

Brain Computer Interfaces (BCIs) based on the P300 Event Related Potential (ERP)

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Abstract

Research in Brain-Computer Interfaces (BCIs) ranges from applications for people with severe motor disorders such as amyotrophic lateral sclerosis (ALS), to applications for the consumer market such as games. During the last decades significant progress has been achieved in this field. BCIs can be based on different techniques that measure brain activity, the most used of them being electroencephalography (EEG). In turn, different EEG signals can be used to control a device via a BCI system, including event related potentials (ERPs) such as the P300. This ERP is particularly interesting for BCI control because it allows to communicate attendance to a choice stimulus with practically no training required. Multimodal presentation enhances P300 amplitude and it is hypothesized to be one way to improve BCI efficiency as attentional capacity for processing concurrent stimuli is larger across sensory modalities than within a single modality. This review focuses on current P300-based BCIs, especially those which use multimodal stimuli. We also cover the differences between P300s elicited in different modalities, suggestions of other ERPs and brain oscillations which might contribute to improve such BCI, and an overview of the neurobiology of multimodal integration. Finally, possible applications of this type of system and proposals for future research are discussed.

Keywords: BCI, P300, EEG, ERP, Multimodal integration

INDEX

Introduction.....	3
Brain-Computer Interfaces.....	4
Definition of BCI.....	4
Types of BCIs.....	5
BCIs based on the P300 ERP.....	6
Event Related Potentials.....	6
The P300 ERP.....	7
Types of P300-based BCIs & applications.....	8
P300 differences across modalities.....	11
Improving P300-based BCIs.....	12
Other ERPs.....	12
Brain Oscillations.....	13
Neurobiology of multimodal integration.....	14
BCI improvement by multimodal stimuli.....	15
Future research.....	17
Faster BCIs: transfer rate & single trials.....	17
Towards a Multi-paradigm BCI.....	18
Assistive technologies and mainstream applications.....	18
Conclusion.....	19
Acknowledgments.....	19
References.....	20

Introduction

A Brain Computer Interface (BCI) is a communication system that allows to control an external device by brain activity without the use of the normal pathway involving also peripheral nerves and muscles (Wolpaw et al., 2002). Thus, BCIs can assist or even augment human cognitive or sensory-motor functions (Wolpaw et al., 2002; Birbaumer, 2006; Millán et al., 2010), or just become a new way of human-computer interaction, for instance in gaming (Allison et al., 2007; Allison et al., 2007b; Nijholt & Tan, 2007; Nijholt et al., 2008; Reuderink, 2008; for review see Bos et al., 2010). Since the mid-90's neuroprosthetic applications are developed for people with severe motor disorders (Hochberg et al., 2006). This breakthrough in BCI research is due to multidisciplinary contributions from Cognitive Neuroscience, Computer Science, Engineering or Mathematics.

Different non-invasive techniques can be used to channel brain activity. The most studied of them is electroencephalography (EEG) due to its fine temporal resolution and despite disadvantages like low spatial resolution, non-stationarity (i.e. high variability over time and space), or presence of artifacts introduced by eye movements. Within EEG there are several electrophysiological characteristics that can be applied to control a BCI system. One of them, the P300 event related potential (ERP), was first reported by Sutton et al. 45 years ago, first used in a BCI 22 years ago (Farwell & Donchin, 1988), and in the past 5 years it has experienced a research boom. Its name is due to its occurrence around 300 ms after presentation of a cognitively salient and/or unexpected stimulus. The P300 is particularly interesting for BCI control because it is a consistent response (Guan et al., 2004) and it allows to communicate attendance to a choice stimulus with the asset that users do not need training. Nonetheless, P300-based BCIs rely also on other ERPs and can be affected by changes in attention, motivation and/or tiredness (Wolpaw et al., 2002).

The P300 component is measured by assessing its amplitude and latency. According to these characteristics two subcomponents have been distinguished: P3a and P3b (Polich, 2007). Each subcomponent has been attributed different neuropsychological and neural circuitry foundations, the P3a being earlier and passive while the P3b comes later and it needs an active subject role (Mühl et al., 2010). How exactly and why the brain produces this ERP remains undetermined. Amplitude, shape and topography of the P300 are influenced by various factors, such as the target-to-standard ratio, the presentation modality, attendance and task relevance. Moreover, multimodal presentation enhances P300 amplitude (Brouwer et al., 2010) and it is hypothesized to be one way to improve BCI efficiency as attentional capacity for processing concurrent stimuli is larger across sensory modalities than within a single modality (Talsma et al., 2006; Green et al., 2006; Moran et al., 2008). The extent and the mechanisms by which factors such as attention or multimodal stimuli influence BCI operation still need to be investigated further. Current real-life application also needs to be improved. Examples of such applications are word-spelling devices (Farwell & Donchin, 1988), wheelchair control (Rebsamen et al., 2007), or games such the *MindGame* (Finke et al. 2009).

Current BCI systems have certain disadvantages like low transfer rates, which limit their widespread application. Future research should try to improve transfer rates and accuracy, but as this avenue is prone to lead only to a slight improvement, it should also focus on making a more efficient use of bit rates. A research line to improve accuracy is based on the use of multimodal stimuli (i.e. visual and tactile). The P300 component differs across modalities (Polich & Heine, 1996; Romero & Polich, 1996; Bennington & Polich, 1999; Brouwer et al., 2010), it does not result in a superadditive effect in bimodal presentation, and while it is clear that multimodal information is integrated in the brain (Eimer et al., 2001; Kayser & Logothetis, 2007), whether this happens at an early sensory stage, at a later attentional stage, or both, remains elusive. Allison in 2003, and Elshout & Garcia Molina in 2009, reviewed BCIs based on the P300 in general, in this review an up date of the current knowledge is given, especially

focused on BCIs which use multimodal stimuli. We also cover the differences between P300s elicited in different modalities, suggestions of other ERPs and brain oscillations which might contribute to improve such BCI, and an overview of the neurobiology of multimodal integration. Finally, possible applications of this type of system and proposals for future research are covered below.

Brain-Computer Interfaces

Definition of BCI

A Brain Computer Interface (BCI) is a communication system that allows controlling an external device by brain activity without the use of the normal pathway involving also peripheral nerves and muscles (Wolpaw et al., 2002). Thus BCIs can assist or even augment human cognitive or sensory-motor functions. The game industry has already developed games that can be controlled by neural activity. An example is Hjelm's Brainball (2003) where electroencephalography (EEG) signals are used to control the direction of a ball. However, most games developed never make it out of the scientific sphere to the consumer market. Neuroprosthetic applications have also been developed for people with severe motor disorders (Hochberg et al., 2006). This breakthrough in BCI research is due to multidisciplinary contributions from Cognitive Neuroscience, Computer Science, Engineering or Mathematics. From brain activity to device control there are several steps: (1) signal acquisition, amplification and digitization, (2) noise filtering and feature extraction, (3) classification into logical controls using translation algorithms, (4) transfer of logical controls to device controller via a control interface, (5) conversion of controls into physical device-specific execution. In addition, there might also be an external display for stimulation (i.e. a monitor for visual stimulation, or other type of stimulating devices like a vest with tactors for tactile stimulation), which can also give feedback to the user (see figure 1 for a schematic diagram of a BCI system). Please note that the type of external display for stimulation can hindered the application in the ambulatory paradigm.

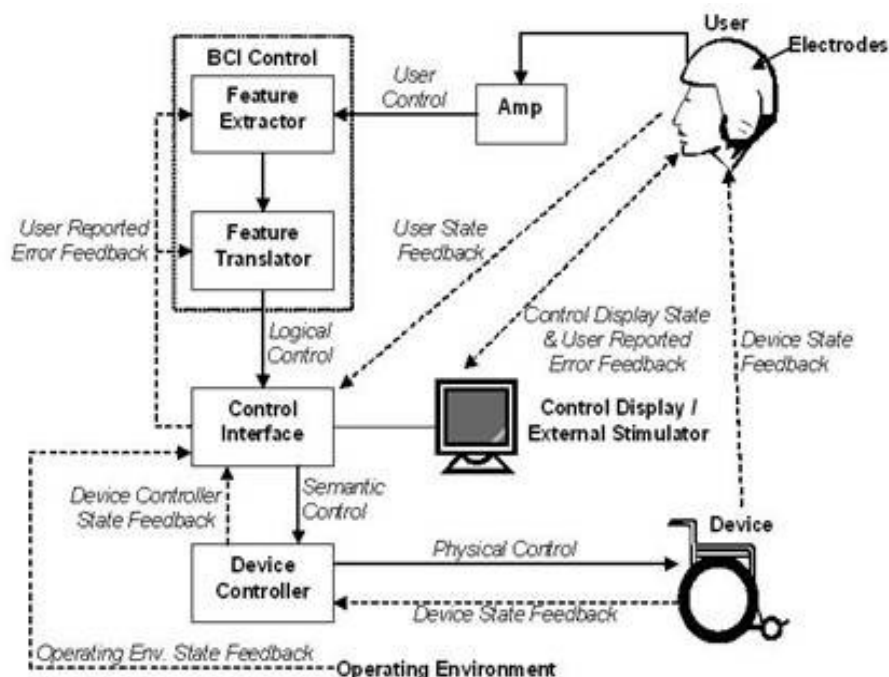


Figure 1. Schematic diagram of a BCI-system (from He, 2005)

Types of BCIs

Different techniques can be used to channel brain activity, the most studied technique is EEG due to its non-invasive nature and relatively high time resolution. Brain activity can also be monitored using other methods such as magnetoencephalography (MEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIRS) (Wolpaw et al., 2002). On the other hand, there are also BCIs that rely on invasive (i.e. intra-cranial) recordings. Invasive BCIs have the drawback that electrodes have to be surgically implanted, equipment is expensive, and most technology has only been tested in animals (Lebedev & Nicolelis, 2006). Nonetheless, invasive BCIs can measure brain signals more precisely to successfully control prosthesis with multiple degrees of freedom (Nicolelis et al., 1995). EEG signals are usually recorded using a cap with fixated silver/silver chloride electrodes placed at the standardized positions of the international “10/20 system”, in which electrodes are either 10 or 20% of the total left-right or front-back distance of the skull (Teplan 2002) (figure 2).

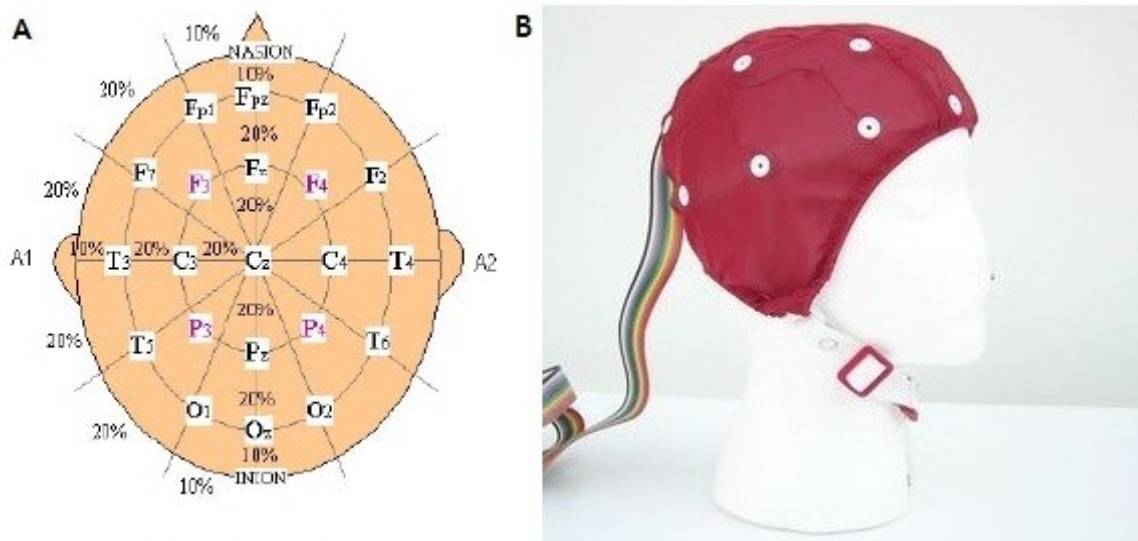


Figure 2. A. Electrode placement following the international 10/20 system on head as seen from above, with nose represented as triangle on top (nasion) (Teplan, 2002) B. Commercial EEG cap (www.bio-medical.com)

EEG measures the combined electrical activity of massive neuronal populations (Niedermeyer & Lopes da Silva, 2004). Therefore, both the spatial and temporal resolution are limited by the overlap in electrical activity generated by different cortical areas. The typical transfer rate obtained by EEG is currently 5-25 bits/s (Wolpaw et al., 2002; Birbaumer, 2006). The signal also has lower resolution due to the low-pass filtering of brain tissue, bone and skin. Furthermore, electromyographic (EMG), electrooculographic (EOG) and mechanical artifacts can also affect the EEG recording (Lebedev & Nicolelis, 2006). Within EEG there are several electrophysiological characteristics that can be applied to control a BCI system. The P300 event related potential (ERP) is one of them. Mühl et al. (2010) divide the different BCI paradigms in a two-dimensional classification derived from the 3 category classification of Zander et al. (2010), which spans across the axes wilfulness (passive vs. active), and stimulus dependency (user induced vs. stimulus evoked) (Figure 3). Thus, one axis stretches from activity evoked by exogenous stimuli (synchronous), to self-paced activity that is endogenously induced and which might be affected by external stimuli but does not depend on them to be generated (asynchronous); while the other axis stretches from activity that requires an intention to control brain activity (active), to activity that is spontaneously generated (passive) (Mühl et al., 2010).

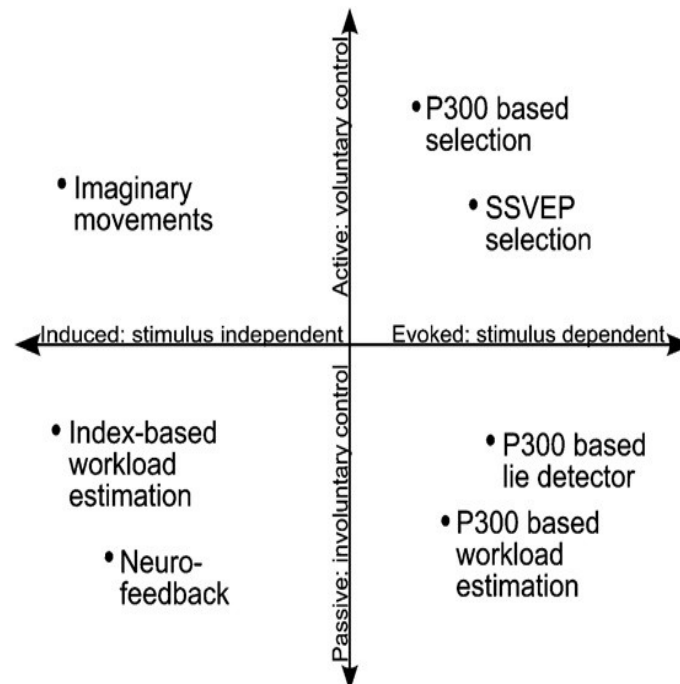


Figure 3. Classification of BCI paradigms, spanning willfulness (passive vs. active) and stimulus dependency (user induced vs stimulus evoked) (from Mühl et al., 2010)

According to this classification all P300 paradigms are evoked by exogenous stimuli, but can either be passive (i.e. lie detector) or active (i.e. P300-based selection). The latter is the type which is of use for BCI control as can be voluntarily manipulated. Other paradigms depicted include: (1) Steady state visually evoked potentials (SSVEPs) which are, like P300-based selection, active and stimulus evoked (i.e. by visual stimulation at specific frequencies), but differ in that while ERPs are visible in the raw signal, a fourier transformation has to be carried out to visualize the frequency evoked (i.e. which is the same or a multiple of the stimulus frequency); (2) Neurofeedback is based on another type of frequency signals or brain oscillations (i.e. beta or gamma), so a fourier transformation is also required, but in this case oscillations are passively generated and independent of a stimulus (please note that brain oscillations have also been reported to be phase-locked to stimuli [Kanayama et al., 2007]); and (3) imaginary movements, which are placed on the upper left corner due to their actively induced generation.

BCIs based on the P300 ERP

Event Related Potentials

Event Related Potentials (ERPs) are synchronous potentials elicited by specific events or stimuli in the external environment and can be divided into two classes: passive, which are the result of automatic processing of the frequency of stimulus occurrence (i.e. ‘oddball’ stimuli elicit a larger response), and active, which result from attendance to task relevance (Mühl et al., 2010). Detecting the changes between target and nontarget EEG signals on the different ERPs in a minimum number of trials, or even a single trial, is essential for a practical BCI application. Data from any ERP normally contains too much noise, which makes single trial classification with current methods almost impossible. Instead, ERPs are normally recorded over a number of trials and averaged to cancel out irrelevant activity. Noise reduction is proportional to the square root of the trials averaged (Gratton et al., 1983). After averaging, the components are scored

according to peak amplitude (highest/lowest point in a time period) and latency (time between stimulus onset and peak amplitude). These characteristics are used to name each ERP, using “P” for positive or “N” for negative followed by the latency time (i.e. a negative peak at 100 ms is named “N100” or just “N1”).

The P300 ERP

The P300 was first reported by Sutton et al. 45 years ago and its name is due to a positive deflection in voltage occurring approximately 300 ms after presentation of a cognitively salient and/or unexpected stimulus (figure 4).

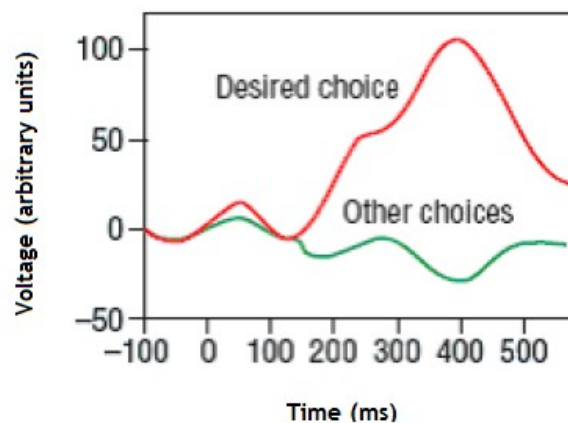


Figure 4. Illustration of a P300 wave evoked by the desired choice, which required focused attention -depicted by the red line, as compared to other choices -depicted in green (from Rebsamen et al., 2007).

The first P300-based BCI was developed 22 years ago (Farwell & Donchin, 1988) but it has only developed significantly quickly during the past few years. This is due to the increasing computational power and the new algorithms for signal processing, but also to the fact that, while other BCI paradigms require a previous long training, the P300 is particularly interesting for BCI control because it allows to communicate attendance to a certain stimulus without training. This means that the P300 ERP has a dual passive/active nature, as it can be elicited by voluntarily attending a stimulus, but also by low-level perceptual properties (Comerchero & Polich, 1999; Jansen et al., 2004), rareness (Polich & Heine, 1996; Croft et al., 2003), and inherent meaning (Polich et al. 1991; Lang & Kotchoubey, 2002). Polich (2007) found that these differently elicited P300s differ in latency and amplitude, and he termed the early subcomponent as P3a (passively stimulus-driven) and the later as P3b (actively attention-driven). Furthermore, he associated P3a to frontal/dopaminergic pathways, and P3b to originate from temporal-parietal/norepinephrine activity. The scalp distribution of the P300 has a maximum over the mid-line electrodes (Fz, Cz, Pz), typically increasing in amplitude from the frontal to parietal electrode (Johnson, 1993; Nieuwenhuis et al., 2005). It is also remarkable that although P300 amplitude is maximal at parietal electrodes, the highest association between amplitude and latency is found at frontal electrodes (Polich et al., 1997). A BCI can be based on this ERP given the consistency of the response and the relatively easy detection in the EEG signal (Guan et al., 2004), with the asset that users do not need training. Please note that P300-based BCIs are not based solely on the P300 component, but also rely on other ERPs (i.e. N100), although the exact contribution of these other EEG components remains to be clearly defined. On the other hand, P300-based BCIs can be affected by changes in attention, motivation and/or tiredness (Wolpaw et al., 2002). More importantly, it has been indicate that up to 75% of ALS patients display abnormal P300 patterns (Paulus et al., 2002), as the disease seems to damage the prefrontal cortex where attention is processed and thus alter BCI use (Rockstroh et al.,

1989; Müller et al., 1997). This is extremely important for the clinical application, as many BCIs are particularly developed as communication devices for this type of locked-in patients. Thus researchers should take into account the possible limitations of ALS users. Furthermore, some P300-based BCI studies reported subtle reductions in performance during repeated sessions, which could be caused by a habituation effect (Sellers and Donchin, 2006). This is especially relevant for oddball based BCIs, where P300 is largest for new/relevant events, and presenting repeated rare events results in shorter P300 amplitudes and thereby reduced performance. Nevertheless, P300 amplitude returned to initial levels in unexpected experimental sessions (Sellers and Donchin, 2006). In summary, this possible response habituation does not seem to affect performance significantly. Additionally, it is possible to obtain a relatively stable P300 in individual trials (Polich & Heine, 1996; Jung et al., 2001; Blankertz et al., 2003; Jansen et al., 2004).

Types of P300-based BCIs & applications

So far P300-based BCIs have relied mainly on visual stimuli (Farewell & Donchin, 1988; Polikoff et al., 1995; and Piccione et al., 2006). However gaze dependency is a disadvantage for both patients and healthy subjects (Macaluso et al. 2005). Some BCIs have used auditory paradigms (Hill et al., 2005; Sellers & Donchin, 2006; Kübler et al., 2009; Furdea et al., 2009; Schreuder et al., 2010), and only few BCIs are tactile-based (Rinsma et al., 2009; Thurlings et al., 2009). Only recently the P300 has been also studied in olfaction (Morgan & Murphy, 2010), but there is no BCI application, nor it seems to be feasible in the coming years. A new strategy is to investigate the effect of multimodal stimulation (Aloise et al., 2007; Brouwer et al., 2010) which is hypothesized to be a way to improve BCI efficiency as attentional capacity for processing concurrent stimuli is larger across sensory modalities than within a single modality (Talsma et al., 2006; Green et al., 2006; Moran et al., 2008). Within this line of research little is known about whether the super-added effect expected when adding a second modality would be greater if both stimuli converge spatially and temporally.

As mentioned above, both bottom-up and top-down attention can generate a P300, which Polich (2007) termed as P3a and P3b, respectively. Some studies compare P300s elicited by both of these kinds of attention. Hence, participants are not only required to attend to the target stimulus, but also the target differs from the standards, which boosts larger P300s. Brouwer & van Erp (2010) showed that even tactile stimuli around the waist can elicit P300s by only top-down attention, which would probably be needed for real-world P300-based BCI applications.

Typical applications range, as in other BCI types, from assistive technologies to mainstream-targeted. The P300 speller (Farwell & Donchin, 1988), the P300 internet browser (Mugler et al., 2008), and wheelchair control (Rebsamen et al., 2007) are significant examples of former, while the *MindGame* (Finke et al. 2009), *Brain Painting* (Kübler et al., 2008; Halder et al., 2009), and the P300-based control of a virtual apartment (Bayliss, 2003) represent the latter.

The P300 speller system allows subjects (especially designed for locked-in ALS patients) to communicate a sequence of letters to a computer (Farwell & Donchin, 1998) (Figure 5). A 6 by 6 matrix with the alphabet, numbers and space symbol, is displayed on a computer screen. To create an oddball paradigm, rows or columns are randomly flashed so the subject can select the desired character by focusing attention on the cell containing it. As the target stimulus elicits a larger P300 amplitude, an algorithm can recognise this “thought-spelled out” letter and add it to the display for user feedback.

In a modified version (Sellers & Donchin, 2006) patients can answer simple yes or no questions with a transfer rate up to 20 bits/min (For a comparison of the classification techniques for the P300 speller see Krusienski et al. 2006). Finally, Sellers and colleagues (Guger et al., 2009) tested how many healthy users can spell a 5-letter word (i.e. 'water' or 'lucas') with only 5 minutes of training. They found that 72.8% of them were able to spell without any mistake, which is way superior to the 6.2% obtained in a similar study using motor imagery to control a

cursor to either left or right (Guger et al., 2003). This comparison illustrates the advantage of the P300 due to the minimal training required to obtain high accuracy classification. It is for this reason that during the past 5 years the field has experienced a research boom, as more and more researchers choose to base their BCI systems on a naïve brain signal like the P300 over other types of brain activity. After all, in order to implement BCIs for patient and consumer use, the device should not be difficult to control.



Figure 5. A 6 by 6 speller matrix with the 3rd row flashed (Seller & Donchin, 2006)

Existing prototypes of BCIs for steering a wheelchair can be based on both invasive and non-invasive techniques, but the system has to be extremely reliable if the device is to be used in a potentially hazardous environment such as city traffic. Rebsamen et al. (2007) developed a P300-based wheelchair prototype which uses a motion guidance strategy to navigate in a preconditioned building safely and efficiently. Instead of indicating angular direction and movement speed, the user instructs the device by choosing destination on a menu (e.g. kitchen, bathroom, etc.) by counting the number of times the desired destination is flashed (similarly as spelling a letter in the P300 speller). The wheelchair then takes the user to the indicated destination on a predefined path (Rebsamen et al., 2007). This idea has also been evaluated by Iturrate et al. (2009).

To date, P300-based neuroprosthetics have not been developed. However, Taylor et al. (2002) BCI-based robotic arm is able to control 3D movements by invasively measuring activity of cortical neurons in monkeys, Hochberg et al. (2006) developed a prosthetic device for humans with tetraplegia, and McFarland et al. (2008) showed that an EEG-based BCI can provide comparable 3D movement control. The group of Cincotti and colleagues works also in the development of such device (Cincotti et al., 2008).

In the *MindGame*, a P300-based BCI was used for the first time as a device for game control that replaces common control by motor actions and devices like mice or joysticks (Finke et al., 2009). P300s are translated into movements of a character on a three-dimensional game board by linear feature selection and a single-trial classification (preceded by a training scheme to optimize the classifier to each player) that achieves rates of 65% accuracy (Finke et al., 2009). The *MindGame* is played on a game board with 28 by 18 fields and 12 randomly positioned trees, which are used as potential destinations on a menu in an analogous fashion to the automated navigation paradigm used in Rebsamen's et al. (2007) wheelchair control. To achieve single-trial classification, the oddball is no longer created by rows or columns highlighted as group-wise stimuli (like in the P300 speller), nor by counting the number of times the choice is flashed (like

in Rebsamen's wheelchair control). Instead, all 12 target fields are consecutively highlighted but target and nontarget stimuli are coded in red and yellow respectively, so that when the player focuses on a choice, an eventual red flash will elicit a P300 while yellow flashes will not (Finke et al., 2009). During the online operation of the system the player is provided with gradual feedback, which gives the *MindGame* the potential to become a neurofeedback system allowing for training attention.

Yet two other mainstream applications with variations of the P300 matrix are the P300 internet browser (Mugler et al., 2008) and *Brain Painting*, developed by Kübler and colleagues (Kübler et al., 2008; Halder et al., 2009). The latter has also been successfully control by an ALS patient both in the laboratory and during an art exhibition, as after all these patients would be the ones who benefit most from this type of developments (Lulé et al., 2009). In *Brain Painting* each cell of an 8 by 6 matrix contains shape, size and opacity of the brush, colour, intensity and other commands which are used to paint, while in the P300 internet browser, the elements of the matrix are a selection of links (for a 6 by 6 matrix that is 36 links). Kübler proves that paintings produced with *Brain Paint* are not just random selection of figures and shapes by reproducing one of this paintings (figure 6).

In addition Bayliss (2003) described a P300-based control of a virtual apartment, where the television, stereo, HI sign, BYE sign, and lamp are the controllable items. She showed that the P300 can be used also in virtual reality (Bayliss, 2003). This “mental remote control” opens new avenues for the consumer market.

Finally, there exist two non-BCI applications in forensics and clinical diagnostic. The P300 component has been proposed in forensics as “lie detector”, as the amplitude elicited by seen objects/places is larger than for new ones, thus it can be used for instance to prove the subject's presence in a crime scene (Rosenfeld et al., 2006). A conflicting issue with this method is whether false recognition of associatively related (Lure) items can be distinguished from true recognition of previously presented (Old) ones, since the P300 elicited by them do not differ in amplitude. However, Rosenfeld et al. (2006) showed that the P300 latency of Lures was significantly shorter than those for Old words. Moreover, the P300 is also proposed in the clinical diagnostic of first-episode schizophrenics (Salisbury et al., 1998; McCarley et al., 2008) and early Alzheimer's disease (Polich & Corey-Bloom, 2005), as both disease are characterized by attentional deficits. Particularly, the former group seems to suffer a left temporal lobe dysfunction that reduces P300 on this hemisphere as well as gamma oscillations (Spencer et al., 2008), while the latter group showed smaller amplitudes and longer latency than elderly control subjects (Polich & Corey-Bloom, 2005).

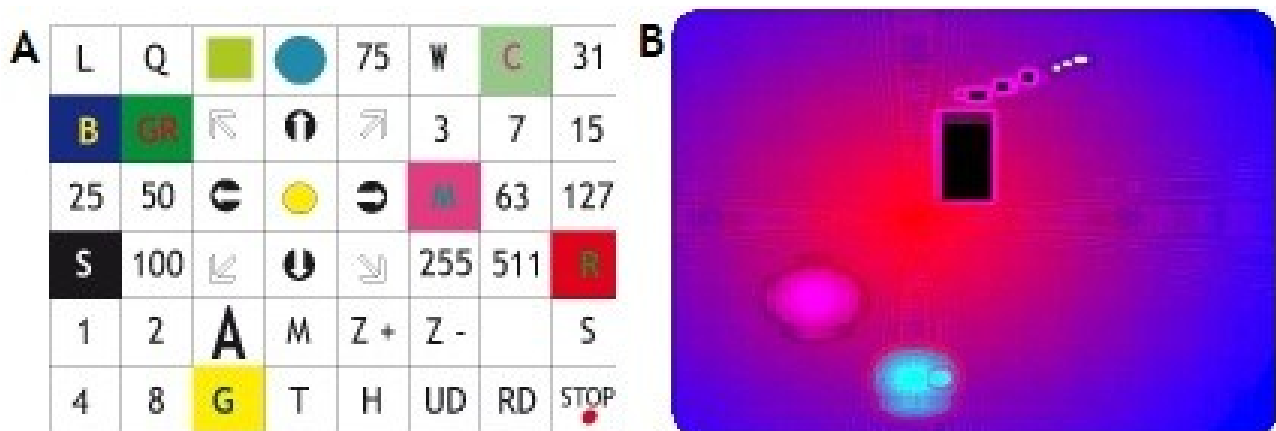


Figure 6. A. The 8 by 6 Brain Painting matrix. B. Painting by an ALS patient (Kübler et al., 2008)

P300 differences across modalities

It is challenging to analyze the exact effect of modality alone on P300 amplitude, latency, classification accuracy (i.e. % correct interpretation of commands as extracted by algorithm, accounting for chance level), or scalp distribution, since manipulating modality may affect many other variables like saliency of the stimulus. It is however possible to manipulate stimuli saliency aiming at “equisaliency” (Kayser et al., 2005b). Moreover, multimodal saliency-based bottom-up attention is used in artificial intelligence for robot's eye and neck movements (Ruesch et al., 2008). Despite the challenges, some studies have compared P300s across modalities. Polich and colleagues compared visual and auditory P300s and found the P300 latency to be shorter for auditory than for visual targets (Polich & Heine, 1996; Romero & Polich, 1996), and the P300 amplitude to be either larger for auditory than for visual targets (Bennington & Polich, 1999) or smaller (Polich & Heine, 1996; Sangal & Sangal, 1996). This contradictory finding shows that P300 differences depend on the sensitivity of the modality used and stimuli parameters in the specific study. Modality has been reported to do not affect which electrode location displayed the P300 most strongly (Sangal & Sangal, 1996; Ji et al., 1999; Polich & Heine, 1996; Romero & Polich, 1996). This is counter-intuitive, since a topographical difference between modalities would be expected with each would eliciting higher amplitudes over its sensory cortex. Either the spatial resolution of these studies (all from the mid-90's) is not good enough, or the P300 component is indeed medial prefrontal. There are some reports of P300 scalp distribution differences (Işoğlu-alkaç et al., 2007; McCarley et al., 2008), but these are between bimodal and unimodal conditions but not differences between target and non-target needed to recognize the subject's choice.

Brouwer et al. (2010) investigated P300s elicited by tactile stimuli around the waist and compared these to visual P300s with respect to their amplitudes and latencies and as a function of electrode location. Using a linear discriminant analysis they found that while latency remained unaffected, at Oz there were stronger effects for visual than tactile stimuli, and at Fz and Cz tactile stimuli produced significantly larger P300 amplitudes, and similar or larger absolute difference between target and standard EEG signals (from onset until 800 ms) than the visual ones. Nevertheless, classification accuracy did not differ between the two modalities, which disputes the results of Aloise et al. (2007), who reported better classification of visual stimuli than of vibro-tactile stimuli delivered to the hand. The two studies differed in certain aspects: (1) the location where the tactile stimuli were presented (i.e. hand vs. waist), (2) congruence between the locations of visual and tactile stimuli (i.e. congruent in [Aloise et al., 2007] vs. incongruent in [Brouwer et al., 2010]), (3) inter-stimulus interval used (i.e. 150 ms and 400 ms respectively), and more importantly (4) eye fixation (i.e. no instructions vs. cross in the center of the schematic waist visually displayed). Such contradictory results had also been reported when comparing amplitudes elicited by visual and auditory stimuli (Polich & Heine, 1996; Bennington & Polich, 1999), and the effects of different target-to-target intervals (Polich, 2007). These disparities are probably attributed to methodological differences between studies, which make generalizations almost impossible. Please note that these groups have not published second papers replicating the results.

Furthermore, Treder and Blankertz (2010) investigated the effect of covert attention (i.e. stimuli in visual periphery) and overt attention (stimuli in foveal focus) in a P300-based visual speller design with focus also in other ERPs. They have shown that overtly attending to stimuli resulted in less errors, larger ERP amplitude, and better classification by enhancing mainly early ERPs (i.e. P100, N100, P200, N200 and P300). On the other hand, covert attendance enhanced later ERPs (i.e. N200 and also P300), which is in accordance with the already mentioned active/passive nature of the P300 component. Another interpretation is that covert and overt actually differ in sensitivity of the sensory modality. For instance in vision, the fovea contains cones that can distinguish color and fine details, while outside there are mostly rods that are more sensitive temporally to motion (Szél et al., 1996). Similarly, two tactile stimuli applied to

the finger tip can be distinguished within mm, while the same stimuli applied to the back is on the range of cm (Vallbo et al., 1984). The participants in the study of Aloise et al. (2007) were not instructed with respect to eye movements, so they probably fixated on the target, which most likely enhanced the visual P300. This would explain the better visual classification, as in the tactile modality there is no equivalent of visual fixation. In addition, according to Eimer et al. (2001) humans use an abstract spatial reference-frame which mediates selectivity across modalities, thus attending to one modality in a certain side enhances ERPs cross-modally at that same side. Hence, differences in classification between the studies of Brouwer et al. (2010) and Aloise et al. (2007) could be partially explained by location congruence disparity and the particular cross-modal transfer of information between touch and vision (Hadjikhani & Roland, 1998). There are two other types of stimuli congruence: mainly temporal and semantic (i.e. a picture of a dog with simultaneous bark) (Laurienti et al., 2004; Chen & Spence, 2010). In summary, although comparing modalities has its inherent challenges, comparisons have been studied with certain variability in results. Some of the contradictory findings might be due to sensitivity of the modality, saliency of stimuli, incongruent concurrent stimuli, or different ISIs used. Greater differences between multimodal and unimodal or other ERPs/oscillations across modalities can be alternative ways of improving BCI accuracy, as it is suggested next.

Improving P300-based BCIs

Other ERPs

Farwell & Donchin (1988) already suggested in their groundbreaking paper that “it may be [...] possible to enhance the speed of the system by incorporating additional components of the ERP”. In fact, most P300-based BCIs rely also in other ERPs, although on which ones and to one extent exactly is normally not described. Allison & Pineda (2006) already mentioned that there are important non-P300 components being used to differentiate targets from non-targets and in visual BCIs that did not control fixation, early visually evoked potentials seemed to also have an important role (Kaper et al., 2004). Furthermore, Shishkin et al. (2009) showed that this effect was not based simply on “foveating” the target, as the N100 is not sensitive to the physical characteristics of stimuli. Thus, N100 may be elicited by visual spatial attention, which is inherent to P300 BCI use. This possibility was demonstrated in another study (Koivisto et al., 2008), where a posterior negative amplitude shift 130 to 320 ms after stimulus onset was associated with visual awareness independent of the scope of attention, while a parietal positive peak around 400 ms was enhanced in unrecognised stimuli but attenuated by local attention. In other modalities such as hearing and touch, N100 has been found to be enhanced at short inter-stimulus intervals (ISIs) at the expense of P200 reduction, which the authors (Wang et al., 2008) hypothesized to be caused by a Mis-Match Negativity (MMN) like that observed in the presentation of a deviant auditory stimulus within a constant stream of repeated sounds (Näätänen & Picton, 1987; Näätänen et al., 2007), which has also been reported for tactile (Kekoni et al., 1997; Akatsuka et al., 2007) and visual modalities (Czigler et al., 2006). MMN amplitude has been shown to not be affected by unattendance, so it should be elicited by automatic processes. However, latency is affected by attention so it is also mediated by top-down processes. Furthermore, it changes topographically (each modality over its cortex when attended and more fronto-central when unattended) (Luo & Wei, 1997). Alternatively, at very short ISIs the positive deflection associated with the formation of a memory representation could be disrupted (Haenschel et al., 2005), implicating not only attention mechanism, but also memory rehearsal.

Brouwer et al. (2010) found that visual and bimodal targets elicit (at Oz) positive rather early peaks followed by negative peaks, which they hypothesized to reflect lower level visual processes, as the components were measured over the visual cortex and only when visual stimuli were presented. On the other hand, at Cz they reported a negative peak only for tactile targets,

and a conspicuous target post-P300 negativity was present at all electrodes for all conditions. This prominent difference was found to be likely used to recognize targets from standards by further epoch classification analysis in which samples between 550 and 800 ms resulted in similar classification accuracies to those in the epoch around the P300 (i.e. 300-550 ms) (Brouwer et al., 2010). This is in accordance with other studies (Bayliss, 2003; Rosenfeld et al., 2006; Kotchoubey & Lang, 2001; Piccione et al., 2006; Sellers & Donchin, 2006), although none of these authors commented on the effect. One possible account points to an increase in alpha activity after target presentation, as this rhythmic EEG activity in this frequency band has been associated with differences in attended versus ignored events (Spencer & Polich, 1999; Yordanova et al., 2001; Jung et al., 2001). Nonetheless, Brouwer et al. (2010) were more kin on attributing the effect to sustained negativity than a 12 Hz wave.

Recently, Treder & Blankertz (2010) investigated the P300 component considering also P100, N100, P200, and N200. While P100, N100 and P200 are early ERPs elicited by automated stimulus processing in early attention (Näätänen & Picton, 1987), N200 is associated with deviant stimuli processing (Näätänen & Gaillard, 1983). Similarly, Bianchi et al. (2010) combined EEG and MEG data and applied a stepwise linear discriminant analysis which indicated that non-P300 components maximally represented in the occipital region could improve classification accuracy. In addition, Işoğlu-alkaç et al. (2007) compared also the amplitudes of N100, N200 and P200. They found N100 and N200, but not P200 to be significantly higher and distributed differently over the scalp during bimodal.

Furthermore, Bianchi et al. (2010) plotted the classification accuracies topographically and dividing it into two time intervals: (1) 0 to 250 ms, in which N100 is most prominent, and (2) 250 to 500 ms, in which is the P300 to be most prominent (figure 7)

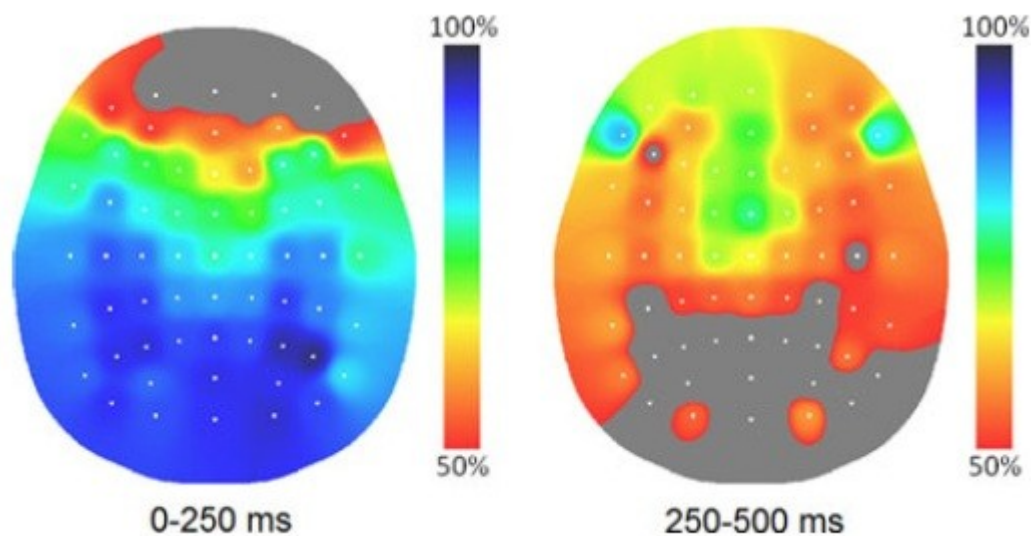


Figure 7. Topographical distribution of the classification accuracies, in the 0-250 ms (i.e. N100) and 250-500 ms (i.e. P300) time intervals (Bianchi et al., 2010).

To conclude, new algorithms aim at comparing as many components as possible between target and non-target so they can be more easily and reliably distinguished. One of them is Probability Independent component analysis, P-ICA (Lang et al., 2010).

Brain Oscillations

In 1989, Gray et al. published a seminal paper on the association between stimulus feature integration processes and gamma oscillations in the cat visual cortex (Gray et al. 1989). This

association suggested that similar oscillatory mechanisms might be involved in multisensory processing, for instance, when speech is integrated with visual lip movements (Kayser, 2007). Probably, oscillatory synchronization in low cortical areas has an important role in integration of multisensory inputs of a particular event (Senkowski et al. 2005). Furthermore, recent work indicates that oscillatory responses can be more sensitive to certain experimental manipulations than ERPs (Bertrand and Tallon-Baudry, 2000; Herrmann and Mecklinger, 2001; Senkowski and Herrmann, 2002; Kanayama et al., 2007), emphasizing the importance of examining multisensory interactions in oscillatory responses. Senkowski and colleagues have investigated the effects of spatial selective attention on multisensory processing and oscillatory activity in a simple audio-visual integration paradigm, and they found that multisensory interactions revealed a significant superadded effect on gamma oscillation (i.e. 30 to 80 Hz) around 40-50 ms post-stimulus over medial-frontal brain areas (Senkowski et al., 2005) and beta oscillations (i.e. 15 to 20 Hz) around 60 ms post-stimulus over visual cortical areas (Senkowski et al., 2007). In another study using a different combination of modalities (i.e. visual & tactile), the same superadded effect on gamma oscillation was observed but in this case at 200-250 ms post-stimulus and only when the stimuli were congruent (Kanayama et al., 2007) (see figure 8). Hence, certain oscillations should be considered for BCI control as they correlate with attentional processes and might be even more sensitive than current ERPs.

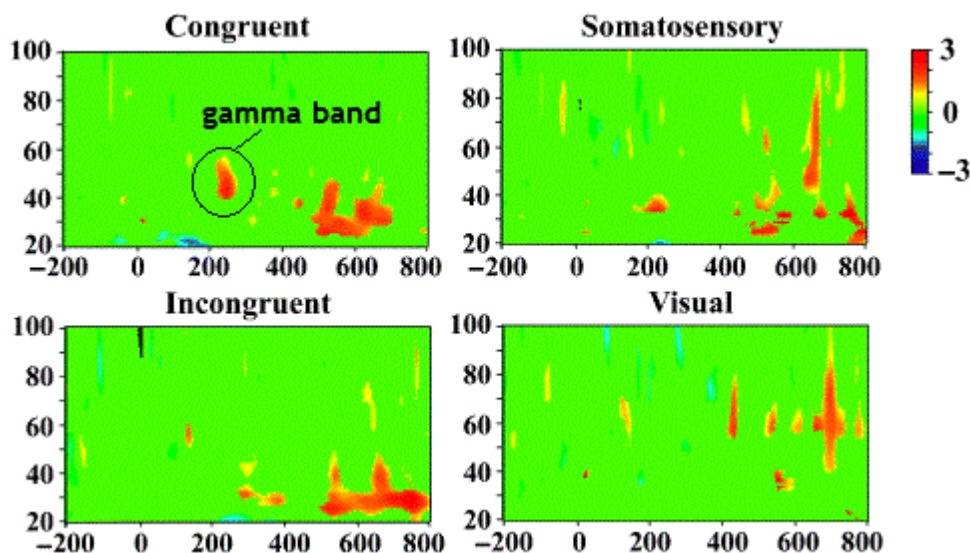


Figure 8. Significant power values indicated by bootstrap test at electrode Pz, circled: increase in gamma band around 200-250 ms post-stimulus only found in bimodal congruent condition (Kanayama et al., 2007)

Neurobiology of multimodal integration

Recent studies have also reported that the distinct sensory features of a multisensory object are integrated not just in the classical “multisensory areas” (i.e. temporal lobe, superior colliculus) but also in low level cortical regions that were commonly believed to have a pure unisensory function (Foxe et al. 2000; Foxe and Schroeder 2005; Molholm et al. 2002; Moran et al. 2008; for review see (Spence et al, 2008; Lakatos et al., 2009; Murray & Spierer, 2009).

In an fMRI study, multisensory integration (MI) activated visual areas in lateral occipital cortex, somatosensory areas in inferior parietal lobe, and multisensory areas in the intraparietal sulcus (IPS) (Beauchamp et al., 2010). Another group investigated P300 in an auditory oddball paradigm alone or combined with passive visual stimuli. The combined condition elicited more fronto-central P300s, while the unimodal condition was at centro-parietal locations (İşoğlu-alkaç et al., 2007). Furthermore, certain studies have found attentional capacity for processing concurrent stimuli to be larger across sensory modalities than within a single modality (Talsma et al., 2006;

Green & McDonald, 2006; Moran et al., 2008). Werner and Noppeney (2007) found a superadditive effect in primary auditory cortices (Heschl Gyrus -HG) for automatic integration of low-level audio-visual features, while the inferior frontal sulcus (IFS), intraparietal sulcus (IPS), and the insula (INS) reflected multi-sensory facilitation of response selection. On a different bimodal integration, that of visual and tactile inputs of a multisensory stimulus, Helbig et al. (2007) and Holdstock et al. (2009) found that shape is integrated by the perirhinal cortex.

The claustrum, a subcortical structure with extensive anatomical connectivity to sensory and association cortices, is one of the areas most studied on its involvement in early multisensory integration (Crick & Koch, 2005; Kayser et al., 2005; Remedios et al., 2007; Fernández-Miranda et al., 2008). Other areas include the superior temporal sulcus, the intra-parietal sulcus and regions in the frontal lobe (figure 7), for a review of functional and anatomical studies supporting cross-modal interactions in these regions see Ranganath & Rainer (2003) or Kayser and Logothetis (2007). For the neurophysiological correlates of mental imagery in different sensory modalities see Fallgatter et al., 1997.

Overall, accumulating evidence demonstrates that early multisensory integration can occur at both: (1) close to primary sensory areas, given that it has been recorded in anesthetized animals there should be pre-attentive integration bottom-up-mediated (Talsma et al., 2006), and (2) at higher attentional areas (i.e. prefrontal area) which are more top-down mediated (Werkhoven et al., 2009; Latinus et al., 2009).

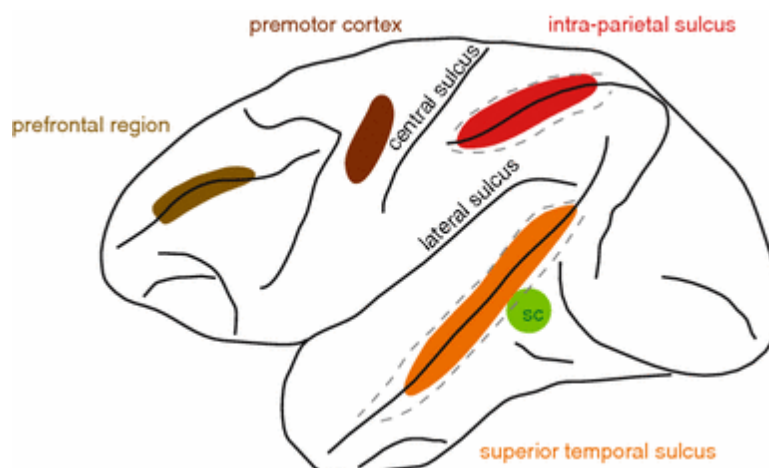


Figure 9. Association areas related to sensory integration. sc: superior colliculus. Dashed gray lines indicate regions where sensory integrations has been reported (see text) (Kayser & Logothetis, 2007)

BCI improvement by Multimodal stimuli

For BCI systems, a high signal to noise ratio is important to recognize user's intentions with an acceptable uncertainty in a minimum number of trials. It is hypothesized that bimodal stimulus presentation can improve BCI efficiency by enlarge P300 amplitude (Schröger & Widmann, 1998) or other EEG components, and thus result in better classification. One possible cause for this is the increased attentional capacity for processing concurrent stimuli observed across sensory modalities as compared to single modalities (Talsma et al., 2006; Green et al., 2006; Moran et al., 2008). It is important to keep in mind that sensory systems become less sensitive with aging and disease, thus constant relearning is needed to update the reliability weights for each modality during multisensory integration (Beauchamp et al., 2010). BCIs should be based on the modality which allows for better communication and usability of the device, while taking into account the sensitivity of the modality, especially important in multisensory design as a modality with greater weight could influence performance.

Proposed reasons for a larger bimodal P300 range from energy summation (Nickerson, 1973) to superadditive effects (Stein & Meredith, 1993; Standford & Stein, 2007). Based in the fact that

bimodal stimuli firmly enhance various (early) EEG components (Stein & Meredith, 1993; Foxe & Schroeder 2000; Foxe et al., 2000; Molholm et al., 2002; Talsma et al., 2007; Teder-Sälejärvi et al., 1999), one would await a great bimodal enhancement that could be used to improve BCI classification and thus reduce the number of trials needed. Brouwer et al. (2010) found that bimodal (visual and tactile) presentation elicits significantly larger absolute difference at Pz than either of the unimodal conditions, although this increase was far from the sum of the tactile and visual signals. Why would increase be so marginal? This might be due to the fact that also standards result in larger amplitudes, hence the absolute difference is not as much affected. Notwithstanding the lack of a super-additive effect, bimodal presentation of the stimuli still improved classification by 11% compared to the unimodal conditions (the model was correct in 67% of the cases in the bimodal condition and 56% in the unimodal ones). Please note that the classification improvement was found, using different epoch timings, to rely on more ERPs than the P300 alone, especially later components seemed to contribute in distinguishing between targets and nontargets. Moreover, the enhancement they showed might have been due to top-down rather than bottom-up attention effects.

Talsma et al. (2007) reported that a superadditive effect on an early ERP (P50) only happened if participants attended to both auditory and visual stimulus modalities. Furthermore, it is assumed that multimodal integration requires temporal and spatially congruent stimuli (Stein & Meredith, 1993; Sambo & Forster, 2009), yet it might be possible, albeit with lower effects and later integration, when stimuli are not colocated (Philippi et al., 2008). Consequently, further improvement of classification in multimodal BCI is expected when multisensory stimuli are also physically congruent.

In an fMRI study, Dionne et al. (2010) found an increase in percent blood oxygenation level in visual plus tactile as compared to unimodal tasks, with fronto-parietal activation (i.e. involved in attention processes). Finally, crossmodal plasticity in individuals like synesthetes and early blind also results in EEG differences. A recent study suggests that supramodal processes lead to enhanced sound localization or tactile orientation in early blind as compared to controls, and it shows that these enhancements are reflected in increased posterior negativity in EEG studies (van der Lubbe et al., 2010). On the other hand, synesthetes have been found to differ from controls in early sensory components after visual evoked potentials (Barnett et al., 2008), and cross-modal interaction in controls during a selective attention task seems to have an effect dependent of synesthetic correspondance (i.e. high pitch sounds are faster classify in presence of white vs. black visual stimuli) even when one of the modalities (i.e. hearing vs. vision or touch vs. vision) is unattended (Martino & Marks, 2000). These findings further support the theory of multisensory integration resulting in EEG differences which could be used to better control a BCI system. A graphical model of the mechanism involved in attentional and multimodal effects on P300, other ERPs and brain oscillations, is depicted in figure 10.

It can be concluded that multimodal integration seems to act at two different levels: (1) an earlier sensory evoked that would affect processing attentional capacity, and (2) a later attention-induced process that would determine attention allocation. Both of these processes can increase activity, and thus lead to better classification accuracies. On the other hand, processing capacity varies for each sensory modality depending on its sensitivity. At a third level, task demands influence also the recorded signal. Two of the factors at this level are congruence of the multimodal stimuli in temporal, spatial and semantic representation, and target-to-standard ratio.

Finally, adaptation algorithms like P-ICA combined with a complete analysis of the ERP signal, including not only the P300 but also other components such as N100, P100, N200, P200, and post-P300 negativity, plus brain oscillations like gamma band, would result in a multi-paradigm BCI with a potentially improved classification accuracy and system efficiency and reliability.

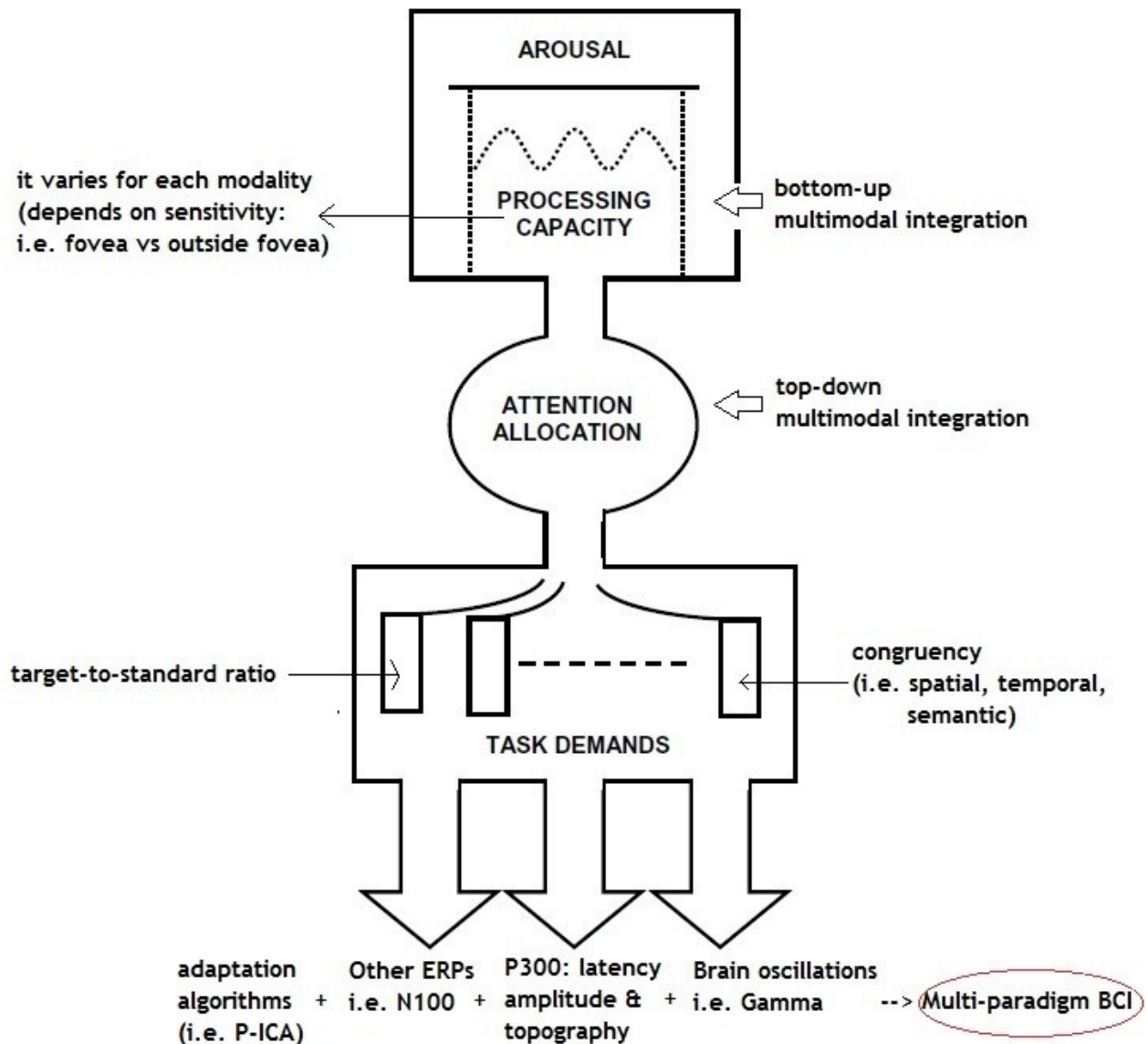


Figure 9. Model depicting the effects of how attentional and multimodal effects can affect brain activity as measured by P300 and other ERPs, as well as by brain oscillations such as gamma (modified from Kahneman, 1973)

Future Research

There are different ways toward improving future P300-based BCIs: (1) speed could be increased by higher transfer rates, single trials, or deriving more information from the bit rates; (2) other non-P300 components could be added to the classification criteria, ranging from other ERPs to brain oscillations, eventually leading to a multi-paradigm BCIs; and (3) improving signal detection so that the BCI can be use in a normal-life context for both patients and mainstream.

Faster BCIs: transfer rate & single trials

The efficiency of the system is often an issue in BCI systems, as a minimum 70% accuracy is necessary for effective communication, and an increase in accuracy from 75 % to 90 % (given 4 choices) almost doubles the bit rate (Sellers and Donchin, 2006). Please note that balance between accuracy and speed is needed. For instance, the bit rate record in a 6x6 matrix speller

is of 84.7 bits/min, but as the accuracy level was below 50% the device could not correctly spell even a single word (Meinicke et al., 2002). Typical P300-based BCIs reach transfer rates of approximately 10 bits/min (Elshout & Garcia Molina, 2009), but more recent experiments achieved higher accuracy rates (up to 100%) and transfer rates up to 25 bits/min even in disabled subjects (Hoffmann et al., 2008). Moreover, offline EEG analysis of P300 speller data has achieved higher transfer rates (up to 97.57 bits/min and a mean of 47.26 bits/min) using an algorithm based on support vector machines (Kaper et al., 2004). This method has never been implemented online and it is unclear whether it is even possible (Sellers and Donchin, 2006). Overall, P300-based BCIs need at least 70% accuracy and rapid transfer rates, but reaching that of current devices such as keyboards and mice (up to 350 bits/min) (Krepki et al., 2007) is still a far away horizon. Notwithstanding, the lower transfer rates compared to other electrophysiological signals, P300-based BCIs still have the advantage of lacking user training. Another avenue to increase efficiency is by optimally using present bit rates. Rebsamen et al. (2007) already based the steering of a wheelchair on this approach. Instead of moving by indicating angular directions, the user selects choices of locations (e.g. kitchen, bathroom etc.). Moreover, the achievement of classification in single trials has been studied by integration of a BCI-based online error-detection system (Blankertz et al., 2003; Buttfield et al., 2006). P300-based BCI systems using single trials have to be further investigated (Finke et al., 2009), as this would increase transfer rates. In summary, future BCI research should not only try to increase transfer rates with high accuracy, but also to use present bit rates in a more efficient way.

Towards a Multi-paradigm BCI

Other ERPs, oscillations (i.e. gamma), or even multi-paradigm BCIs could be a way of improving current P300-based BCIs, but then they probably should not be called like that anymore. Other ERPs have been reviewed above, and brain oscillations are probably even more sensitive than ERPs, with the advantage that can also be used to extract information about motivation and emotions (for review see Knyazev, 2007), which can be useful for BCI operation (Allison et al., 2007). Thus, a multi-paradigm BCI seems to be the best way forward. Such system has only recently been tested in a 2-D cursor control in which Mu/Beta rhythm was measured during motor imagery to control horizontal movements, while the P300 was simultaneously and independently measured to control vertical movements (Li et al., 2010). This approach was reported to allow cursor movement between arbitrary positions and to improve system efficacy as compared to prior systems. Advances in this direction are expected to yield more successful results than each of the paradigms independently.

Assistive technologies and mainstream applications

Most limitations on the extent of P300-based BCIs application are inherent to EEG. Mainly, the electrical sensitivity of EEG limits the use to still subjects in a laboratory setting, while in the real-world there are many noises and the signal needs to be recorded when the user is moving. Lotte et al. (2009) have been able to detect the P300 in walking subjects, which makes the feasibility of a wearable BCI a step closer. Using a P300-based BCI requires attention, which in real-life could be potentially difficult as the user could be distracted by the environment, other people, etc. Hence, testing BCIs by patients and healthy users in home environment is extremely important.

Further progress is expected in the coming years due to findings in hybrid BCI design, development of adaptation algorithms (i.e. Liang et al. 2010: Probabilistic Independent component analysis, P-ICA), assessment of mental states, integration of human-computer interaction principles, and conception of new BCI technology and EEG devices (Millan et al. 2010).

Conclusion

BCIs allow people to communicate or control external devices using brain activity alone. As no movements are needed, it is especially interesting for communication assistance of locked-in ALS patients. Different electrophysiological signals and components can be extracted to fulfill this aim. On the one hand, invasive BCIs require surgery and equipment is still relatively bulky and expensive. On the other hand, non-invasive BCIs are currently too slow to be practical for most situations. The P300 ERP is common in BCI systems due to its naive response to a task relevant stimulus (Wolpaw et al., 2002). Thus, a user can indicate a desired choice without requiring training. However, the P300 can be affected by different factors like attention (and per se age), motivation or fatigue (Allison, 2003). P300-based BCIs can be valuable for patients with severe motor disabilities such as in ALS, but also for the healthy user. However, current systems have certain drawbacks compared to conventional interfaces such as keyboards and mice, like lower transfer rates, lower accuracy, or bulky and expensive equipment (i.e. electrode cap and computer equipped with special software). In addition, the user often cannot set up the device alone and the signal is extremely sensitive to noise induced by movement or simply by the environment. All together, BCI are not going to replace current interfaces in the coming years (Allison et al. 2007), but they might improve the quality of life of locked-in ALS patients by helping them: (1) to communicate & control devices (i.e. P300 speller and internet browser) (2) in motor substitution (i.e. wheelchair with automated-navigation), (3) entertainment (i.e. Brain Paitning). For them, it is possible to benefit of present BCIs even without being yet as efficient as standard interfaces. Furthermore, P300-based devices might become useful in other application than BCIs. For instance in the diagnostic of early attentional deficits characteristic of schizophrenia or Alzheimer's disease, or in the court room as a "lie detector. The only P300-based BCIs which might have a short-term application are a game not with recreational purposes but rather as a neurofeedback system allowing for training attention, and a P300 BCI as supplemental controlling device for gaming (Finke et al., 2009) or painting (Kübler et al., 2009). However, it is not realistic to envision P300 BCIs replacing conventional gaming interfaces or being used as a "mental remote control" for lights, television or stereo. The exact effect of the different factors affecting BCI usability needs to be investigated as well as the application of BCIs in normal life conditions. Current BCI systems are often evaluated under highly controlled laboratory settings. As the aim of BCIs is to provide patients with a communication device, as well as to become mainstream applications, they should take into account the needs and limitations of ALS user and real-world environments. Applications for entertainment such as games or painting tools have already been developed. To be successfully implemented in the market, BCIs should not be difficult to use, while being fashionable, reliable and more affordable. New electrodes that do not need gel and can be integrated with current devices like headphones, caps or glasses, make it a step closer to mainstream applications. Overall, disabled and healthy users can still benefit of P300-based BCIs, and adding multisensory stimuli to existing unimodal BCIs may provide different benefits. More research is needed to examine the interaction between modality and attention, the role of multimodal congruency in space, time and semantic representation, and the contributions of bottom-up and top-down processes. It has been proposed a model toward the integration of other non-P300 ERPs, and/ or brain oscillations, that would lead to a multi-paradigm BCIs with the potential to improve classification accuracies and thus the efficiency and reliability of the system.

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