encourage excellence in BCI research, identify key directions, and promote BCI research around the world. The projects summarized in this book represent some of the most promising accomplishments from the top research groups. Although many submissions scored high on some **Award Criteria**, these projects had some of the most promising ideas, devices, methods, and results that could ultimately help a growing number of real-world users. The updated work from each group, developed in late 2013, has generally shown that the nominated groups continued to produce high-impact research with the ideas presented in their chapters. Hence, the jury's decisions seem further justified by the nominees' follow-up work.

g.tec hosted the fourth annual BCI Award in 2013. This BCI Award was the most competitive ever, with over 160 submissions, showing the growing interest in both BCI research and the BCI Award. The winner was announced at a ceremony attached to the Fifth International BCI conference in Pacific Grove, California in June 2013. The nominees, winning team, and additional information can be found at bci-award.com.

This website will also include information about the BCI Award in future years, including the submission instructions and deadline. We also plan to continue this book series to highlight the top BCI projects each year, including a book coming soon summarizing the 2013 nominees, their follow-up work, and further analyses of major trends. Given the outstanding submissions in recent years, and the ongoing increase in BCI research, we expect that future awards will be even more competitive.

We editors would like to conclude by thanking the groups that submitted BCI Awards in 2012, and in prior years, as well as the jury and staff who helped make the award possible. We also thank our many colleagues in BCI research whose enthusiasm and devotion have been responsible for the many fascinating and promising developments in our research field. Finally, we thank you, the reader, for your interest in the 2012 Awards and BCI research in general.

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