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Using brain–computer interfaces to induce neural plasticity and restore function

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Abstract

Analyzing neural signals and providing feedback in realtime is one of the core characteristics of a brain–computer interface (BCI). As this feature may be employed to induce neural plasticity, utilizing BCI technology for therapeutic purposes is increasingly gaining popularity in the BCI community. In this paper, we discuss the state-of-the-art of research on this topic, address the principles of and challenges in inducing neural plasticity by means of a BCI, and delineate the problems of study design and outcome evaluation arising in this context. We conclude with a list of open questions and recommendations for future research in this field.

1. Introduction

While in the past decade research on brain–computer interfaces (BCIs) was primarily focused on providing alternative communication devices, recent years have witnessed a growing interest in extending the application range of BCI technology. Among these new research directions, the use of BCIs for inducing neural plasticity and restoring function has gained particular attention, as it substantially enlarges the size of the population that may benefit from BCI technology. A particular emphasis of this paper will be on stroke rehabilitation, as stroke is one of the leading causes of long-term motor disability among adults. Furthermore, despite intensive rehabilitative efforts, about one-third of affected patients show poor recovery 1 year post-stroke [1]. Here, BCI technology could complement traditional rehabilitation efforts by providing patients with feedback on their brain states, which may be utilized to support the process of cortical reorganization required for functional recovery. The potential utility of BCI technology, however, is certainly not limited to stroke rehabilitation. In general, BCI technology may be applicable whenever the long-term changes of cortical connectivity, induced by some form of feedback, can be expected to have a beneficial impact on quality-of-life measures. Many open questions and

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technological problems remain to be addressed, however, before BCI technology may be routinely used for such purposes.

In this paper, we summarize the discussions of the one-day workshop that was held on this topic at the 4th International BCI Meeting 2010 in Asilomar, CA, USA. In particular, we review the state-of-the-art as discussed at the workshop in section 2, address the problems and technical challenges in inducing neural plasticity in section 3, and broach the intricate issue of study design in section 4. We conclude with a list of open problems and recommendations that the workshop participants considered crucial for establishing a beneficial impact of BCI technology on therapeutic efforts.

2. State-of-the-art

In this section, we give a brief overview of the state-ofthe-art in this field as discussed at the workshop. A more general overview can be found in [2]. In general, diverse patient groups with a variety of cognitive disorders may benefit from receiving feedback on their neural states, including but not limited to those affected by stroke, epilepsy, ADHD, chronic pain, Parkinson's disease, schizophrenia, and anxiety disorders. Unfortunately, for most patient groups, empirical evidence for a positive impact of BCI technology is scarce. Notable exceptions are in the domain of epilepsy research and treatment of ADHD. In [3], evidence is presented that the volitional modulation of slow cortical potentials (SCPs) positively affects the seizure frequency of epileptic patients. Also utilizing SCPs, Strehl *et al* [4] demonstrate a beneficial effect of neuro-feedback on ADHD symptoms. While these studies provide proof of principles for a positive impact of BCI technology in specific patient groups, such studies remain outstanding in other domains. There have been substantial efforts in utilizing BCI technology for stroke rehabilitation, and stroke patients have been shown to be capable of operating a BCI based on MEG [5] and ECoG [6]. Empirical evidence to date, however, does not provide a convincing demonstration of a positive impact of BCI technology on functional recovery in this patient group [5, 7]. Potential explanations for this are discussed in section 3. For most potential patient groups, convincing demonstrations of the utility of BCI technology thus remain outstanding.

3. Inducing neural plasticity

When speaking of the induction of neural plasticity, it is important to be aware that neural plasticity may refer to a multitude of different processes of reorganization within the brain, each of which affects the way information is processed and may ultimately result in behavioral changes. These processes include, but are not limited to, the sprouting of new axons, changes in synaptic strengths, or even the formation of new neurons [8]. When investigating neural plasticity, it is thus crucial to precisely define what kind of metric is being used to measure experimental outcomes, e.g., whether changes are measured on a neuro-physiological or behavioral level. This issue will be discussed in more detail in section 4. In this paper, we define the induction of neural plasticity as the process by which lasting—if not permanent—changes leading to desirable behavioral outcomes are caused by feedback of neural states. We consider any signal that is derived from recordings of the neural activity as a representation of a neural state. Note that there exists some controversy about what qualifies a system as a BCI [9]. Here, we consider a BCI to represent a system that provides a signal to its user that is a deterministic function of her or his brain activity. According to this definition, any BCI constitutes a neuro-feedback system that may possess the capability of inducing neural plasticity.

These considerations naturally lead to the question why neuro-feedback procedures may affect behavior, i.e., the neural basis for inducing plasticity by means of BCI technology. This certainly constitutes a complex process, and may vary substantially across patient groups and experimental paradigms. One common concept crucial for the induction of neural plasticity may be that of Hebbian plasticity: coincident activation of pre-synaptic and post-synaptic neurons reinforces synaptic strength, resulting in increased and more reliable communication between the activated neurons. The potential relevance of this concept for changes in behavior can be illustrated particularly well in the context of stroke rehabilitation [10]: assuming that the connection between peripheral muscles and the sensorimotor cortex has been disrupted due to a sub-cortical stroke, a coincident activation of sensory feedback loops and primary motor cortex may reinforce previously dormant cortical connections by Hebbian plasticity and thus support functional recovery. Here, BCI technology may be used to detect primary motor cortex activation, i.e. movement intent, and provide matching sensory stimulation according to some haptic feedback procedures.

Unfortunately, it is currently unclear which properties of a BCI system are relevant for inducing neural plasticity. This is of particular relevance because, to date, optimization of BCI technology primarily focuses on speeding up its performance for communication purposes. While certain characteristics of BCIs relevant for communication can also be expected to be of importance for therapeutic purposes, there may be challenges in BCI design unique to the problem of inducing neural plasticity. In the following, we discuss several characteristics of BCI systems that the workshop participants considered likely to affect the extent of induced plasticity.

- *Choice of neural states for feedback.* There was a consensus among the workshop participants that the choice of neural states employed for feedback will have a large impact on experimental outcomes. In most patient groups, however, it is at present unclear which neural states may be optimal for inducing beneficial long-term changes in behavior. In particular, this concerns the choice of the signal modality (e.g., single-cell recordings, fMRI, EEG, ECoG, or MEG), the brain areas from which signals are recorded, and the signal characteristics (e.g., spike rate, bandpower and coherence) that are utilized for providing feedback. In general, the choice of the neural states used for feedback may be driven by prior knowledge of desirable brain states, or it may be outcome driven. In the former case, certain target areas and signal characteristics may be identified in advance, and BCI technology may be designed to utilize these features only. The drawback of this approach would be that the chosen brain areas and signal characteristics may not be optimal for providing accurate feedback. The outcome-driven determination of neural states, on the other hand, would aim to identify those brain states that are optimal for providing accurate feedback, at the probable expense of employing neural signals unsuitable for inducing beneficial changes in behavior. For example, hemiparetic stroke patients who are being trained with a BCI based on motor imagery may learn to control the BCI by motor imagery involving ipsilesional cortical areas. While this could result in good BCI performance, it may not induce the desired behavioral changes. Ultimately, a methodology would be desirable that learns which neural states to use for optimal feedback accuracy, while allowing the exclusion of certain (anatomically or functionally) pre-defined brain areas or signal characteristics.

- *Feedback accuracy.* It appears to be generally acknowledged that task learning requires accurate feedback. This also holds in the domain of BCIs, with recent evidence suggesting that subjects perform worse if they receive inaccurate feedback on their neural states [11]. While the relation of feedback accuracy and the induction of neural plasticity remains unexplored, it appears sensible to assume that a high degree of feedback accuracy, i.e. a low classification error, is crucial for inducing neural plasticity by means of BCI technology. Accordingly, a BCI for communication as well as a BCI for rehabilitation aims for high classification accuracies. There is one potentially crucial difference, though, in which the latter may differ from the former. While only the objective classification accuracy is relevant for communication purposes, in a rehabilitation setting the subjectively perceived classification accuracy may have an impact on the induction of neural plasticity and thus on subsequent behavioral changes. While the objective and subjective feedback accuracy can be expected to be highly correlated, careful design of feedback procedures may have a beneficial impact on the perceived feedback accuracy for identical classification errors. Unfortunately, an investigation of the impact of the perceived feedback accuracy on the extent of behavioral changes in neuro-feedback paradigms remains outstanding.

- *Feedback delay.* If neural plasticity relies on Hebbian-type learning rules, then the delay between the measurement of a neural state and the subsequent feedback of this state to the subject is of crucial importance. Any feedback that does not fulfill the requirement of coincident activation of the targeted brain regions is unlikely to result in long-term behavioral changes. This issue may be one cause of the so far only moderate success of utilizing BCI technology for stroke rehabilitation [5, 7], as in these studies haptic feedback was not synchronized with movement intent. The maximum feedback delay that still induces coincident activation in the sense of Hebbian learning, however, remains unknown. The workshop participants expected this upper limit to be of the order of 200–300 ms, but agreed that this is one of the open questions that needs to be addressed by the community. There may also exist patient groups, however, in which a short feedback delay is not crucial for inducing behavioral changes. It remains to be clarified which applications pose which requirements on feedback delays.

- *Feedback modality.* Typically, BCI systems designed for communication provide visual feedback, as this is usually simple to interpret by the user and easy to realize for the scientist. It should be noted, however, that visual feedback may not be optimal when BCI systems are utilized for therapeutic purposes. First, due to the complexity of the human visual system, processing of visual stimuli is rather slow.

As such, different feedback modalities, e.g., haptic feedback, may result in smaller effective feedback delays, and hence be more suited to inducing neural plasticity. Experience with non-visual feedback, on the other hand, is limited in the BCI community. For example, providing haptic feedback in motor-imagery-based paradigms is likely to have an effect on sensorimotor areas that are used for intention inference, which may result in reduced performance. However, if the introduction of such feedback loops is properly addressed in the design of the BCI system, this may even have a beneficial impact on BCI performance, as indicated by a recent study on haptic feedback in arm movement imagery [12]. Furthermore, it should be noted that feedback does not necessarily have to be provided through the peripheral nervous system. Recurrent BCIs, which are being pioneered by Fetz and collaborators [13], record neural signals invasively from one cortical site, and feedback (a derivative) of these signals into other cortical target areas. Such direct feedback may provide greater control over alterations in neural processes in comparison to feedback delivered through sensory channels.

Unfortunately, the properties of BCI systems that are potentially relevant for inducing neural plasticity can often not be optimized independently. For example, the occasionally low signal-to-noise ratio (SNR) of neural recordings results in feedback accuracy that typically depends on the length of the recording window used to infer a particular neural state, with longer time windows often resulting in increased accuracy [14]. Extending the length of the recording window, on the other hand, necessarily results in an increase in feedback delay. It is an open question which trade-off between good feedback accuracy and small feedback delay is optimal for inducing neural plasticity. Furthermore, the type of feedback modality is likely to affect the perceived level of control over the BCI system as well as the feedback delay, both of which may influence the induction of neural plasticity. It is at present unclear whether such factors can be optimized congruently. In general, the optimal design of BCI systems for inducing neural plasticity and restoring function is in its infancy, and many open questions remain to be answered by the BCI community.

4. Study design

The use of BCI technology for therapeutic purposes poses challenges in study design and outcome evaluation that do not arise in the context of communication. Here, we give a brief overview of these challenges as discussed at the workshop, and formulate recommendations for how to address these challenges.

While classification errors and various measures of the information transfer rate have been widely accepted as metrics for evaluating experimental outcomes when BCIs are used for communication [15], to date no such consensus exists in the field of BCIs for inducing neural plasticity. Ultimately, the *long-term* impact of BCI technology on a patient's quality-of-life should be the relevant measure, e.g., the Fugl-Meyer score in hemiplegic patients [16]. However, aiming to directly optimize behavioral measures may be overly optimistic. Instead, neuro-physiological markers of neural plasticity may be investigated. These should correlate with a beneficial impact on functional recovery, and ideally provide insights into the neural mechanisms of cortical reorganization. One such potential marker would be the topography of brain areas deemed relevant for a certain feedback paradigm, and the changes in this topography over the course of experimental sessions.

As the goal of future studies should be the demonstration of a long-term beneficial impact of BCI technology on functional recovery relative to traditional therapies, randomized controlled trials are required. This poses substantial difficulties in study design, as withholding established treatments from patients is considered unethical. Several potential solutions to this problem exist. First, therapies based on BCI technology may be offered only to patients for whom traditional therapies have been exhausted. While this probably constitutes the least precarious procedure from an ethical point of view, it is probably also accompanied by the least probability of success. Empirical evidence suggests that there is a ‘window-of-opportunity’, in which stroke patients are most susceptible to treatments [8]. BCI-based therapies offered outside of this time frame may have little impact on rehabilitation. Second, block-randomized trials may be employed. In these trials, patients are divided into two groups, each of which receives traditional as well as BCI-based therapy in a reversed chronological order. It should be noted, however, that this procedure is also constrained by the potential window-of-opportunity. Third, one may aim to develop BCI technology that does not replace but complement existing therapies, such that in a worst-case scenario a patient would only receive the benefit of a classical therapy. While this may be the most difficult scenario to realize, it does not raise any ethical concerns in general, and may be feasible in the form of a randomized controlled trial.

5. Conclusions

We conclude this paper with a brief list of recommendations and open problems, derived from the above discussions, that the workshop participants considered crucial for making the use of BCI systems for therapeutic purposes a clinical reality.

First of all, the workshop participants agreed that clinicians should be involved at an early stage of research, and that experimental work should focus on actual patients rather than on healthy subjects. Today, most studies in the field of a BCI are carried out with healthy subjects, even though insights gained from healthy populations may not generalize to patients actually in need of a BCI. Second, it appears crucial to investigate which neuro-physiological changes correlate with functional recovery. Only if such processes are better understood can BCI systems be optimized to provide feedback on those neural states that are optimal for inducing neural plasticity. In the meantime, it is furthermore of importance to elucidate the effect of feedback accuracy as well as feedback delay on the induction of neural plasticity. It may be expected that the perceived level of control of a subject over a BCI system correlates with the extent of induced plasticity. As such, an optimal trade-off between feedback delay and accuracy may be investigated by questioning subjects about their perceived level of control. Fourth, the impact of different feedback modalities on BCI performance, and potential approaches to harness the resulting effects, should be further explored. Finally, all of these intermediate goals should serve the final purpose of demonstrating a beneficial long-term impact of BCI technology on the quality-of-life of diverse patient groups in large-scale randomized controlled trials.

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