Auditory and visual brain-computer interfaces as communication aids for persons with severe paralysis

Akustische und visuelle Gehirn-Computer Schnittstellen als Kommunikationshilfen für Menschen mit schweren Muskellähmungen

Doctoral thesis for a doctoral degree
at the Graduate School of Life Sciences,
Julius-Maximilians-Universität Würzburg,
Section *Neuroscience*

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from

Hannover, Germany

Würzburg, 2015

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Danksagung (Acknowledgments)

Sehr gerne blicke ich auf die Zeit zurück, in der die vorliegende Arbeit entstanden ist. Dass die letzten Jahre als Doktorand so bereichernd waren, verdanke ich einer Vielzahl von Menschen, die mich in dieser Zeit fachlich und/oder freundschaftlich begleitet haben und ohne deren Unterstützung diese Arbeit nicht gelungen wäre.

Zunächst möchte ich Andrea Kübler, Stefan Debener und Erhard Wischmeyer, meinem Promotionskomitee, herzlich danken. Ihre durchweg positive Art und die angenehmen Gespräche habe ich als sehr motivierend empfunden und sie waren mir eine große Hilfe. Andrea Kübler und Stefan Debener haben mein Dissertationsvorhaben mit großer fachlicher Expertise begleitet und ich habe sehr von ihrem Wissen profitiert. Stefan Debener möchte ich zudem für die spontane Bereitschaft zur Begutachtung der Arbeit und Erhard Wischmeyer für sein Interesse an unserer Forschung und seine Unterstützung danken.
Vielen Dank an Paul Pauli für sein großes Engagement im Rahmen des Graduiertenkollegs und die Übernahme des Prüfungsvorsitzes.

Besonders dankbar bin ich für das Vertrauen, das mir meine Chefin, Andrea Kübler, entgegengebracht hat und die damit verbundenen Freiheiten. Außerdem konnte ich trotz ihres hohen Arbeitspensums in den entscheidenden Momenten immer auf ihre Unterstützung bauen. Aufgrund der angenehmen und anregenden Atmosphäre in ihrer Arbeitsgruppe am Institut für Psychologie der Universität Würzburg habe ich mich stets wohl gefühlt. Sebastian, Teresa, Tobias, Sonja, Andreas, Adrian, Ruben, Loïc, Elisa, Lena, Barbara, Julia, Yvonne, Karo, Matthias und Annie gebührt dafür mein Dank. Danke für die kollegiale und entspannte Zusammenarbeit, die kleinen und großen Hilfen über die Jahre und die gemeinsamen Unternehmungen und geselligen Abende. Barbara Hörning danke ich zudem für so manche administrative Entlastung.

Besonders hervorheben möchte ich Sebastian Halder und Teresa Sollfrank, meine wunderbaren Bürokollegen, die der Grund dafür waren, dass ich mich auf die Tage im Büro gefreut habe und durch die der (manchmal graue) Arbeitsalltag bunt wurde. Danke an Teresa für das Gute Laune verbreiten und das Teilen von Freud und Leid während unseres Doktorandendaseins.
Ein großes Dankeschön nochmal an Sebastian, der mich nach Würzburg gelotst und als Betreuer meiner Doktorarbeit wesentlich zum Gelingen beigetragen hat. Seinen Beitrag kann ich ihm nicht hoch genug anrechnen. Mit der freundschaftlichen und produktiven Zusammenarbeit sind viele schöne Erinnerungen verknüpft - nicht zuletzt da unsere Dienstreisen uns an die unterschiedlichsten Orte und bis an die Küste Südamerikas geführt haben.

Meiner Tübinger Kollegin Carolin Ruf danke ich dafür, dass sie mir den Einstieg in die BCI-Welt einfach gemacht hat. Nadine, Sebastian und Tobi für die wunderbare Zeit in Kalifornien.

Im Mittelpunkt der vorliegenden Arbeit stehen Menschen mit schweren Muskellähmungen, denen die Kommunikation über Gehirn-Computer Schnittstellen ermöglicht werden soll. Im Rahmen meiner Tätigkeit bin ich dabei zahlreichen Menschen begegnet, die trotz schwerer Schicksale nicht ihren Lebensmut verloren, unserer Forschung großes Interesse entgegengebracht und sich als Studienteilnehmer engagiert haben. Auch wenn teilweise die Kommunikation auf ein Minimum reduziert war, strahlten doch immer einzigartige und starke Persönlichkeiten durch und ich bin dankbar für diese Begegnungen. Ein herzliches Dankeschön an alle Studienteilnehmer und deren Angehörige für die Offenheit, das willkommen heißen in ihrem Zuhause und die Geduld während der Durchführung der Studien.

Ermöglicht wurde die Forschung auch durch die finanzielle Unterstützung im Rahmen des Projekts *BackHome*, das im 7. Forschungsrahmenprogramm der Europäischen Kommission gefördert wurde. Während ich auf das Schreiben von so manchem *Deliverable* innerhalb des Projekts gerne verzichtet hätte, möchte ich die Zusammenarbeit mit dem Konsortium nicht missen; ebenso wenig wie die Koordinationstreffen in Barcelona. Mit fortschreitender Projektdauer sind wir immer mehr zu einer Forscherfamilie zusammengewachsen. Danke an alle Projektpartner und insbesondere die Grazer BCI Kollegen Gernot Müller-Putz, Selina Wriessnegger, Andreas Pinegger und Josef Faller für die gute und erfolgreiche Zusammenarbeit.

Meinen herzlichen Dank an meine großartigen Freunde, meinen Bruder und meine Eltern. Die schönen Momente mit euch abseits der Arbeit sind von unschätzbarem Wert.
Von ganzem Herzen möchte ich meinen Eltern Karin und Ingo danken, die mich während meines gesamten Studiums bedingungslos unterstützt haben. Danke, dass es euch gibt und ihr mich auf meinem Weg begleitet!

Mein innigster Dank an Katha. Mit dir gemeinsam ist das Leben so viel wundervoller!

Abstract

Brain-computer interfaces (BCIs) could provide a muscle-independent communication channel to persons with severe paralysis by translating brain activity into device commands. As a means of communication, in particular BCIs based on event-related potentials (ERPs) as control signal have been researched. Most of these BCIs rely on visual stimulation and have been investigated with healthy participants in controlled laboratory environments. In proof-of-principle studies targeted end users gained control over BCI systems; however, these systems are not yet established as an assistive technology for persons who would most benefit from them. The main aim of this thesis is to advance the usability of ERP-BCIs for target users. To this end, five studies with BCIs have been conducted that enabled users to communicate by focusing their attention on external stimuli.

Two studies were conducted in order to demonstrate the advantages and to further improve the practical application of visual BCIs. In the first study, mental workload was experimentally manipulated during prolonged BCI operation. The study showed the robustness of the visual ERP-BCI since users maintained a satisfactory level of control despite constant distraction in the form of background noise. Moreover, neurophysiological markers that could potentially serve as indicators of high mental workload or fatigue were revealed. This is a first step towards future applications in which the BCI could adapt to the mental state of the user (e.g. pauses if high mental workload is detected to prevent false selections). In the second study, a head-mounted display (HMD), which assures that stimuli are presented in the field of view of the user, was evaluated. High accuracies and information transfer rates, similar to a conventional display, were achieved by healthy participants during a spelling task. Furthermore, a person in the locked-in state (LIS) gained control over the BCI using the HMD. The HMD might be particularly suited for initial communication attempts with persons in the LIS in situations, where mounting a conventional monitor is difficult or not feasible.

Visual ERP-BCIs could prove valuable for persons with residual control over eye muscles and sufficient vision. However, since a substantial number of target users have limited control over eye movements and/or visual impairments, BCIs based on non-visual modalities are required. Therefore, a main aspect of this thesis was to improve an auditory paradigm that should enable motor impaired users to spell by focusing attention on different tones. The two conducted studies revealed that healthy participants were able to achieve high spelling performance with the BCI already in the first session and stress the importance of the choice of the stimulus material. The employed natural tones resulted in an increase in performance compared to a previous study that used artificial tones as stimuli. Furthermore, three out of five users with a varying degree of motor impairments could gain control over the system within the five conducted sessions. Their performance increased significantly from the first to the fifth session - an effect not previously observed for visual ERP-BCIs. Hence, training is particularly important when testing auditory multiclass BCIs with potential users.

A prerequisite for user satisfaction is that the BCI technology matches user requirements. In this context, it is important to compare BCIs with already established assistive technology.

Thus, the fifth study of this dissertation evaluated gaze dependent methods (EOG, eye tracking) as possible control signals for assistive technology and a binary auditory BCI with a person in the locked-in state. The study participant gained control over all tested systems and rated the ease of use of the BCI as the highest among the tested alternatives, but also rated it as the most tiring due to the high amount of attention that was needed for a simple selection. Further efforts are necessary to simplify operation of the BCI.
The involvement of end users in all steps of the design and development process of BCIs will increase the likelihood that they can eventually be used as assistive technology in daily life. The work presented in this thesis is a substantial contribution towards the goal of re-enabling communication to users who cannot rely on motor activity to convey their thoughts.

Zusammenfassung

Gehirn-Computer Schnittstellen (engl. brain-computer interfaces, BCIs) könnten Menschen mit schweren Muskellähmungen muskelunabhängige Kommunikation ermöglichen, indem sie Gehirnaktivität in Steuerungsbefehle übersetzen. Zu Kommunikationszwecken wurden insbesondere BCIs erforscht, die auf ereigniskorrelierten Potenzialen (EKPs) als Steuerungssignal beruhen. Die Mehrzahl dieser BCIs basiert auf visuellen Paradigmen und wurde unter kontrollierten Laborbedingungen mit gesunden Versuchsteilnehmern untersucht. In Machbarkeitsstudien konnten auch Menschen mit schweren Muskellähmungen Kontrolle erlangen. Jedoch sind BCIs noch nicht im Alltag als Hilfsmittel für diejenigen etabliert, die am meisten von ihnen profitieren würden. Die Gebrauchstauglichkeit für diese Zielgruppe zu erhöhen, ist das Hauptziel der vorliegenden Arbeit. Zu diesem Zweck wurden fünf Studien mit BCIs durchgeführt, die Nutzern durch die Aufmerksamkeitsfokussierung auf externe Reize ermöglichen zu kommunizieren.

Um die Vorteile der visuellen Paradigmen zu zeigen und die praktische Anwendbarkeit weiter zu verbessern, wurden zwei Studien durchgeführt. In der ersten Studie wurde die mentale Arbeitsbelastung während längerer Benutzung eines BCI experimentell manipuliert. Die Studie demonstrierte die Robustheit des EKP-BCI. Nutzer konnten trotz konstanter Ablenkung durch Hintergrundgeräusche ein zufriedenstellendes Kontrollniveau aufrechterhalten. Darüber hinaus wurden neurophysiologische Marker gefunden, die als Indikatoren hoher mentaler Arbeitsbelastung oder Ermüdung dienen können. Dies ist ein erster Schritt hin zu Anwendungen, bei denen sich das BCI dem mentalen Zustand des Benutzers anpasst (z.B. indem die Anwendung pausiert, wenn hohe Arbeitsbelastung detektiert wird, um Falschauswahlen zu verhindern). In der zweiten Studie wurde ein Head-Mounted Display (HMD) evaluiert, welches sicherstellt, dass alle Stimuli im Gesichtsfeld des Nutzers angezeigt werden. Dabei wurden von gesunden Versuchsteilnehmern hohe Genauigkeiten und Informationstransferraten beim Schreiben von Wörtern erzielt, vergleichbar mit denen eines herkömmlichen Bildschirms. Zusätzlich erlangte ein Nutzer im Locked-in-Zustand Kontrolle über das BCI mittels des HMD. Das HMD könnte sich insbesondere für initiale Kommunikationsversuche für Personen im Locked-in-Zustand eignen, wenn sich das Aufstellen eines konventionellen Bildschirms als schwierig oder unmöglich erweist.

Visuelle EKP-BCIs könnten sich insgesamt als wertvoll für Personen herausstellen, die noch ihre Augenbewegungen kontrollieren können und über ausreichend Sehkraft verfügen. Da eine nicht unerhebliche Zahl von potenziellen Endbenutzern jedoch eingeschränkte Kontrolle über Augenbewegungen und/oder Sehbeeinträchtigungen hat, sind BCIs notwendig, die auf nicht-visuellen Modalitäten beruhen. Im Rahmen dieser Arbeit lag ein Fokus deshalb auf der Weiterentwicklung eines akustischen Paradigmas, welches Nutzern mit motorischen Einschränkungen das Buchstabieren durch die Aufmerksamkeitsfokussierung auf verschiedene Töne ermöglichen soll. Die beiden hierzu durchgeführten Studien zeigten, dass gesunde Versuchsteilnehmer bereits in der ersten Sitzung hohe Buchstabiergenauigkeiten erzielen konnten. Zudem unterstreichen diese Studien die Wichtigkeit der Wahl der Stimuli.

Die in den beiden Studien verwendeten natürlichen Geräusche, führten zu einer Leistungsverbesserung verglichen mit einer vorausgegangenen Studie, die künstliche Töne verwendete. Darüber hinaus konnten drei von fünf Nutzern mit Muskellähmungen innerhalb von fünf Sitzungen Kontrolle über das System erlangen. Für die drei Nutzer war die Leistung in der fünften Sitzung dabei deutlich höher als in der ersten. Ein solcher Trainingseffekt wurde mit visuellen Paradigmen in vorausgegangenen Studien bisher nicht berichtet. Dieses Ergebnis betont daher die Bedeutsamkeit von Training während der Erprobung von akustischen Multi-Klassen-BCIs mit Endbenutzern.

Eine Grundvoraussetzung für Nutzerzufriedenheit ist, dass die BCI Technologie den Bedürfnissen der Nutzer entspricht. In diesem Zusammenhang ist es wichtig, BCIs mit bereits etablierten Hilfsmitteln zu vergleichen. Daher wurden in der fünften Studie dieser Dissertation sowohl blickabhängige Methoden (EOG, Eye-Tracking) als auch ein akustisches BCI zur binären Kommunikation mit einem Nutzer im Locked-in-Zustand evaluiert. Der Studienteilnehmer erlangte über alle getesteten Systeme die Kontrolle und bewertete den Bedienkomfort des BCI am höchsten verglichen mit den anderen getesteten Methoden. Das BCI wurde jedoch aufgrund der hohen Konzentration, die für die Auswahl eines einzelnen Befehls benötigt wurde, als die ermüdendste bewertet. Weitere Entwicklungen sind notwendig, um die Bedienung des BCI noch stärker zu vereinfachen.

Die Einbeziehung von Endbenutzern in alle Schritte des Entwicklungsprozesses eines BCI wird die Wahrscheinlichkeit erhöhen, dass es schließlich als Hilfsmittel im Alltag genutzt werden kann. Die vorliegende Dissertation leistet wesentliche Beiträge, um dieses Ziel zu erreichen: Nämlich Nutzern, welche sich nicht mittels motorischer Aktivität ausdrücken können, eine neue Form der Kommunikation zu ermöglichen.

Contents

Abbreviations

AAC	Augmentative and alternative communication
ALIS	French Association for Locked-In Syndrome
ALS	Amyotrophic lateral sclerosis
ASSEP	Auditory steady-state evoked potential
AT	Assistive technology
BCI	Brain-computer interface
BOLD	Blood-oxygen-level dependent
CLIS	Complete locked-in state
dHb	Deoxygenated hemoglobin
DOC	Disorder of consciousness
ECG	Electrocardiogram
ECoG	Electrocorticography
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ERD	Event-related desynchronization
ERP	Event-related potential
ERS	Event-related synchronization
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
Hb	Oxygenated hemoglobin
HMD	Head-mounted display
ILD	Interaural level difference
ITD	Interaural time difference
ITR	Information transfer rate
LIS	Locked-in syndrome/state
MD	Muscular dystrophy
ME	Microelectrode
MEA	Microelectrode array
MEG	Magnetoencephalography
MS	Multiple sclerosis
NIV	Noninvasive ventilation
SCP	Slow cortical potential
SMR	Sensorimotor rhythm
SQUID	Super-conducting quantum interference device
SSSEP	Steady-state somatosensory evoked potential
SSVEP	Steady-state visually evoked potential
SWLDA	Stepwise linear discriminant analysis
TBI	Traumatic brain injury
TMV	Tracheostomy mechanical ventilation

1 Introduction

"*. . .as long as I can properly communicate with my voice, my eyes or a machine or whatever, I want to have a respirator. . . But as soon as I can no longer communicate, that's it! I don't want anything else to be done.*"

This statement of a person diagnosed with amyotrophic lateral sclerosis (ALS) and interviewed in the study by Lemoignan and Ells (2010) investigating assisted ventilation illustrates the essential importance of the ability to communicate. As for most study participants, communication was identified as the crucial factor in the decision regarding how to manage respiratory failure, which is likely to occur in a late stage of the disease. ALS can lead to a locked-in syndrome (LIS) and communication is the biggest challenge for persons with LIS according to the French Association for Locked-In Syndrome (ALIS, 2015). LIS may result from ALS, but its most frequent cause is damage to the brainstem following a stroke or a traumatic brain injury and more than 20 different etiologies have been described (Haig, Katz & Sahgal, 1987; Lugo et al., 2015; for reviews see Laureys et al., 2005; Patterson & Grabois, 1986).

The herein presented publications focus on brain-computer interfaces (BCIs) as muscle-independent communication aids for persons with severe paralysis. In the introduction, potential end users are described by providing an overview about the locked-in syndrome and its causes. Furthermore, the basic principles and the current state of BCI technology are summarized. Thereby, a focus is put on BCIs that employ event-related potentials (ERPs) evoked by visual and auditory stimulation that are central to the thesis. The research questions are addressed in section 1.4. Chapter 2 comprises the research papers that are the core of the thesis. The findings and implications of the research are discussed in chapter 3.

1.1 The locked-in state

The term 'locked-in syndrome' was first introduced by Plum and Posner in 1966 and refers to the paralysis of all four limbs and the lower cranial nerves, while consciousness and vertical eye movements of the affected person are retained (Posner et al., 2007). The following more precise neurobehavioral diagnosis criteria were suggested by the American Congress of Rehabilitation Medicine (1995): Quadriparesis or quadriplegia, the inability to speak (aphonia or severe dysphonia), awareness of the environment and observable cognitive abilities on examination. Furthermore, eye opening is sustained (if bilateral ptosis can be ruled out) and the principle methods of communication are vertical or horizontal eye-movements or blinking. If no eye movements are possible and the person is completely immobile, Bauer, Gerstenbrand and Rumpl (1979) classify this state as 'total LIS'. They refer to the state described by Plum and Posner with intact vertical eye movements as 'classical LIS' and suggest the use of the term 'incomplete LIS' if any other residual voluntary movements are possible. In the context of the present thesis, it is important to differentiate the locked in-state, in which residual eye movements are possible, from a complete locked-in state (CLIS), in which control over all muscle activity including eye and external sphincter muscles is lost (Birbaumer, 2006; Murguialday et al., 2011).

The mortality rate is highest in the acute phase of LIS. Patterson and Grabois (1986) reported that 87% of deaths occurred within the first four months for the 139 cases described. However, survival rates of persons in LIS can be high and, once they have been in this state for over a year and if they are medically stabilized, it is possible that they can live with the condition for decades (Doble et al., 2003; Thadani et al., 1991). In their ten-year follow-up report on a cohort of 29 persons with LIS who were treated in a major US rehabilitation hospital and first described by Haig et al. (1987), Doble et al. (2003) reported five- and ten-year survival rates of 83% respectively and a 20-year survival rate of 40%. The database of the French Association for Locked-In Syndrome (ALIS; http://www.alis-asso.fr) is a valuable source of information about LIS. The association was created due to the efforts of Jean-Dominique Bauby in 1997. He was the author of the best-selling novel "The diving bell and the butterfly" (1997), which he dictated to an assistant only using eye-blinks, while being locked-in. Laureys et al. (2005) performed a review of the database. For 250 persons in LIS at the time of the study, the mean time spent in LIS had been six years (±4 years). A large proportion of them (44%) lived at home (108 out of 245). The leading causes of death were infections (40%; especially pneumonia) followed by primary or recurrent brain stem stroke (25% and 10%, respectively) for the data recorded for 42 persons.

Although coping with such a severe condition is difficult, there is increasing evidence that the quality of life of persons in LIS can be good and they can lead meaningful lives (Bruno et al., 2011; Doble et al., 2003; León-Carrión et al., 2002; Rousseau et al., 2013). In a survey among members of ALIS, 72% (47 persons) of the study participants expressed happiness and 28% (18 persons) unhappiness (Bruno et al., 2011). The well-being was assessed with the Anamnestic Comparative Self-Assessment Scale, whose anchors represent the level of the worst period of the participant's life (-5) and the best period (+5) prior to the LIS. Participants were divided according to their scores into "happy" (≥0) and "unhappy" (<0). The median score of the "happy" group was +3 and of the "unhappy" group -4, with a longer time in LIS being associated with a greater happiness. The mental and physical state is usually worst in the acute phase of the disease; therefore, several authors have proposed to postpone end-of life decisions until the affected persons have reached a stable mood state in the post-acute phase, and they have been gradually and thoroughly informed about treatment options and the likely consequences of their decision in an unbiased way (Anderson et al., 2010; Bruno et al., 2011, Laureys et al., 2005; Patterson et al., 1993). The possibility to lead a meaningful and happy life in LIS, if proper care and social support is provided, must not be neglected. Efforts toward social integration of these severely motor restricted persons need to be increased (Lulé et al., 2009). It is important to provide adaptive coping strategies, social and medical support and technical aids. Persons in LIS will benefit from improvements in augmentative and alternative communication devices (AAC) in general and particularly in muscle-independent communication channels, such as brain-computer interfaces (Kübler et al., 2001a; Laureys et al., 2005).

Common causes of the locked-in state are described in the subsections below, followed by an overview on methods of alternative communication in this state.

1.1.1 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder and the most common motor neuron disease. It causes a progressive degeneration of upper and lower motor neurons (for reviews see Bulle Oliveira & Batista Pereira, 2009; Kiernan et al., 2011; Mitchell & Borasio, 2007). According to the "El Escorial" diagnostic criteria established by the World Federation of Neurology (Brooks et al., 1994, 2000) a diagnosis of ALS requires signs of upper and lower motor neuron degeneration along with a progressive spread of the symptoms or signs within a region or to other regions (bulbar, cervical, thoracic, lumbosacral) and the absence of evidence of other diseases that could explain the signs. Clinical features of lower motor neuron degeneration include muscle weakness, atrophy and fasciculations, whereas signs of upper motor neuron degeneration are clonus, spasticity and a pathological spread of reflexes (Brooks et al., 1994). Depending on which symptoms occur first, one can differentiate bulbar onset (e.g. dysarthria, dysphagia) from limb onset (e.g. weakness in arms or legs). Most cases of ALS occur sporadic, but in about 5-10% of cases a family history of ALS can be identified (Deng et al., 2011). Several genes have been implicated in the pathogenesis of ALS (Kiernan et al., 2011). Among these is SOD1, for which mutations can be found in 10-20% of cases with an autosomal-dominant pattern of inheritance (Rosen et al., 1993).

Despite a variety of hypotheses that have been suggested for the pathogenesis of ALS, the cause of ALS remains unclear. Evidence that glutamate-induced excitotoxicity may mediate degeneration of motor neurons has led to the first licensed disease modifying treatment with riluzole, which is a glutamate-release inhibitor. A review of four randomized controlled trials indicated that riluzole could prolong median survival by approximately two to three months (Miller, Mitchell & Moore, 2012).

ALS occurs worldwide, but the incidence rate can only be estimated. Results from a systematic literature review from Cronin, Hardiman and Traynor (2007) indicate lower incidence rate for African, Asian, and Hispanic ethnicities. A study based on data from prospective population based ALS registers in Italy, Ireland and the UK, suggested that the incidence rate is homogeneous across Europe (Logroscino et al., 2010). The overall incidence was 2.16 per 100.000 person years and 2.7 per 100.000 person years for the European population over the age of 18 years. The incidence rate for the adult population was higher for men compared to women (ratio 1.4:1). The median age at diagnosis was 65.2 years for men and 67 years for women. Incidence rates steadily increased after the age of 30 and declined after reaching a peak at 70-74 years for men and 65-69 years for women (Logroscino et al., 2010).

The median survival time as reported by a systematic review by Chiò et al. (2009) varied from 20 to 48 months. However, the survival time from onset to death exceeded 10 years in 5 to 10% of all cases, with an older age and a bulbar onset being negative prognostic factors. The natural and most common cause of death in ALS is respiratory failure (Gil et al., 2008; Neudert et al., 2001; Spataro et al., 2010). Noninvasive ventilation (NIV) can prolong survival and increase quality of life for persons with ALS and respiratory insufficiency (Bourke et al., 2006; Carratù et al., 2009; Lechtzin et al., 2007). If, at a later disease stage, NIV is no longer effective or respiratory failure occurs, a tracheotomy and invasive mechanical ventilation (TMV: tracheostomy mechanical ventilation) can be considered to prolong life. It has been shown in a study by Spataro et al. (2012) that the median survival time was 16 months longer for participants receiving TMV compared to non-tracheostomized participants. The positive effect on survival time was even more pronounced for persons younger than 60 years at the time of onset (19 month). The number of performed tracheotomies has increased, but large differences exist regarding the late stage treatment of ALS between and within countries. In several European ALS centers, TMV is discouraged due to the high burden placed upon caregivers and the fear of a locked-in syndrome (Héritier Barras et al., 2013). In Japan, where discontinuation of mechanical ventilation is illegal once initiated, a much higher proportion of persons with ALS receive TMV than in European countries or the US. For instance, Chiò et al., (2010) report that 10.6% of an Italian ALS population received TMV and the reported percentages were lower for Ireland (0.9%, O'Toole et al., 2008) and Germany (3.3%, Neudert et al., 2001). In Japan, on the other hand, 36% received TMV according to the "Japan ALS association" (2003, cited by Hirano et al., 2006). A recent survey among neurologists in the US and Japan revealed that Japanese neurologists were more likely to recommend TMV and a higher number of their patients (32%) received TMV as compared to 10% reported by the US American neurologists (Rabkin et al., 2013). A Japanese nationwide survey with 709 persons diagnosed with ALS indicated that 89 (13%) developed a complete locked-in syndrome and the majority (70%) of whom reached CLIS within five years of receiving TMV (Kawata, Mizoguchi & Hayashi, 2008; cited by Héritier Barras et al., 2013). When deciding whether to use or continue ventilatory support, the ability to communicate is a key factor for persons with ALS and healthcare professionals, but cultural, social and economic factors also play an important role (Héritier Barras et al., 2013; Hirano et al., 2006; Lemoignan & Ells, 2010).

Due to the progressive character of the disease and its comparably high incidence rate, persons with ALS participated in several studies concerned with the evaluation of brain-computer interfaces for communication (for reviews see Kübler & Birbaumer, 2008; Marchetti & Priftis, 2014). Other neuromuscular diseases and auto immune disorders can lead to a progressive loss of motor control. Among those for which cases of LIS were reported are multiple sclerosis (MS) and Guillain–Barré syndrome (Forti et al., 1982; Medici et al., 2011; Ragazzoni et al., 2000).

1.1.2 Stroke and traumatic-brain injury

As opposed to progressive neuromuscular diseases which might result in a locked-in state for those affected after years of living with the disease, a lesion in the ventral pons can resultf in a more sudden locked-in syndrome. The most common cause of LIS is an ischemic stroke, which is caused by either an basilar artery thrombosis or a secondary occlusion of the perforating arteries. Other frequent causes are hemorrhagic strokes originating in or infiltrating into the ventral pons, or traumatic brain injuries (TBIs) that cause contusions in the same region or a dissection of the vertebrobasilar axis (Patterson & Grabois, 1986; Smith & Delargy, 2005). The ventral pons contains the corticospinal and corticobulbar tracts. Lesions of the corticospinal tract can lead to quadriparesis or quadriplegia. Paralyses in the region of the face, head and neck are caused by damage to the corticobulbar tract. The impairments may vary depending on which cranial nerves are affected (see Figure 1 for an illustration of the cranial nerves of the brain stem and their functions). In the classic LIS, vertical eye movements are retained which indicates that the oculomotor nerve (III) with nuclei located in the mesencephalon is intact. The other nerves (IV and VI) involved in the control of eye movements, however, are damaged. Damage to the facial nerve (VII) and lower cranial nerves (IX-XII) may manifest as facial palsy and problems with speech and swallowing (Trepel, 2004).

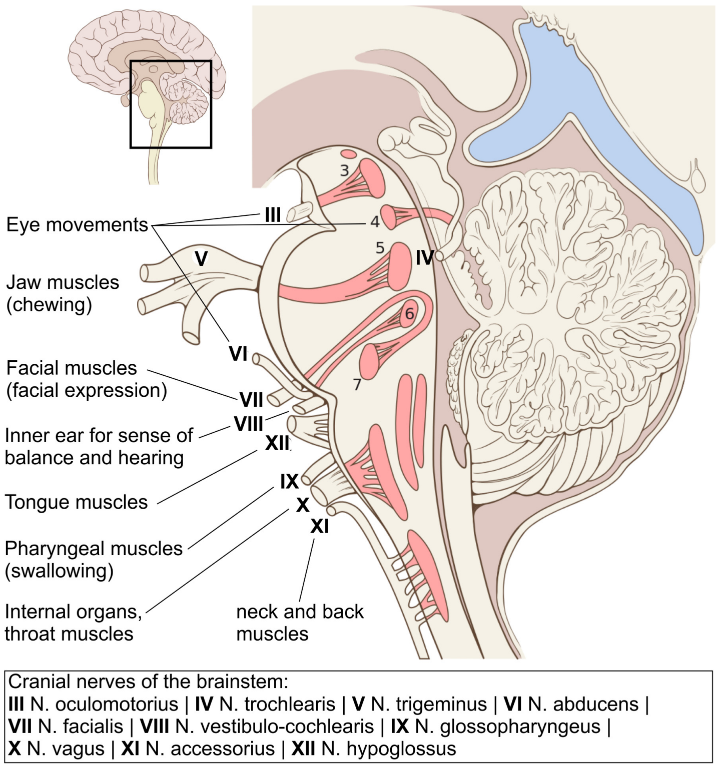

Figure 1. Schematic illustration of the cranial nerves of the brainstem, their motor nuclei and their main functions. Tracts inside the brainstem and motor nuclei are printed in red. The figure is a modification of illustrations created by Patrick J. Lynch and provided under the terms of the Creative Commons License 2.5.

Stroke is the second leading cause of death worldwide and, along with TBI, a leading cause of adult disability; however, no incidence rates for the rare locked-in syndrome have been reported (Smith & Delargy, 2005; World Health Organization, 2014). Only a few persons in LIS due to a stroke or TBI participated in BCI studies aimed at improving communication, although they constitute the largest group of potential end users (Schreuder et al., 2013a).

1.1.3 Alternative communication in the locked-in state

Augmentative and alternative communication (AAC) systems can help persons, who are unable to use speech as their primary method of communication. *Augmentative* refers to processes supplementing existing speech abilities and *alternative* to those that replace speech. Unaided communication systems rely only on the user's body to produce symbols (e.g. gestures and sign language), whereas aided communication systems require additional equipment. These aided communication devices can range from low-tech methods, such as letter boards, to high-tech computer-aided methods with synthesized speech options (Glennen, 1997).

For persons in LIS, it is important to establish a simple communication code that allows them to reliably answer closed questions. A yes/no code should rely on the movements that are easiest to perform for the person in LIS. Usually, this is an eye code where movements in one direction indicate "yes" and in the opposite direction "no"; eyelid blinks could also be used. If the attention span of the user allows it, a higher level of communication could be reached with letter boards. These boards allow letter-by-letter spelling, but also impose a higher workload on the caregiver. For instance, if the letter board lists the letters by the frequency that they appear in their respective language, the interlocutor has to pronounce the letters until the user indicates the desired letter (e.g. with a blink of the eye), note the letter and then repeat the process until the user has conveyed his message (Laureys et al., 2005). Many different low-tech communication board methods have been proposed and should be chosen according to the user's needs (for an overview of available methods see Gaudeul, 2015; Laureys et al., 2005). A method that allows for communication independent of the caregiver is based on gaze tracking. If the users have sufficient control over their eye movements, an eye tracking system allows them to choose symbols presented on a computer screen by visual fixation of the desired item (for a state of the science in AAC for persons with acquired neurological conditions see Beukelman et al., 2007).

A recent survey among members of ALIS showed that all 88 respondents used a yes/no code primarily relying on eye movements and 62% used assistive technology (Lugo et al., 2015). The majority of the participants in the survey (73%) had recovered some functional movements and almost half could communicate verbally. However, only a minority (43%) of the originally

204 invited members of LIS responded. Spataro et al. (2014) performed a telephone survey among 30 persons with late-stage ALS about the usage of a provisioned eye tracking system. While average daily usage, mainly for communication with caregivers/relatives, browsing the internet, social networking and writing e-mails, was high (300 minutes), a proportion of participants (23.3%) reported irregular and limited daily usage. The most frequent reasons for non-use were the inability to properly move the eyes and eye muscle fatigue. All the methods mentioned above rely on the ability of the users in LIS to control their eye movements. Hence, for those users with severe oculomotor impairments and no other residual muscle activity, a communication aid is needed that does not rely on muscle activity. Such a non-muscular communication channel could be provided by brain-computer interfaces (Kübler & Neumann, 2005).

1.2 Brain-Computer Interfaces

The discovery and description of the human electroencephalogram by Hans Berger (1929) paved the way for brain-computer interfaces (BCIs). It sparked the idea that brain signals could be used for communication without the need for muscle activity, but it was not until decades later that the fiction of a BCI became reality with the study of Fetz et al. (1969). They demonstrated that rhesus macaques could modulate the firing activity of single neurons to gain food rewards in an operant learning paradigm. The term 'brain-computer interface' however, was later introduced by Vidal (1973) to denote a system that provides a direct link between the brain and a computer. With advances in neurophysiology and recording techniques, increased computing power and improved signal analysis techniques, BCIs allow nowadays near real time feedback of brain-activity and translation into device commands to replace, restore, improve or enhance functions of the user (for reviews see Kübler et al., 2001a; Wolpaw & Wolpaw, 2012). The basic principles of brain-computer interfaces can be illustrated with a diagram termed 'the BCI cycle' (see Figure 2). The cycle begins with the user, who has a specific intention or task to fulfill. To operate a BCI, brain signals need to be acquired. This can be achieved with invasive recording methods, such as electrocorticography (ECoG), microelectrode (ME) or microelectrode array (MEA) recordings, or non-invasive methods, such as electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) or near-infrared spectroscopy (NIRS). In the next step, the recorded data is preprocessed and relevant features are extracted. This step is a prerequisite for the prediction of the intended outcomes. A classification algorithm determines the class a data point belongs to depending on its features. This information is translated into commands for the output devices, such as computer applications, or hardware, such as orthoses, prostheses or wheelchairs. Thereby, different modalities (e.g. visual, auditory, tactile) can be applied to provide the user with feedback and to close the BCI cycle (Kübler & Kotchoubey, 2007; van Gerven et al., 2009; Wolpaw et al., 2002). Both the user and the computer system can learn to adapt to each other. All components of the cycle are essential for the system and improvements can target all steps in the cycle, ranging from the training of the user and employing easy-to-use paradigms to providing appropriate feedback (Kübler et al., 2011).

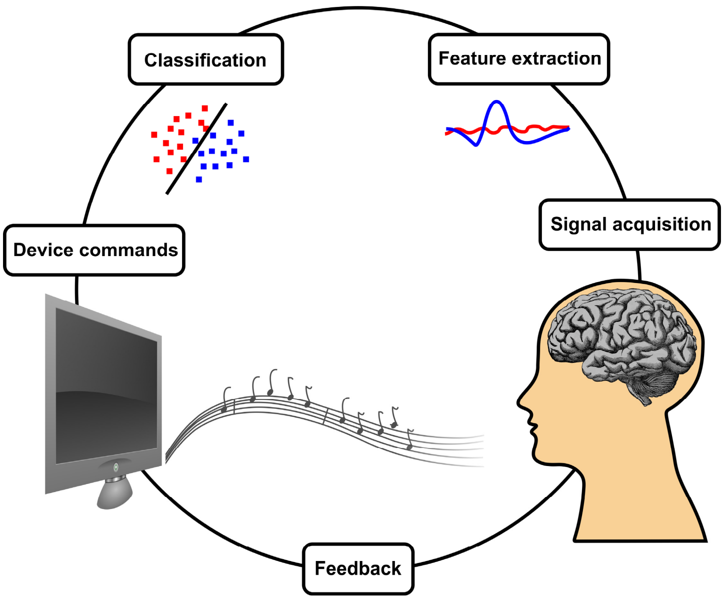

Figure 2. The BCI cycle. The steps required to translate intentions of the user into device commands using willful modulation of brain activity are displayed.

In the following sections, the most applied recording techniques and BCI paradigms are introduced with a focus on EEG-based BCIs. Furthermore, the state of current visual and auditory brain-computer interfaces based on event-related potentials (ERPs) is summarized.

1.2.1 Recording techniques and control signals

Electroencephalography (EEG) is the method of recording electrical activity of the brain using electrodes placed on the scalp. The signal represents the summed activity of a large number of inhibitory and excitatory postsynaptic potentials. Postsynaptic potentials of neurons that are aligned perpendicularly to the cortical surface contribute most to the signal. During EEG recordings, voltage differences between positions on the scalp are amplified and changes in the voltage are plotted over time. The resulting graph is called an electroencephalogram. The electrical signals of the brain are blurred as they travel through the brain and skull; spatial resolution is therefore low – in the centimeter range (Luck, 2005). On the other hand, the EEG allows for the recording of brain signals with a high temporal resolution in the millisecond range with relatively low equipment costs (van Gerven et al., 2009). As every electrical current is surrounded by a magnetic field and the magnetic signal is not disturbed by the skull, the magnetic activity can be recorded as another direct measure of the electrical activity of the brain. This technique is called magnetoencephalography (MEG). It allows higher spatial resolution of brain activity but is more expensive and, unlike EEG, not portable, because a magnetically shielded room with a super-conducting quantum interference device (SQUID) is needed for recordings (Hämäläinen et al., 1993).

Invasive recording methods, such as microelectrodes (ME) or microelectrode arrays (MEA), allow to directly measure the activity of single neurons or groups of neurons with an even higher temporal resolution; however, only a few clinical studies exist and the risks associated with the implant procedure, the questions of recording longevity and the signal stability have yet to be adequately investigated (Hochberg et al., 2006; Otto, Ludwig & Kipke, 2012). Recordings with electrodes placed on the surface of the brain (electrocorticography, ECoG) yielded promising results for real-time BCI applications, but the question still remains as to whether the benefits of invasive methods outweigh the risks (Brunner et al., 2011; Leuthardt et al., 2004).

In contrast to the methods described above, which measure the direct consequences of neural activity, functional magnetic resonance imaging (fMRI) and functional near infrared spectroscopy (fNIRS) depend on the blood-oxygen-level dependent (BOLD) contrast and are therefore indirect measures of brain activity. The BOLD contrast was first described by Ogawa et al. (1990) in rat brain studies. Metabolic processes require oxygen that is supplied through the hemoglobin contained in red blood cells. Oxygenated hemoglobin (Hb) is diamagnetic, whereas deoxygenated hemoglobin (dHB) is paramagnetic which disturbs the MR signal intensity. With brain activation, the oxygen consumption increases and hence the amount of dHB initially increases, but an over-compensatory increase in blood flow in the active region results in a higher supply of Hb compared to the baseline and a brighter MR image due to the decreased amount of dHB (Huettel, Song & McCarthy, 2009). Logothetis (2002) presented evidence that neural responses elicited by a stimulus are directly reflected in the BOLD contrast.

However, the BOLD hemodynamic response takes several seconds; therefore, the temporal resolution of fMRI is low, but its spatial resolution is higher compared to EEG and it also allows the imaging of subcortical structures. The high costs associated with an fMRI scanner, mainly for operating the superconducting magnetic coils, and its immobility are disadvantages for practical BCI use, but nevertheless useful applications have been demonstrated (Monti et al., 2010). Functional near infrared spectroscopy (fNIRS) also relies on the BOLD contrast (the absorption spectra for dHb and Hb differ) and has therefore a low temporal resolution, however, due to its portability it might become an option for BCI aided communication (Gallegos-Ayala et al., 2014; Ramsey, 2012). An estimate of the spatial and temporal resolution of the described recording methods is depicted in Figure 3.

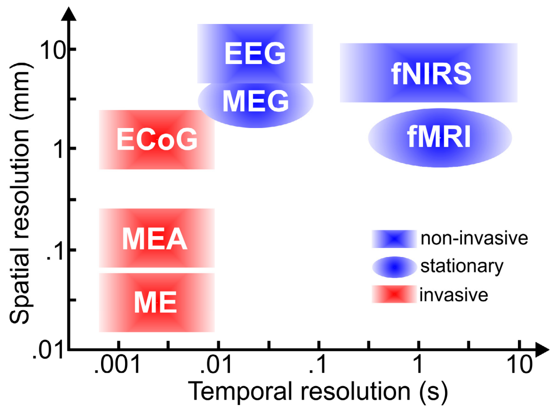

Figure 3.Recording methods used for BCIs and estimates of their temporal and spatial resolution. Figure adapted from van Gerven et al., 2009.

Depending on the desired function, each presented method has its advantages and disadvantages. Due to its high temporal resolution, portability and low costs the EEG has been the method of choice for many BCI applications. The survey by Mason et al. (2007) demonstrated that it was the applied method in the vast majority (83%) of conducted BCI studies. In the following sections, different EEG-based control signals, namely sensorimotor rhythms (SMRs), slow cortical potentials (SCPs), steady-state visually evoked potentials (SSVEPs) and event-related potentials (ERPs), are presented with a focus on ERP-based BCIs.

1.2.1.1 BCIs based on sensorimotor rhythms

Sensorimotor rhythms (SMRs) are oscillations that can be recorded over sensorimotor cortices (Pfurtscheller & Lopes da Silva, 1999). They can be divided into three major frequency bands: 1) ~8-12 Hz referred to as μ, 2) ~18-30 Hz (β) and 3) >30Hz (γ). These frequency bands can be modulated with motor behavior. With motor activity, the SMRs decrease. This decrease was termed *event-related desynchronization* (ERD; Pfurtscheller & Aranibar, 1979). The opposite phenomenon, *event-related synchronization* (ERS) can be recorded following movement execution. Most importantly for the use of ERD as a control signal for BCIs is the observation that ERDs occur not only with actual movement, but also with motor imagery (Jasper & Penfield, 1949; Pfurtscheller & Lopes da Silva, 1999). There is strong evidence that both movement imagery and executed actions share, to some extent, the same neural substrates (Decety, 1996). For BCI control, the users need to learn to regulate their SMRs. In a typical task, the participant is asked to imagine particular movements (e.g. hand or foot movement vs. relaxation) and the changes in SMR activity are translated into device commands, such as cursor movements on a screen. This is possible because changes in SMRs are usually somatotopically localized (Pfurtscheller & Lopes da Silva, 1999; Pfurtscheller & McFarland, 2012). Wolpaw and McFarland (2004) have demonstrated that multidimensional movement control is possible with an SMR-BCI. Their study participants learned to move a cursor to one of eight targets appearing on the screen. A spelling application ("Hex-O-Spell") was introduced by Blankertz et al. (2006) that allowed the users to choose between six different options and spell letters in a two-step procedure controlled by only two mental states (imagined movements of the right hand or foot). In a field study by Guger et al. (2003), 93% of participants (N=99) gained some control over an SMR-BCI within two sessions (>60% accuracy). Four participants with ALS learnt to modulate their SMR activity and achieved control over vertical cursor movements (>75% accuracy) after training over the course of three to seven months (Kübler et al., 2005). This training has been explored in recent years as an opportunity for motor rehabilitation, in particular following a stroke (Ramos-Murguialday et al., 2013; Silvoni et al., 2011).

1.2.1.2 BCIs based on slow cortical potentials

Slow cortical potentials (SCPs) are slow shifts in polarizations in the EEG lasting from 300 ms to several seconds (for a review see Birbaumer, 1999). Negative voltage shifts usually occur during the preparation of voluntary movements or precede motor imagery and cognitive tasks, such as mental arithmetic. Early studies employed self-regulation of SCPs to investigate the influence on epilepsy, alcohol dependency and schizophrenia (Kotchoubey et al., 1997; Rockstroh et al., 1993; Schneider et al., 1992, 1993). Neurofeedback to learn regulation of SCPs continues to be explored as treatment for a variety of disorders, such as attention-deficit/hyperactivity disorder (Heinrich et al., 2004; Strehl et al., 2006). Kübler et al. (1999)

presented a spelling system ("the thought translation device") that enabled users to move a cursor on the screen upwards or downwards by regulating their SCPs. A positive potential shift moved the cursor downwards and a negative upwards. Letter strings were presented on the screen and the user could either make a selection by moving the cursor towards the bottom or could refrain from a selection. The alphabet was firstly split into two halves, one of which the patient would select, and the chosen group would split again into two halves and so forth until only one letter remained that was displayed on the top of the screen. In the best case, a selection was possible every 4 seconds. Birbaumer et al. (1999) went on to show that two persons with ALS were able to reach a letter selection rate of about 0.5 characters per minute after 288 and 327 training sessions, respectively. Drawbacks of SCP based BCIs are their slow speed, the extensive training necessary and the lack of good multidimensional control (Allison, Faller & Neuper, 2012).

1.2.1.3 BCIs based on steady-state visually evoked potentials

Steady-state visually evoked potentials (SSVEPs) are periodic voltage oscillations that can be recorded over visual cortices and are time-locked and phase-locked to the onset of flickering visual stimuli (for a review see Vialatte et al., 2010). These visual stimuli can either be simple or complex flickers. Examples of simple flickers are blinking light-emitting diodes or flickering squares displayed on a computer screen. Different user commands can be encoded by presenting stimuli with different stimulation frequencies because spectral decomposition of the EEG allows to reveal the same frequencies of the stimulation and also peaks at higher harmonic frequencies (Müller-Putz et al., 2005). Complex flickers are alternatively reversing checkerboards that produce more pronounced SSVEPs compared to simple stimuli but, because they are usually larger, less user commands can be encoded (Vialatte et al., 2010). Hwang et al. (2012) designed a spelling system with simple flickers that allowed the users to choose from 30 different commands. Rapid stimulation (usually >6Hz) in other sensory modalities also yields EEG frequencies over the primary cortices involved in the processing of the stimuli at the rate of the stimulation. Recently, Kim et al. (2011) showed the feasibility of a BCI based on auditory steady-state evoked potentials (ASSEPs). For binary selections, study participants were asked to listen to one of two auditory pure tone streams that differed in their low frequency amplitude modulation (37 Hz and 43 Hz). Furthermore, it was demonstrated that steady-state somatosensory evoked potentials (SSSEPs) could be elicited with tactile stimulation and employed for a BCI (Müller-Putz et al., 2006).

1.3 BCIs based on event-related potentials

Event-related potentials (ERPs) are neural responses embedded in the EEG that are associated with specific cognitive, sensory or motor events. They can be identified during single trials; however, usually they are extracted by averaging several trials to increase the signal-to-noise ratio. These ERPs are named either according to their ordinal position in the EEG waveform, e.g. the first negative potential is called N1, or according to their latency, e.g. N100 (100 ms post stimulus onset). However, the latency of a component can vary depending on the experimental conditions (Luck, 2005). One of the most researched components is the P3 or P300 component. It was first described by Sutton et al. (1965). In their experiment, they observed a large positive potential that peaked approximately 300 ms after the occurrence of a stimulus for which participants could not predict whether it would be auditory or visual. In the majority of studies, the P3 component is elicited in paradigms that are variants of the classic oddball paradigm (Donchin, Ritter & McCallum, 1978; Polich, 2007). In this paradigm, an infrequent ("odd") target stimulus is embedded in a train of frequent standard stimuli. The study participants are instructed to respond overtly (e.g. by pressing a button) or covertly (e.g. by counting mentally) to the target stimuli. The target stimuli elicit a positive peak. The amplitude of this peak is usually largest over the centro-parietal electrode sites with latencies between 250 ms to 500 ms; however, these values can vary depending upon participants and experimental conditions (Polich, 2007). It was shown that P3 latency is increased if categorization of the eliciting stimulus becomes more difficult (Courchesne, Hillyard & Courchesne, 1977; Kutas, McCarthy & Donchin, 1977; Magliero et al., 1984). Furthermore, the P3 amplitude has been associated with the intensity of processing (for a review, see Kok, 2001). It was demonstrated that the P3 decreases if attention is diverted from the eliciting stimuli (Wickens, Isreal & Donchin, 1977). A major factor that modulates P3 amplitude is the subjective probability of a stimulus, with less expected stimuli eliciting larger amplitudes (Duncan-Johnson & Donchin, 1977; Johnson, 1986). Furthermore, there is a positive association between the P3 amplitude and the meaning/salience and the task relevance of a stimulus (Johnson, 1986). All mentioned factors seem to influence the mental resource allocation and, therefore, the P3 amplitude has been suggested as a measure of processing capacity; however, in a recent review Kok (2001) concluded that the usefulness of the P3 for this purpose is limited.

The first BCI based on the oddball paradigm was introduced by Farwell & Donchin (1988). They presented participants with a 6x6 matrix containing letters of the alphabet and additional commands displayed on a computer screen. During the stimulation, rows and columns of the matrix were highlighted in random order. Participants were asked to observe a predefined letter/command and keep a mental count of the number of times it was highlighted. In this paradigm, each flashing row and column that contains the target cell elicits a P3 component. Hence, the target rows and columns can be classified and the target letters identified at their crossing (see Figure 4). In a typical BCI based on event-related potentials, a so-called calibration or training run has to first be performed. Participants are asked to spell given letters and the acquired data is then used to train a classification algorithm. Afterwards, participants can freely choose letters and feedback is provided online according to the classifier results. In a comparison of different classification techniques, stepwise linear discriminant analysis (SWLDA) yielded best performance characteristics (Krusienski et al., 2006). With a probabilistic model and transfer learning approach, spelling might be possible without a designated calibration run (Kindermans et al., 2014a, b). Numerous studies have been conducted that employed the paradigm suggested by Farwell & Donchin (1988) and the influence of various factors, such as matrix size, timing parameters (stimulus duration and interstimulus interval), psychological factors and signal processing methods, were investigated (for reviews see Kleih et al., 2011; Mak et al., 2011).

These studies often refer to this type of BCI as P300 speller or P300 BCI. While the P300 is often the most prominent component that is elicited in this paradigm, other ERPs contribute to the classification, most notably the N200, which was the most pronounced component for about 30% of study participants in the investigation of Kaufmann, Hammer & Kübler (2011). Thus, the term ERP-BCI is more precise.

It was demonstrated that most healthy users were able to write a short word (>80% accuracy) within the first session (Guger et al., 2009). Because of the little necessary training and the good signal-to-noise ratio, ERP-BCIs have been widely researched and several applications have been developed that allow for artistic expression, browsing the internet and controlling a media player (Halder et al., 2015; Mugler et al., 2010; Münßinger et al., 2010; Zickler et al., 2013). A BCI system that allows to control and switch between the mentioned applications (speller, painting, web browser, media player), to turn on and off electrical devices and to perform games intended for cognitive rehabilitation was implemented (Käthner et al., 2014a; Miralles et al., 2015). Persons with severe motor impairments (e.g. persons with late stage ALS) were also able to gain control over ERP-BCIs (Kübler & Birbaumer, 2008; Nijboer et al., 2008; Townsend et al., 2010). However, for these users, who constitute the main target group of BCIs, the level of control achieved varied widely depending on the applied paradigm, level of impairment and other factors (see review by Mak et al., 2011; Marchetti & Priftis, 2014). ERP-BCIs are not yet widely utilized as assistive technology. Nevertheless, some pilot studies demonstrated the feasibility of long-term independent home use for persons affected by ALS (Holz et al., 2015; Holz, Botrel & Kübler, in press; Seller, Vaughan & Wolpaw, 2010).

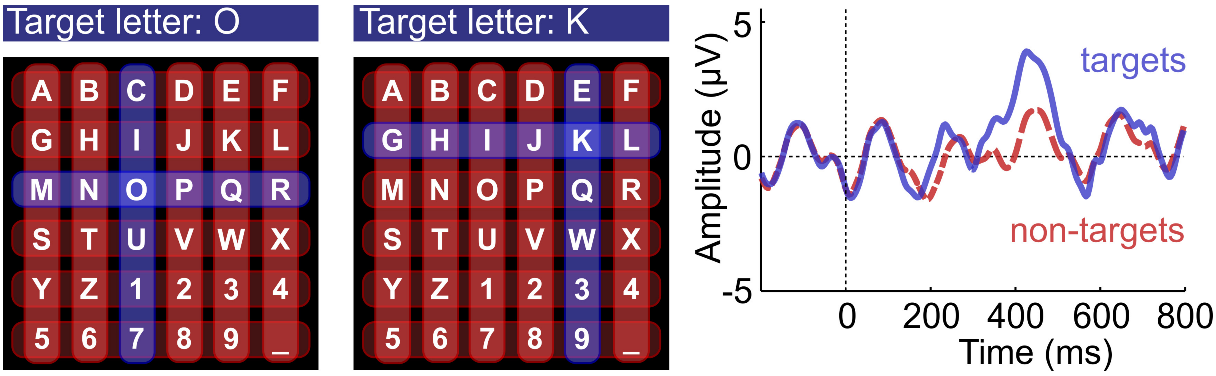

Figure 4. Illustration of the classic P300 speller paradigm and exemplary waveforms that are elicited by it. During stimulation, the rows and columns are highlighted in a random order. The user is asked to focus his gaze on the letter to spell in the matrix and silently count whenever it is highlighted. For illustration purposes, target rows and columns are colored in blue and non-target rows and columns in red. The target letter can be identified at the intersection of the target row and column. The exemplary ERP waveforms on the right depict averaged data at electrode Cz for targets (blue) and non-targets (red) for a single person, who selected several letters with a P300 speller.

Recently, Kaufmann et al. (2011, 2013) demonstrated that performance with an ERP-BCI could be substantially improved by changing the stimulation method. Instead of highlighting the characters of the matrix directly, symbols of the matrix were overlaid with pictures of faces during stimulation. This procedure elicited additional face-specific ERP components (N170, N400f) that contributed to the classification. Online classification performance was significantly higher for healthy participants and persons with neurodegenerative disorders compared to the classic stimulation method. The benefit was particularly large for two potential end users, who spelled with ≤40% accuracy with the classic paradigm that increased to >80% accuracy with the face stimuli.

With the classic stimulation method of highlighting the rows and columns directly, most studies reported maximum information transfer rates (ITRs) of 10-25 bits/min (Wolpaw et al., 2002). These ITRs could be substantially improved with the stimulation by face stimuli (Kaufmann et al., 2013). For spelling a five-letter word, bit rates were in the range of 15-50 bits/min, depending on the number of sequences. With an invasive recording method (ECoG), the participant in the study of Brunner et al. (2011) could achieve an ITR of 69 bits/min (86% correctly selected letters). These bit rates were exceeded by some users in the proof-of-principle study by Kaufmann and Kübler (2014) using EEG as the recording method and overlaying two rows or columns simultaneously to speed up selections (bit rates of up to 150 bits/min were obtained, however, offline).

A major shortcoming of the presented BCI approach is that it relies on visual stimulation and requires the user to focus his eye gaze on the desired item (Brunner et al., 2010). For potential end users with most severe paralysis, visual impairments and/or difficulties to control eye movements, gaining control over the described visual ERP-based BCI is not possible. For persons with ALS the most frequent oculomotor dysfunction, particularly in the late-stage, is ophtalmoparesis and hence, they are unable or have difficulties to move their eyes (Huggins, Wren & Gruis, 2011; Sharma et al., 2011). Other possible dysfunctions include nystagmus and defective saccadic or pursuit movements. In a study involving 25 persons diagnosed with ALS by McCane et al. (2014), the main obstacle of use for a 6x6 matrix speller were visual impairments of the participants (e.g. ptosis, nystagmus, diplopia).

Box 1: Performance metrics

To assess the effectiveness of a BCI in a specific application, the accuracy as the percentage of correct selections is usually determined. A possible measure of the efficiency is the information transfer rate (ITR) as it combines both the accuracy and speed of selections in one value and takes into account the number of possible choices. The bits transmitted per trial (B) can be calculated with the formula derived from Pierce (1980), based on Shannon's communication theory (Shannon and Weaver, 1964), and suggested for BCI research by Wolpaw et al. (1998, 2002):

$$B = \log_2 N + P * \log_2 P + (1-P) * \log_2 \frac{(1-P)}{(1-N)}$$

Where N is the number of possible choices and P the probability that the wanted choice will be selected. The information transfer rate (in bits/min) can be obtained by dividing B by the trial duration in minutes.

Because the assumption of unequal error distributions for this formula is not met by most BCIs, Kronegg, Valoshynovskiy and Pun (2005) proposed to use a different bit rate definition that could, however, not establish itself.

The ITR alone does not allow to adequately judge the performance of a BCI. If for instance, the ITR is high, but the accuracy level is below 50%, spelling a word correctly would become an impossible task. Hence, the ITR should not be used as single evaluation metric. The accuracy threshold that needs to be reached to achieve satisfactory control depends on a variety of factors such as the user, the paradigm and algorithms implemented. Because a language support software could operate at a level of 70% correct, this value was used by Kübler et al. (2001b) and has been defined as a threshold value for satisfactory communication since (e.g., Furdea et al., 2009; Kübler et al., 2005; Nijboer et al., 2008). Particularly for a multiclass BCI for spelling, lower accuracies might result in unacceptable long trial durations for correct letter selections (Sellers et al., 2006). In other applications, such as navigating a wheelchair near 100% classification accuracy is needed. For a discussion on evaluation metrics see McFarland et al. (2006). In order to assess usability according to ISO recommendations (9241-210), user satisfaction should be assessed along with effectiveness and efficiency in a user-centered design process (Zickler et al., 2011). For this, several metrics have been proposed (for a review see Kübler et al., 2014).

If control over the eye gaze is impaired but vision is still intact, visual BCIs that rely on covert attention could be an option (i.e. a shift in the focus of attention without head or eye movements). Several studies proposed paradigms that allow high performance through the presentation of all items on a central position on the screen or in close proximity to each other (Acqualagna & Blankertz 2013; Aloise et al., 2013; Liu, Zhou & Hu, 2011; Marchetti et al., 2013; Treder, Schmidt & Blankertz, 2011).

As the control signal can also be evoked by non-visual stimuli, BCIs based on tactile and auditory stimuli have been proposed (for a review see Riccio et al., 2012). These BCIs potentially allow users, who have no visual abilities or are completely paralyzed (e.g. persons in CLIS or blind users), to gain control over BCIs. Following a proof-of-principle study using SSSEPs by Müller-Putz et al. (2006), Brouwer & van Erp (2010) proposed a tactile BCI based on ERPs. Two, four or six tactors (vibrating elements) were placed around the waist of the study participants to present vibro-tactile stimuli and they were asked to focus on a designated target tactor during the stimulation. During the online classification, accuracies above the chance level were achieved. A spelling system was designed by van der Waal et al. (2012) with tactile stimuli applied to six fingers that allowed the participant to select letters in a two-step procedure. Five out of eight study participants succeeded in writing a word of their own choice with error correction online. Most study participants in the study by Kaufmann, Herweg and Kübler (2014) could navigate a virtual wheelchair with four tactile stimulators that coded for directions. Moreover, Kaufmann, Holz and Kübler (2013) demonstrated the feasibility of a tactile BCI for spelling for a participant in the locked-in state with tactors placed on her arm, but concluded that further development is needed before tactile BCIs can be considered as a communication option for the use in daily life. The current state of auditory BCIs is summarized in the next section.

1.3.1 Auditory BCIs

Auditory BCIs have been realized twofold: Depending on how the stimuli are presented they can be classified as sequential or streaming (Hill & Schölkopf, 2012). In the sequential approach, stimuli are presented in a variant of the oddball paradigm. Frequent tones are presented sequentially, interspersed with rare target tones. To allow for a binary choice, Halder et al. (2010) proposed a three-stimulus oddball with target tones differing in pitch, direction or loudness. Participants were instructed to listen to one of two rare target tones and ignore the frequent tones to make a selection. The sequential approach has the advantage that the number of target tones can be increased; thus, it allows for multiclass selections and spelling. Based on this principle, Furdea et al. (2009) designed a BCI similar to the visual matrix based BCI for communication, but that required a two-step procedure. Rows of a 5x5 letter matrix were coded by voice recordings of the numbers one to five and columns by the numbers six to ten. Tones were played in a random order. To select a letter, participants first had to select the row with the target letter by silently counting the appearance of the corresponding number in the sequence of the row stimuli. In the second step, they had to do the same but with the number coding for the target column. The desired letter could then be determined at the crossing of the target row and column.

In the streaming approach, stimuli are presented such that they are perceived as separate auditory streams. The streams can either be presented separately, one to each ear (e.g. Hill et al., 2004, 2005; Lopez-Gordo et al., 2012), or to the same ear (e.g. Kanoh, Miyamoto & Yoshinobu, 2008). Participants are instructed to shift their attention to one of the auditory streams, which results in different brain responses for the stimuli in the attended stream compared to those in the unattended stream(s), which can be classified. The mode of presentation and the EEG signals used for the classification differ between studies, but usually they allow only binary communication by attention shifts to one of two auditory streams. For instance, in the aforementioned study by Kim et al. (2011), low frequency amplitude modulation (37 Hz and 43 Hz) of high frequency carrier tones allowed for the identification of the attended stream since the ASSEPs were more pronounced for the attended stream compared to the unattended. Voice stimuli presented in rapid succession (5 Hz) elicited a steady response with a time shift for the two streams which allowed for classification in the study by Lopez-Gordo et al. (2012). Hill et al. (2012, 2014) presented streams of tones from left and right speakers and each of the two streams consisted of target and non-target tones. Based on the differences in event-related potentials between all attended and all unattended stimuli, high classification accuracies could be achieved. Recently, Treder et al. (2014) demonstrated that it is possible to correctly classify shifts in attention to one of three auditory oddball streams that consisted of music produced by different instruments using the differences in ERPs for attended vs. unattended deviants.

The auditory streaming BCIs mentioned above and sequential approaches which allow for a binary choice (e.g. Halder et al., 2010; Pokorny et al., 2013; Sellers & Donchin, 2006) can be operated with simple to understand instructions and impose only little working memory load on the user. Furthermore, they are robust enough to be operated in a mobile setting (de Vos, Gandras & Debener, 2014). Therefore, they could provide a communication channel for persons with short attention spans and severe brain injuries, who have no other method of communication (Halder et al., 2010; Hill & Schölkopf, 2012). For users with longer attention spans and sufficient cognitive abilities, multi-choice BCIs are desirable since they allow for the control of spelling applications.

Table 1 provides an overview of the current state of auditory BCIs. It is apparent from the table that most studies on auditory BCIs are proof-of-principle studies because they have been conducted with few participants, mostly without providing feedback of the classification online and they have rarely been tested with potential end users. Compared to BCIs based on visual stimulation, a lower percentage of users achieved satisfactory control, i.e. ≥70% accuracy, with auditory stimuli. The performance difference has also been shown in studies that directly compared auditory and visual BCIs for spelling (Belitski, Farquhar & Desain, 2011; Furdea et al., 2009; Käthner et al., 2013). One of the reasons that this difference exists is that an auditory multiclass BCI imposes a higher mental workload on the user due to the higher task complexity compared with a visual BCI (Käthner et al., 2013). In a visual BCI, users can focus their gaze on the desired item. No such "focusing mechanism" exists for the auditory system; therefore, it is more difficult to focus on the target and ignore the non-target stimuli. Furthermore, the working-memory load is higher since associations of (groups of) letters and tones have to be memorized and/or users have to complete several steps to choose the desired letter.

As one of the goals of this thesis was to improve and evaluate a multiclass BCI to be used as a communication aid, important previous efforts in this direction are outlined in the following section.

1.3.1.1 Auditory multiclass BCIs

The first auditory multiclass BCI was realized by Furdea et al. (2009), as described above. Unfortunately, severely paralyzed persons with ALS were unable to gain control over the BCI in a subsequent study (Kübler et al., 2009). Following a suggestion by Kübler et al. (2009) that stimuli could be presented from different spatial locations, Schreuder et al. (2010, 2011) demonstrated that spatial cues can be beneficial for multiclass auditory BCIs. Tones of different frequencies were presented from six speakers arranged in a circle around the participants during an online BCI experiment (Schreuder et al., 2011). High accuracies were achieved within the first session (77.4%, 2.84 bits/min) by the 21 study participants. The 15 users who achieved a satisfactory level of control completed a second session in which the reported average accuracies were higher (86.1%, 5.26 bits/min). This paradigm was later tested with a woman who had severe motor and communication deficits due to a brain stem stroke (Schreuder et al., 2013a). Although she could control a visual BCI starting from the first session with 100% accuracy, the highest accuracy achieved with the auditory BCI was 43% in the fourth of five sessions and thus the auditory BCI was insufficient for communication.

To reduce the set-up necessary for this paradigm, Käthner et al. (2013) used directional cues presented via headphones. To allow for spelling, the paradigm proposed by Furdea et al. (2009) was modified. Rows and columns of a 5x5 letter matrix were coded by short artificial tones containing pitch and directional cues. Basic principles of sound localization were applied to create the impression that the sounds originated from different locations. In the horizontal plane, interaural time difference (ITD) and interaural level difference (ILD) are the main factors for sound localization (Middlebrooks & Green, 1991; Wightman & Kistler, 1992). Thus, the tones representing the leftmost column were presented solely over the left headphone speaker and the tones representing the rightmost column over the right speaker. To create the impression of a central sound source for the tone representing the central column it was played over both speakers simultaneously. For the remaining two tones, left and right diagonal source locations were modeled respectively using ITD and ILD. The same directional and pitch cues were applied for tones coding the rows (from top to bottom). Therefore, to select the letter A in the first cell, participants had to focus attention on the tone from the left (coding the leftmost column) and, after a short pause, focus on the same tone, this time representing the top row. Different timing parameters were evaluated and the highest mean accuracy achieved was 66% and the highest bitrate 2.76 bits/min. However, several users complained about the unnatural stimuli and it was suggested that more natural stimuli could lead to a higher user acceptance (Käthner et al., 2013). Höhne et al. (2012) compared spoken syllables to artificial tones in a nine-class offline BCI experiment with nine study participants and could show that ergonomic ratings and performance were higher for the natural stimuli. While high bitrates were reported (5.31bis/min), only a minority of participants achieved a level of satisfactory control over the BCI. In an earlier study, Klobassa et al (2009) had explored environmental sounds (bell, bass, ring, thud, chord, and buzz) as stimuli with limited success. A mean bit rate of 1.86 bits/min was reported and only 40% of study participants achieved accuracies above 70% despite having taken part in 11 sessions.

To conclude, in some proof-of-principle studies healthy study participants achieved satisfactory spelling accuracies with auditory multiclass BCIs. However, studies conducted prior to the work of this thesis could not demonstrate that spelling is possible for potential end users with this type of BCI. Therefore, further improvements in the paradigms are necessary to facilitate spelling.

Table 1. Performance overview of auditory BCIs. The first category "Sequential / Spelling" lists the studies that are most relevant to the present thesis. For these studies, mean accuracies refer to accuracies for character selections. The second category lists studies with sequential approaches that did not evaluate a spelling application. The third category lists studies with streaming approaches. For each category, studies are listed by year of publication with the exception that paradigms that were evaluated with end users in subsequent studies are listed directly below the original publication (indented). Values marked with an *F* were estimated from figures. If data analysis was performed online, it is indicated in the respective column. The column that lists the percentage of users who achieved ≥70% accuracy takes all participants into account, who were originally enrolled in the study. The table does not include studies on communication attempts with persons with disorders of consciousness.

	Classes	Healthy Users	End users (diagnosis)	Online	Mean accuracy	Users ≥70% acc.
Sequential / Spelling						
Furdea et al. (2009)	**25**	**13**	**-**	✓	**65%**	**69%**
Kübler et al. (2009)	**25**	**-**	**4 (ALS)**	✓	**12.1%**	**0%**
Klobassa et al. (2009)	**36**	**10**	**-**	✓	**64%**	**40%**
Höhne et al. (2011)	**9**	**12**	**-**	***n*=9**	**89.3%**	**75%**
Schreuder et al. (2011)	**6**	**21**	**-**	 ***n*=15**	**77.4% offline** **86.1% online**	**62%**
Schreuder et al. (2013a)	**6**	**-**	**1 (stroke)**	✓	**39%**	**0%**
Höhne et al. (2012)	**9**	**9**	**-**	**-**	**66%^{F}**	**33%**
Käthner et al. (2013)	**25**	**20**	**-**	✓	**66%**	**80%**
Höhne et al. (2014)	**30**	**10**	**-**	***n*=9**	**43.7%**	**11%**
Kleih et al. (2015)	**7+5**	**11**	**4 (ALS, MD, 2 'traumatic accident')**	✓	**84%** **74% (end users)**	**73%** **75%**
Sequential						
Sellers & Donchin (2006)	4	3	3 (ALS)	-	65% 65.9% (end users)	33%
Guo et al. (2009)	8	8	-	-	89.1%	100%
Halder et al. (2010)	2	20	-	-	76.5%	75%
Schreuder et al. (2010)	5	5	-	-	94%	100%
Gao et al. (2011)	5	7	-	-	80%	n/a
Cai et al. (2013)	8	10	-	-	70.7%	50%
Nambu et al. (2013)	6	7	-	-	89.5%	100%
de Vos et al. (2014)	2	20	-	-	83%	n/a
Streaming						
Hill et al. (2004, 2005)	2	15	-	-	82.3%	87%
Farquhar et al. (2008)	2	3	-	-	64.3%	33%
Kanoh et al. (2008, 2010)	2	6	-	-	60-70%	n/a
Kim et al. (2011)	2	6	-	 *n*=1	86.3% offline 71.4% online	n/a
Hill & Schölkopf (2012)	2	13	-	✓	84.8%	100%
Hill et al. (2012)	2	16	-	✓	79.9%	81%
Lopez-Gordo et al. (2012)	2	12	-	-	69%	58%
Hill et al. (2014)	2	14	2 (ALS)	✓	76.9% 67.5% (end users)	86%
Treder et al. (2014)	3	11	-	-	71.5%	45%

1.4 Motivation and research goals of the doctoral dissertation

Persons with severe paralysis could benefit from BCIs as muscle independent communication aids. BCIs based on event-related potentials are promising candidates as access methods for AAC, because they allow for high accuracies and fast information transfer rates without requiring much practice. Substantial progress has been made since the introduction of the first ERP based BCI by Farwell and Donchin (1988). In particular, the visual paradigm has been widely investigated and improved (Kleih et al., 2011). Furthermore, the size and cost of the required hardware has been reduced. It is now possible to record EEG activity with small amplifiers and a wireless signal transmission to a laptop or smartphone that can handle all aspects of stimulus presentation, data acquisition and classification (Debener et al., 2012; Wang, Wang & Jung, 2011). These are good prerequisites for bringing BCIs to those persons who would benefit from BCIs as communication aids. Nevertheless, studies involving potential end users are rare and usually encounter several practical problems, such as direct or indirect causes of the health condition and the home or clinical environment of the participants. These can lead to decreases in signal quality and difficulties to gain control over the BCI. Thus, end users usually perform worse compared to healthy study participants (Marchetti & Priftis, 2014). Particularly for those users with severe paralysis (e.g. in LIS or CLIS) control is difficult to achieve (Kübler & Birbaumer, 2008; Marchetti & Priftis, 2014). Hence, it remains the biggest challenge to transfer BCIs tested in laboratory environments to the end users' homes, where they are intended to be used as assistive technology in daily life. For the participants who do not have sufficient control over eye muscles and/or visual impairments, BCIs based on auditory stimuli have been proposed. It remains to be shown that potential end users can gain control over auditory multiclass BCIs for spelling.

The central motivating factors for this thesis are to enhance the understanding of the end users' needs and to improve and evaluate BCIs for communication to ultimately allow them to be used as ATs. More specifically, this thesis addresses both fundamental and practical research questions regarding BCIs based on ERPs elicited by visual stimuli and auditory stimuli. Based upon the current state of BCI technology several research questions were identified.

1.4.1 Research questions of the doctoral dissertation

To pave the way for BCIs as AAC devices, research questions were derived from limitations of the current state of BCI technology that are described below.

1 | INTRODUCTION

In order to be used as communication aids in daily life, BCIs must be robust enough to be used despite noisy environments. Nevertheless, most studies with visual ERP-BCIs for communication are conducted in a controlled laboratory environment. One study (Ortner et al., 2011) demonstrated that a large number of participants was able to spell with an average accuracy of 86% correctly selected letters during ad-hoc testing at a trade fair. However, as in most ERP-BCI studies, participants only spelled few letters (five). A study that systematically manipulated the level of distraction and showed the robustness of the ERP-BCI during prolonged usage was missing. Therefore, for this thesis the following question was identified:

→ Can users maintain a satisfactory level of control over a visual ERP based BCI despite constant distraction for a long period of time?

If users pursue a spelling task with the BCI for a long time, performance is likely to decrease due to an increase in fatigue and/or higher mental workload following distraction. A BCI that adapts to the mental state of the user, e.g. pauses the system if high mental workload or fatigue is detected to prevent false positive selections (Aloise et al., 2013), is highly desired. In a variety of real-life tasks, such as driving a car (Kohlmorgen et al., 2007), gauge monitoring and/or arithmetic tasks (Ullsperger, Freude & Erdmann, 2001) and during computer gaming (Allison & Polich, 2008; Miller et al., 2011), markers in the EEG were identified that could serve as indicators of different levels of mental workload. It has been further demonstrated in previous studies that the EEG contains valuable information for the detection of fatigue (for a review see Lal & Craig, 2001). It is unclear to what degree the findings can be generalized across tasks because this issue is rarely addressed (Johnson et al., 2011). Therefore, it seems inevitable to study the task of interest. In contrast to the aforementioned studies, EEG data would be acquired anyhow during BCI operation; therefore, no additional equipment would be required for the detection of mental states. The following question was defined:

→ Is it possible to identify markers of high mental workload and fatigue in the EEG during a visual ERP-BCI spelling task?

Visual ERP-BCIs require that stimuli are presented in the field of view of the user. While this is usually not a problem during testing with healthy study participants, who can be seated in front of a computer screen, it can be challenging during testing with target users. Mounting a conventional monitor is sometimes difficult in a home or hospital environment, where the end user is lying in a bed or sitting in a wheelchair, and if head movements are restricted due to paralysis. For these situations, a display is desirable that can be easily mounted and adjusted such that it displays all control elements in the field of view. Previously, Takano, Hato and Kansaku (2011) explored a see-through head-mounted display (HMD) as an option for environmental control (TV control panel and light switch) with healthy study participants. Recently, virtual reality headsets have attracted much attention (mainly from the gaming industry) and could become a mass-market product in the near future (Wingfield, 2013). Thus, they could also serve as HMDs for other user groups. Within this thesis, a virtual reality headset was compared to a conventional monitor to answer the question:

→ Can a head-mounted display increase usability of visual BCIs for communication?

The necessity of BCIs that do not depend on the visual modality for stimulation was already stressed in section 1.3. To expand the group of potential users to those with difficulties controlling eye movements or visual impairment, auditory BCIs have been proposed (see section 1.3.1). Multiclass auditory BCIs could allow for spelling and promising results have been obtained in feasibility studies (for a review see Riccio et al., 2012). The applicability of the proposed paradigms to potential end users remained to be demonstrated. Therefore, an important goal of this doctoral thesis was to further improve multiclass BCIs and to demonstrate that motor impaired users can gain control over this type of BCI. Changes in the stimulus material can boost performance as demonstrated for visual ERP-BCIs in the studies of Kaufmann et al. (2011, 2013). The crucial importance of the choice of the stimulus material was also stressed in studies with auditory BCIs (Höhne et al., 2012; Höhne & Tangermann, 2014; Lopez-Gordo et al., 2012). The paradigm implemented by Käthner et al. (2013) yielded promising results, but participants complained about the artificial tones. By replacing them with more natural stimuli, the following question could be addressed:

→ Can changes in the stimulus material improve classification accuracies for an auditory multiclass brain-computer interface?

As previously discussed, auditory multiclass BCIs impose a substantial amount of workload on the user. Thus, it is likely that control cannot be achieved within the first session and a training effect might be particularly prominent for end users. A question central to this thesis was therefore:

→ Can motor impaired end users learn to operate an auditory multiclass BCI with training over the course of multiple sessions?

If participants are completely paralyzed, muscle-independent communication aids, i.e. BCIs, could be the only option to express their thoughts. For those users who have residual muscle control, it needs to be determined if and to what degree they can benefit from BCI technology as possible communication aids. In a review of visual ERP-BCI studies performed with persons diagnosed with ALS, Marchetti and Priftis (2014) stated that no studies exist that directly compare performance of conventional AAC devices (e.g. eye-tracking) with BCIs and concluded that these are necessary to judge the usefulness of visual BCIs. Such a study was recently published by Pasqualotto et al. (2015) and showed that visual ERP-BCIs trail behind in performance and speed compared to eye-tracking devices. It is important to engage with potential users in all steps of the design process of BCIs in order to develop systems that fulfill user requirements (Kübler et al., 2014). In the context of this thesis, a goal was to shed light on the question:

→ How does an auditory BCI for binary communication compare to eye-gaze dependent access methods to AAC for a person in the locked-in state?

1.4.2 Studies of the doctoral dissertation

A total of five studies were performed to answer the research questions described above. In the following, an outline of the studies is provided that are included in the second chapter of this thesis.

Chapter 2.1 "Effects of mental workload and fatigue on the P300, alpha and theta band power during operation of an ERP (P300) brain-computer interface", published in *Biological Psychology* (Käthner et al., 2014b).

To answer the questions as to whether a visual ERP-BCI can be operated despite constant distraction and when pursuing the task for an extended period of time, a study with 20 healthy participants was conducted. A further aim within this study was to answer the question as to whether markers of mental workload and fatigue could be identified in the EEG. Mental workload was experimentally manipulated with dichotic listening tasks in the study, while participants performed a primary, visual ERP-BCI spelling task. Conditions of medium and high workload alternated and a total of 250 letters were spelled with online feedback.

Chapter 2.2 “Rapid P300 brain-computer interface communication with a head-mounted display”, published in Frontiers in Neuroprosthetics (Käthner, Kübler & Halder, 2015a).

In this study visual ERP-BCI performance with a head-mounted display (HMD) was compared to a performance with a conventional display. The study aimed to answer the question whether a head-mounted display can increase the usability of visual BCIs for communication. The feasibility of BCI operation via the HMD was first tested with 18 healthy study participants. Furthermore, additional settings of the HMD were explored, such as new display options for the classic ERP-BCI. Subsequently, the HMD was evaluated as an alternative display method by a participant in the locked-in state.

Chapter 2.3 “An auditory multiclass brain-computer interface with natural stimuli: usability evaluation with healthy participants and a motor impaired end user”, published in *Frontiers in Human Neuroscience* (Simon et al., 2015).

Due to the fact that multiclass auditory BCIs could potentially allow users with visual impairments to operate an ERP-BCI, this study aimed to further improve the paradigm evaluated by Käthner et al. (2013) and reveal a possible training effect. A focus was on the question whether changes in the stimulus material can improve classification accuracies for an auditory multiclass brain-computer interface. For this reason, natural stimuli were used instead of brisk artificial tones. Eleven healthy participants and one person diagnosed with ALS participated in two sessions with the auditory BCI and evaluated its usability.

Chapter 2.4 “Training leads to increased auditory brain-computer interface performance of end-users with motor impairments”, published in *Clinical Neurophysiology* (Halder, Käthner & Kübler, in press).

The study by Simon et al. (2015; chapter 2.4) and the subsequent study by Baykara et al. (in press) could reveal promising performance of the auditory BCI by healthy study participants and a positive effect of training. Since a central goal of the current thesis was to demonstrate that potential end users could gain control over an auditory multiclass BCI, five persons with motor impairments were recruited for the study. The study protocol consisted of five training sessions with the auditory BCI, each one at least one week apart.

Chapter 2.5 “Comparison of eyetracking, electrooculography and an auditory brain-computer interface for binary communication: A case study with a participant in the locked-in state, published in *Journal of NeuroEngineering and Rehabilitation* (Käthner, Kübler & Halder, 2015b).

A person in the locked-in state, who had no means of partner-independent communication, participated in the study. He could only communicate with residual eye-movements in a partner based scanning approach with a letter board. The study set out to answer the question how an auditory BCI for binary communication compares to eye-gaze dependent access methods to AAC for a person in the locked-in state. Therefore, on four consecutive days, the study participant tested and evaluated eye-gaze dependent methods (electrooculography [EOG], eye-tracking) and an auditory BCI for binary choices.

2 Publications

2.1 Käthner, I., Wriessnegger, S. C., Müller-Putz, G. R., Kübler, A., Halder, S. (2014). Effects of mental workload and fatigue on the P300, alpha and theta band power during operation of an ERP (P300) brain-computer interface. *Biological Psychology*

Abstract

The study aimed at revealing electrophysiological indicators of mental workload and fatigue during prolonged usage of a P300 brain–computer interface (BCI). Mental workload was experimentally manipulated with dichotic listening tasks. Medium and high workload conditions alternated. Behavioral measures confirmed that the manipulation of mental workload was successful. Reduced P300 amplitude was found for the high workload condition. Along with lower performance and an increase in the subjective level of fatigue, an increase of power in the alpha band was found for the last as compared to the first run of both conditions. The study confirms that a combination of signals derived from the time and frequency domain of the electroencephalogram is promising for the online detection of workload and fatigue. It also demonstrates that satisfactory accuracies can be achieved by healthy participants with the P300 speller, despite constant distraction and when pursuing the task for a long time.

Originally published in: Biological Psychology, *102*, 118-129
doi: 10.1016/j.biopsycho.2014.07.014

Biological Psychology 102 (2014) 118–129

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Effects of mental workload and fatigue on the P300, alpha and theta band power during operation of an ERP (P300) brain–computer interface

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A R T I C L E   I N F O

Article history:
Received 10 February 2014
Accepted 19 July 2014
Available online 1 August 2014

Keywords:
Brain–computer interface
EEG
P300
Alpha
Mental workload
Fatigue

A B S T R A C T

The study aimed at revealing electrophysiological indicators of mental workload and fatigue during prolonged usage of a P300 brain–computer interface (BCI). Mental workload was experimentally manipulated with dichotic listening tasks. Medium and high workload conditions alternated. Behavioral measures confirmed that the manipulation of mental workload was successful. Reduced P300 amplitude was found for the high workload condition. Along with lower performance and an increase in the subjective level of fatigue, an increase of power in the alpha band was found for the last as compared to the first run of both conditions. The study confirms that a combination of signals derived from the time and frequency domain of the electroencephalogram is promising for the online detection of workload and fatigue. It also demonstrates that satisfactory accuracies can be achieved by healthy participants with the P300 speller, despite constant distraction and when pursuing the task for a long time.

1. Introduction

A brain–computer interface (BCI) can serve as a muscle-independent communication channel (Birbaumer, 2006; Kübler, Kotchoubey, Kaiser, Wolpaw, & Birbaumer 2001; Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). Event-related potentials (ERPs) extracted from the electroencephalogram (EEG) are often used as a control signal for the BCI. Of these ERPs the P300 is often the most prominent, therefore the term P300 BCI was coined. Until today, no study explored the effects of experimentally manipulated mental workload and fatigue during usage of a P300 BCI, although the potential benefits of automatic mental workload/fatigue detection with the BCI would improve usability of BCIs. A system is desirable that adapts to the mental state of the user, e.g. pauses if mental overload or fatigue is detected or adapts the stimulation parameters according to the detected level of fatigue and/or workload. A mental workload detector could be implemented that is based on the signals that are acquired anyhow with the BCI. As a first step toward this goal, this study investigated the effects of time and mental workload on performance and electrophysiological signals during prolonged usage. During spelling with the BCI, mental workload was systematically manipulated with dichotic listening tasks. Two levels of difficulty (medium and high workload) were tested.

As a primary task, participants used the well-established visual P300 speller based on the paradigm by Farwell and Donchin (1988; see Kleih et al., 2011 for a review). To select a particular symbol, participants had to focus attention on a defined character of a 6 × 6 matrix that was presented on a computer screen. Rows and columns of the matrix flashed randomly during the task. Hence, the attended cells can be classified, because rows and columns with the target character constitute an oddball that elicits a P300. The P300 ERP is a positive deflection in the EEG following a rare, task-relevant stimulus that is presented among frequent, non-target stimuli and is reliably elicited in an oddball paradigm (Polich, 2007).

As a consequence of the prolonged BCI usage, we expected participants to experience mental fatigue. In general, the term describes the feeling that may result from prolonged periods of cognitive activity. It is associated with tiredness or exhaustion and a decrease in task performance and commitment (Boksem, Meijman, & Lorist, 2005; Hockey, 1997).

The hope that specific mental activity and states of wakefulness would be reflected in the EEG was already expressed by Berger in 1929. Today, specific frequency bands of the EEG are widely used to

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http://dx.doi.org/10.1016/j.biopsycho.2014.07.014
0301-0511/

identify levels of alertness or arousal and both, the information contained in specific frequency bands of the EEG and in ERPs have been shown to discriminate between different levels of mental workload (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981; Brouwer et al., 2012; Coull, 1998; Dement & Kleitman, 1957; Gevins, Yeager, Zeitlin, Ancoli, & Dedon, 1977; Van Erp, Veltman, & Grootjen, 2010).

In the following we will first focus on ERP findings concerning mental workload and fatigue and secondly on differences in the ongoing EEG that have been found in response to changes in the level of mental workload and fatigue. Since it was demonstrated that the P300 decreases or disappears if attention was diverted from the P300 eliciting stimuli (Wickens, Isreal, & Donchin, 1977), it has received much attention as a potential indicator of mental workload. Based on the observation that P300 amplitude was reduced in dual-task studies, it was suggested that the P300 amplitude represents the distribution of processing capacity between concurrent tasks (Isreal, Chesney, Wickens, & Donchin, 1980; see Kramer, 1991; Kok, 2001 for reviews). More recent studies demonstrated reduced P300 amplitude under high workload conditions in ecologically valid tasks. Allison and Polich (2007) and Miller, Rietschel, McDonald, and Hatfield (2011) used varying levels of computer game difficulty to manipulate workload and in the study by Ullsperger, Freude, and Erdmann (2001) subjects performed gauge monitoring and/or arithmetic tasks. Unlike P300 amplitude, which was found to be related to the depth of processing, latency of the P300 is often increased if categorization of the eliciting stimulus becomes more difficult, thus, representing timing of mental processing (Kutas, McCarthy, & Donchin, 1977; see review by Kok, 2001). The study by Trejo et al. (2005) is one of few that investigated the effects of fatigue on event-related potentials. No significant effect of fatigue on N100, P200 or P300 was found.

For the estimation of mental workload and fatigue most studies use information from the frequency domain of the EEG. While, to our knowledge, only Brouwer et al. (2012) applied measures of event-related potentials and EEG spectral power to estimate workload (with an N-back task), most studies use exclusively information from the ongoing EEG. For instance, Kohlmorgen et al. (2007) were able to detect high mental workload under real life driving conditions. The applied classifier computed the power of selected frequency bands to identify high workload. Several studies identified differences in the alpha band (∼8–12 Hz) and theta band (∼4–7 Hz) to be most sensitive for distinguishing between different levels of workload. Increases in task difficulty and mental workload were most often associated with a decrease of alpha and an increase of theta power (Klimesch, 1999; Scerbo, Freeman, & Milkulka, 2003; Smith, Gevins, Brown, Karnik, & Du, 2001). For instance, this pattern was found in two studies that used continuous interactive control tasks to manipulate workload (Brookings, Wilson, & Swain, 1996; Fournier, Wilson, & Swain, 1999) and a study that used an N-back task to vary working memory load (Gevins et al., 1998). With increasing memory load, workload or attention, changes in theta activity are especially apparent at frontal sites (Gevins et al., 1998; Gundel & Wilson, 1992; Holm, Lukander, Korpela, Sallinen, & Müller, 2009; Mecklinger, Kramer, & Strayer, 1992).

Changes in alpha and/or theta power seem to be not only the most reliable indicators of mental workload but also that of fatigue. During a reduced level of arousal, an increase in activity in the alpha and theta band can often be observed (Klimesch, 1999). Increases in power of the theta and alpha band during sleepiness (with eyes open) were repeatedly found in sleep deprived persons and/or during vigilance tasks (Boksem et al., 2005; Lal & Craig, 2001; Makeig & Jung, 1996; Paus et al., 1997; Stampi, Stone, & Michimori, 1995; Yamamoto & Matsuoka, 1990).

It was previously pointed out that in some studies the relationship between workload and alpha band was only found for participants that were classified as high alpha generators. For this reason, there may exist strong individual differences in the sensitivity of alpha frequencies for changes in workload (Kramer, 1991; Pigeau, Hoffmann, Purcell, & Moffitt 1987). There are not only individual differences with regard to the sensitivity of indicators of mental workload in the EEG, but there appear to be also strong differences depending on the studied task and environmental factors (Humphrey & Kramer, 1994; Van Erp et al., 2010). Further, task dependency is also often observed in studies investigating the effects of fatigue and while a variety of approaches were taken to implement EEG based drowsiness detection algorithms, generalizability across tasks is rarely addressed (Johnson et al., 2011). Due to the task dependence of the effects of fatigue and workload on the EEG, it seems to date inevitable to study the task of interest.

So far, BCIs have mainly been tested in laboratory settings. Ultimately, they are intended to be used as an assistive technology in a home-environment and thus, efficiency, and usability in general are of utmost importance (Kleih et al., 2011; Zickler et al., 2011). In order to function in real-life settings, the P300 speller must also be robust during conditions of distraction. Robustness can either mean good performance despite a noisy environment or good online detection of mental overload and automatic standby mode of the BCI. One study (Ortner et al., 2011) showed that 50 participants were able to spell with an average accuracy of 86% correctly selected letters with a visual P300 BCI during ad-hoc testing at the CEBIT 2011 in Hannover, where other visitors were walking around and talking. As in most P300 BCI studies, subjects spelled only few letters (five) and a study that systematically manipulates the level of distraction, using this type of BCI, was missing.

Consequently, the current study aimed at identifying markers of mental workload and fatigue during prolonged usage of a visual P300 BCI. The effects on P300 and the EEG were investigated. Mental workload was experimentally manipulated with dichotic listening tasks. Thus, the effects of different levels of distraction on performance with a P300 BCI could also be revealed. The following hypotheses were derived from the studies mentioned above: In the high workload condition, we expected a significantly lower performance in the BCI task along with a subjectively higher level of workload compared to the medium workload condition. As for the electrophysiological signals, we hypothesized a decrease in P300 amplitude and alpha activity and an increase in theta band power with increasing workload. Over the course of the experiment, we expected performance to decrease and the subjective level of fatigue to increase. We hypothesized that higher mental fatigue would be reflected in an increase in activity in the alpha and theta bands and a reduced P300 amplitude in the last compared to the first run of each workload condition.

2. Methods

2.1. Participants

Twenty healthy subjects (12 female, M = 24.9 years, SD ± 5.1) participated in the study. All participants were paid 8€ per hour. None of the subjects had previously participated in a P300 BCI study nor reported a history of psychiatric or neurological disorders. Further, no hearing impairments were reported. Before the start of the experiment, each participant gave informed consent to the study that was carried out in accordance with the Declaration of Helsinki and the guidelines of the Ethical Review Board of the Institute of Psychology, University of Würzburg.

2.2. Data acquisition

The electroencephalogram (EEG) was recorded with 31 active Ag/AgCl electrodes mounted in an elastic fabric cap (g.GAMMAcap, g.tec Austria) following the modified version of the 10–20 system of the American Electroencephalographic Society (Sharbrough et al., 1991). These were located at positions F3, Fz, F4, FC5, FC3, FCz, FC4, FC6, C5, C3, Cz, C4, C6, CP5, CP3, CPz, CP4, CP6, P3, P1, Pz, P2, P4, PO7, PO3, POz, PO4, PO8, O1, Oz and O2. Channels were referenced to the right earlobe and a ground electrode was positioned at AFz. The EEG was sampled at 256 Hz with two g.USBamp amplifiers (g.tec, Austria). A high pass filter of 0.1 Hz and a low pass of 30 Hz were applied and data was notch filtered at 50 Hz. Data collection and stimulus presentation were controlled by the BCI2000 software package (Schalk, McFarland, Hinterberger, Birbaumer, & Wolpaw, 2004). Data processing, storage and online display were conducted on a laptop (Intel Core i5 2.5 GHz, 4 GB RAM, Microsoft Windows 7 Professional 64bit).

2.3. Procedure

During the experiment, participants simultaneously performed two tasks, a primary, P300 brain–computer interface (BCI) spelling task and a secondary, dichotic listening task (see description of the tasks below and Fig. 1a). The experiment was divided into ten blocks. In each block, participants had to spell 25 characters with the P300 BCI. In half of the blocks, difficulty of the additional dichotic listening task was intended to induce medium and in the other half, high workload. Blocks of medium and high workload alternated according to a particular scheme (see caption of Fig. 1B). Participants were seated about 1 m from a 22-in. monitor that displayed the P300 speller matrix. Stories for the dichotic listening tasks were presented using circumaural headphones to attenuate ambient noise (Sennheiser HD 280 Pro). Prior to recording periods, participants were asked to minimize eye movements and muscle contractions during the experiment.

2.4. P300 speller

To obtain data for classifier training, participants had to copy the words BRAIN and POWER during two screening runs, before the start of the experiment. The discriminant function was subsequently used for online spelling during the consecutive runs (see online signal classification). In each of the ten online spelling blocks, participants had to select 25 predefined letters, character by character, from a 6×6 matrix using the copy spelling mode of the BCI2000 software. All 25 characters were displayed in a line above the matrix and the current letter to be spelled was shown in parentheses next to it. Participants were instructed to focus on the target letter in the matrix and to notice/silently count whenever it was highlighted. Rows and columns of the matrix flashed randomly during spelling.

After a discriminant function is derived from the EEG data, the attended cell can be identified at the crossing of rows and columns containing the target character.

In the current study, flash duration was 62.5 ms and the inter-stimulus interval (ISI) was set to 125 ms. Each row and column was highlighted 5 times, before signals were classified and the selected letter was fed back to the participants. Therefore, participants had to focus on 10 target stimuli and ignore 50 non-target stimuli for the selection of one letter. In between trials, there was a break of 3 s to focus on the next letter. Hence, the time needed for one character selection was 14.25 s.

2.5. Dichotic listening tasks/mental workload manipulation

During the first 5 min of all online spelling runs (20 characters to be copied), two concurrent stories were presented over headphones. One story was presented over the left and another over the right headphone speaker. Both stories were from the Arabian Nights and one was told by a female, the other by a male professional narrator. The presentation side (left or right speaker male/female voice) was changed from block to block.

In half of the blocks, participants were instructed to ignore the stories (medium workload condition). In the other five, participants were instructed to pay attention to the context of both stories (high workload condition). The flashing of the rows and columns of the speller matrix started 10 s after the onset of the stories. After 5 min, the stories stopped. Participants were asked to spell the remaining five letters without additional mental load (Spelling Only condition).

After the first and last run of the medium and high workload conditions, the NASA-TLX questionnaire was administered as a measure of subjective workload. After every run, participants answered 6 questions about the content of the stories to ensure successful manipulation of workload.

2.6. Questionnaires

Subjective workload was assessed with an electronic version of the NASA Task Load Index (NASA-TLX; NASA Human Performance Research Group, 1987). It consists of six factors (mental, physical and temporal demands, effort, frustration and own performance). A total score (range 0–100) can be obtained, where a higher score indicates higher overall workload. First, the individual factors have to be rated by the participants on a 20 point scale with anchors such as high/low. Subsequently, a pair-wise comparison of all factors is performed to determine the degree each of them contributes to the overall workload. The NASA-TLX is a well validated instrument (Hart, 2006), has been introduced for evaluation of BCI-controlled applications (Zickler et al., 2011) and has been used to measure subjective workload in several BCI studies (Holz, Höhne, Staiger-Sälzer, Tangermann, & Kübler, 2013; Käthner et al., 2013; Riccio et al., 2011; Zickler et al., 2011; Zickler, Halder, Kleih, Herbert, & Kübler, 2013).

As manipulation check, we asked participants to fill in a multiple response questionnaire about the content of the stories after every block. For every block, it contained three questions about the content of each story. For each question, there were three possible answers, thus the chance level was .33. To verify that the difficulty level of all response options was similar, participants were asked to mark the questions that they had guessed. We checked if the number of correctly guessed questions differed from chance.

Before and after the experiment, the level of fatigue was assessed with a visual analog scale (VAS). This was a 10 cm horizontal line with the anchor points "0 = not at all tired" and "10 = extremely tired". Participants should mark the position on the line that best represented their level of fatigue. Visual analog scales were frequently used by sleep researchers to assess fatigue and the validity of the instrument was demonstrated repeatedly (Dinges et al., 1997; Gift, 1989; Smets, Garssen, Bonke, & Dehaes, 1995).

2.7. Online signal classification

For data classification, stepwise linear discriminant analysis (SWLDA) was used. It is an established method that was shown to surpass other classification algorithms with regard to performance and implementation characteristics in a P300 speller application (Krusienski et al., 2006). The applied algorithm determines a function that discriminates between epochs containing the target row/column and non-target rows/columns. It determines features from amplitude values from each of the 31 electrodes. To do so, the data was decimated and filtered with a moving average of 20 Hz. An epoch of 800 ms was used (starting at stimulus onset) that yielded 16 voltage values for each stimulus (flashing row or column). From this set, the feature that best predicted the target label using least square regression was added to the discriminant function (p-value ≤ 0.1). After adding another feature to the function, a backward stepwise discriminant analysis was performed to remove the features that were no longer significant ($p > .15$). This process was repeated until no additional features met the inclusion/exclusion criteria or 60 features were reached (Krusienski et al., 2006; Sellers, Vaughan, & Wolpaw, 2010). The parameters were determined with Matlab (The MathWorks, version R2012b) using the P300-GUI (part of the BCI2000 software). After the parameters had been determined for each participant, they were used for online classification during BCI operation.

2.8. Offline data analysis

The EEG was analyzed with Matlab (version R2012b) in combination with the EEGLab and ERPLab toolboxes (version 10.2.2.4b; Delorme & Makeig, 2004). No artifacts were removed or corrected with regard to online classification systems where this would also not be possible.

Auditory stimulation stopped during spelling of the 21st letter, therefore, data was analyzed for the first 20 letters of the medium and high workload conditions (first 295 s), and separately for the last 4 letters without the dichotic listening tasks. Spelling of these 4 letters was labeled as Spelling Only condition. This condition served as a control condition to reveal the effects of time on spelling accuracy, P300, alpha and theta power during spelling without auditory distraction.

For the ERP analysis, data was segmented into epochs of 800 ms starting at the onset of a stimulus and baseline corrected with a pre-stimulus interval of 200 ms. Averages were calculated for targets and non-targets. This yielded 200 target and 1000 non-target trials per block per condition (medium and high workload) per participant. After visual inspection of the waveforms for each participant, a post-stimulus interval between 300 and 550 ms was chosen for peak detection. The maximum positive peak in this interval was defined as P300.

Fast Fourier transform (FFT) was used to generate EEG spectra. The average power in the theta (4–7 Hz) and alpha (8–12 Hz) bands was log-transformed for normalization (Gasser, Bächer, & Möcks, 1982). Statistical analysis was performed with SPSS 19.

To assess the effect of workload, data of the five medium workload and the five high workload runs was averaged. Afterwards, repeated measures analyses of variance (ANOVAs) with the two levels of workload (medium/high) were calculated separately for the dependent variables spelling accuracy, correct answers to control questions, P300 amplitude and latency, alpha and theta power.

To assess differences between the first and last run of both workload conditions, 2×2 repeated measures analyses of variance (ANOVAs) with workload (high/medium) and time (first/last run) as within subject factors were calculated for the dependent variables spelling accuracy, NASA-TLX score, P300 amplitude and latency, alpha and theta power.

To assess the sole effect of time (over all ten runs) independent of workload, we calculated repeated measures ANOVAs for the Spelling Only condition for spelling accuracy, P300 amplitude and latency, and alpha and theta power. We checked for trends in the data when main effects were found. Post hoc t-tests (Bonferroni corrected) were used for pairwise comparisons.

All of the analyses described above were restricted to electrode positions Pz for P300 amplitude and latency and alpha power and to Fz for theta power. P300 amplitude was analyzed for the electrode at which the amplitude had the highest predictive value for spelling accuracy. We found significant positive correlations (Pearson) between P300 amplitude and spelling accuracy at parietal electrodes for the medium workload condition (P1 and Pz) and at parietal and parietal-occipital electrodes for the high workload condition (P1, P3, Pz, PO3 and POz). Predictive value of the P300 amplitude was higher at Pz than at P1 for both conditions, therefore, analysis of the EEG data was restricted to electrode Pz. P300 amplitude at Pz explained 23.9% of the variance in spelling accuracy in the medium workload

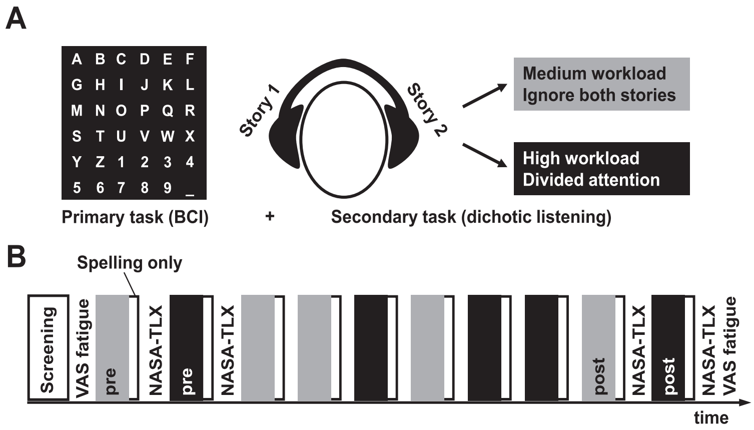

Fig. 1. Experimental tasks and design. Part A illustrates the tasks that had to be performed during the different conditions. During the medium and high workload conditions, participants had to spell predefined letters with the P300 BCI and two concurrent stories were presented over headphones. In the medium workload condition, they were instructed to ignore the stories and in the high workload condition they were supposed to pay attention to both stories. Part B depicts the block design of the experiment. After the screening, runs of medium and high workload alternated. The experiment always started with a medium workload condition followed by a high workload condition and ended that way. The six runs in between were pseudo randomized between subjects, with the constraint that no more than two runs of the same condition were presented consecutively. Each run ended with a "Spelling Only" condition in which subjects spelled 4 letters without auditory distraction. After every run, there was a short break during which subjects answered six questions about the content of the stories that were presented in that run. In addition, NASA-TLX and VAS were prompted at the indicated time points.

condition ($r = .49$, $p < .05$) and 25.2% in the high workload condition ($r = .50$, $p < .05$). Further, explorative analyses were performed that are described in the results section.

2.9. Information transfer rate

To measure the amount of data transmitted per time unit, we used the formula suggested by Wolpaw, Ramoser, McFarland, and Pfurtscheller (1998) and first described in Pierce (1980) to calculate bit rate. Despite its disadvantage of not taking into account unequal error distribution, it is the most widely used in BCI studies (Kronegg, Valoshynovskiy, & Pun, 2005).

$$B = \log_2 N + P \log_2 P + (1 - P)\log_2 \left(\frac{1-P}{N-1}\right)$$

N represents the number of possible targets (36 with the 6×6 matrix) and P represents the probability that these are correctly classified (average spelling accuracy). The Information transfer rate in bits/min was obtained by multiplying the bit rate B by the average number of selections per minute.

3. Results

3.1. Behavioral data

3.1.1. Effects of mental workload

The results of the experimental manipulation of mental workload on BCI spelling accuracy, subjective workload and number of control questions answered correctly are summarized in Fig. 2. The spelling accuracies for all experimental conditions are listed in Table 1.

A repeated measures ANOVA with the 2 levels medium workload and high workload revealed a main effect of workload on spelling accuracy, $F_{(1,19)} = 45.79$, $p < .001$. BCI spelling accuracy was significantly higher for the medium workload condition (80% accuracy; 14.75 bits/min) as compared to the high workload condition (65% accuracy; 10.78 bits/min).

The number of correct answers to the multiple-choice questions served as manipulation check. Participants answered more questions correct after the high workload (4.28) than the medium workload conditions, in which participants were instructed to ignore the stories (3.01), $F_{(1,19)} = 30.06$, $p < 0.001$. The total number of correctly answered questions (38%) of all the questions marked as guessed, did not differ significantly from chance (33%), $\chi^2 = 2.17$, df = 2, $p = .338$, which demonstrates that correct answers were not merely guessed.

3.1.2. Time effects (pre/post differences)

On average, participants needed 101 min (SD ± 10) to complete the experimental protocol after the classifier had been trained. Fig. 3 shows the subjective level of fatigue before and after the experiment and the BCI performance over the course of the experiment for the medium and high workload conditions. A repeated measures ANOVA with time (pre/post) as within subject factor revealed a main effect of time for the subjective ratings of fatigue (VAS scores). They were significantly higher at the end of the experiment (5.98) than at the beginning (2.37), $F_{(1,19)} = 115.04$, $p < .001$.

The repeated measures 2×2 ANOVA revealed main effects of workload, $F_{(1,19)} = 53.74$, $p < .001$, and time, $F_{(1,19)} = 19.11$, $p < .001$, on spelling accuracy. Average spelling accuracies for all conditions are listed in Table 1. For both, the medium, $t(19) = 3.18$, $p < .01$, and high workload conditions, $t(19) = 2.13$, $p < .05$, spelling accuracy in the last run was significantly lower than in the first.

There were main effects of workload, $F_{(1,19)} = 12.97$, $p < .01$, and time, $F_{(1,19)} = 7.33$, $p < .05$, and a significant workload X time interaction, $F_{(1,19)} = 6.47$, $p < .05$, for the subjective workload (NASA-TLX score). Post hoc t-tests revealed that only for the medium workload condition, ratings of workload were significantly higher after the last run (62.43) than after the first (50.51), $t(19) = -3.29$, $p < .01$. Only after the first run, subjective workload was significantly higher in the high workload condition (61.83) as compared to the medium workload condition (50.51), $t(19) = -4.78$, $p < .001$.

3.1.3. Spelling Only condition

For the Spelling Only condition, a repeated measures ANOVA (10) revealed a main effect of time, $F_{(9,171)} = 2.51$, $p < .01$, on spelling accuracy. Post hoc t-tests revealed significantly lower spelling accuracy in run 8 compared to runs 2 and 3 ($p < .05$). Mean spelling accuracies over the course of the experiment are depicted in Fig. 4.

3.2. Electrophysiological data

Mean P300 amplitudes and latencies for all experimental conditions are listed in Table 1.

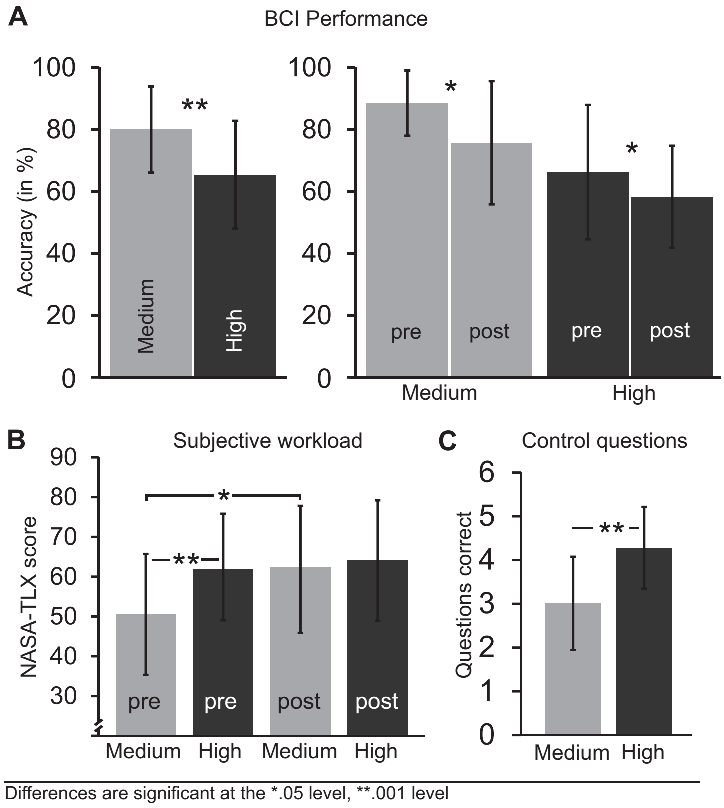

Fig. 2. Behavioral data for the different workload conditions. A shows the average BCI performance for the medium and high workload conditions and the differences between the accuracy in the first (pre) and last (post) run, respectively. B depicts the subjective level of workload and C the average number of correctly answered multiple response questions per run.

Table 1
Average P300 amplitude, latency, BCI performance and bitrate for all experimental conditions.

Condition	P300 amplitude at Pz in μV (SD)	P300 latency at Pz in ms (SD)	Accuracy in % correct	Bitrate (bits/min)
Medium (all)	3.45 (1.23)	427.98 (53.89)	80.00 (13.90)	14.41
High (all)	3.02 (1.38)	415.63 (63.83)	65.40 (17.41)	10.38
Medium pre	4.32 (1.23)	430.07 (66.85)	88.50 (10.52)	17.12
Medium post	3.59 (1.63)	421.93 (56.50)	75.75 (19.89)	13.17
High pre	3.55 (1.22)	427.51 (67.37)	66.25 (21.70)	10.60
High post	2.89 (1.57)	429.95 (55.00)	58.25 (16.49)	8.62
Spelling Only	3.34 (1.25)	427.27 (49.56)	78.40 (14.67)	13.82

3.2.1. *Effects of mental workload*

The grand average waveforms for the medium and high workload conditions are depicted in Fig. 5. The repeated measures ANOVA (2) revealed a main effect of workload, $F_{(1, 19)} = 5.70$, $p < .05$, on P300 amplitude. It was significantly smaller in the high as compared to the medium workload condition. For the latency, no effect for condition was found, $F_{(1, 19)} = 3.51$, $p = .08$.

The repeated measures ANOVA (2) revealed no difference in the alpha band (8–12 Hz) at Pz between the medium and high workload condition, $F_{(1, 19)} = .01$, $p = .938$. Further, no differences in the theta band between the two workload conditions were found, $F_{(1, 19)} = .33$, $p = .577$.

3.2.2. *Explorative analyses*

The effects of workload on the alpha and theta band might be too small to be visible in a comparison of the two workload conditions. However, they might be apparent compared to a baseline condition that does not include a secondary task. In our study design we did not include such a condition, however, the data from the screening run and the data from the Spelling Only condition may serve as baselines, since they do not include auditory distraction. To reveal differences in the medium and high workload conditions as compared to conditions without distraction, we performed the following explorative analyses.

A repeated measures ANOVAs with condition (4 levels: screening run, Spelling Only, medium workload and high workload condition) as factor yielded a main effect of condition on power in the alpha band at Pz, $F_{(3, 57)} = 6.85$, $p < .01$. Post hoc tests revealed significantly less activity in the alpha band during the screening runs as compared to the medium ($p < .01$) and high workload condition ($p < .001$) and compared to the Spelling Only condition ($p < .05$). Likewise, a main effect of condition was found for power in theta range at Fz, $F_{(1.88, 35.69)} = 5.59$ Greenhouse–Geisser corrected, $p < .01$. Post hoc tests revealed higher theta power in the medium and high workload condition as compared to the screening run ($p < .05$). In addition, theta power was significantly higher in the

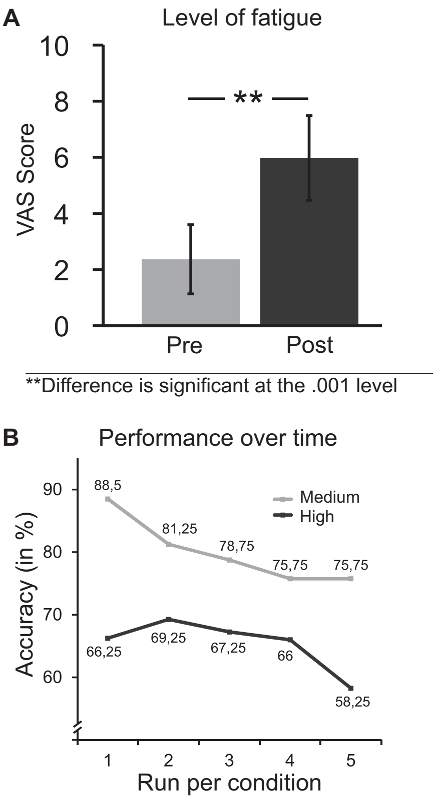

Fig. 3. Effects of time on performance and level of fatigue. A depicts the differences in the subjective level of fatigue as assessed with the visual analog scale before (pre) and after (post) the BCI tasks. B shows the course of performance as a function of time for the medium and high workload conditions.

high workload condition as compared to the Spelling Only condition ($p < .05$). The amount of data that was included in the analysis differed for the four conditions. It consisted of the averaged data of 200 target and 1000 non-target trials for the screening run, 400 target and 2000 non-target trials for the Spelling Only condition and 1000 target and 5000 non-target trials for each of the workload conditions.

The primary analysis was restricted to Pz (for alpha power) and Fz (for theta power). To further explore differences at all 31 electrode positions for the medium and high workload condition, we compared alpha and theta power in these conditions to the screening run. Multiple *t*-tests were conducted and

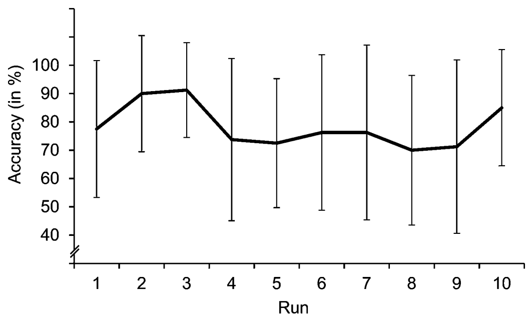

Fig. 4. Spelling accuracy over the course of the 10 Spelling Only runs.

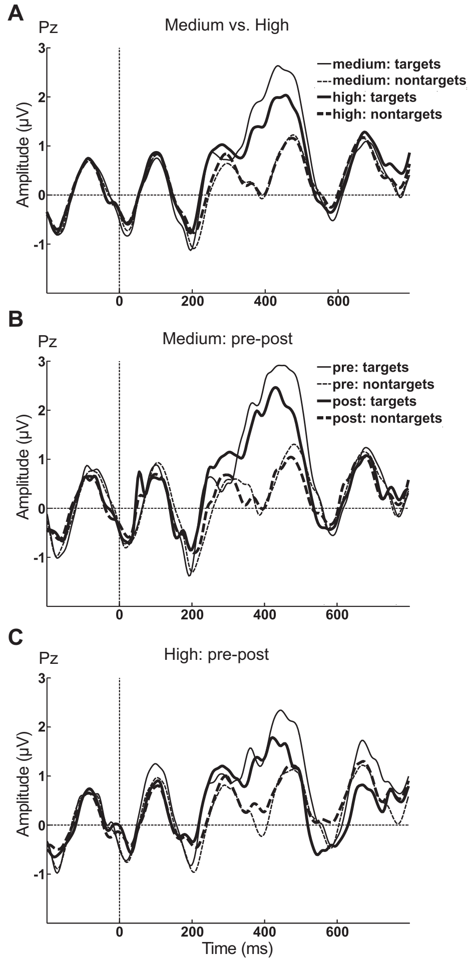

Fig. 5. Grand average waveforms at Pz. A shows the average waveforms for the medium and high workload conditions. The averaged waveforms for the first and last run of the medium workload condition are depicted in B and for the high workload condition in C.

differences that were significant at the uncorrected levels ($p < .05$ and $p < .01$) are reported along with the differences that remained significant after Bonferroni correction ($0.05/31 = p < .0016$ and $0.01/31 = p < 3.2 \times 10^{-4}$).

Significant differences are depicted in Fig. 6. Alpha power was significantly higher at widespread electrode positions for both workload conditions compared to the screening run. Significance values were highest at parietal and parieto-occipital sites. For theta power significant differences were only found at frontal and fronto-central electrode sites in the high workload condition as compared to the screening run using adjusted *p*-values.

3.3. *Time effects (pre/post differences)*

Main effects of time, $F_{(1,19)} = 19.36$, $p < .001$, and workload, $F_{(1,19)} = 6.40$, $p < .05$, and a significant workload X time interaction, $F_{(1,19)} = 21.83$, $p < .001$, were found for P300 amplitude at Pz. P300 amplitude was significantly smaller during the last run (3.59 µV) of the medium workload condition as compared to the first run (4.32, $p < .05$). The P300 was also smaller during the last run of the high workload condition (2.89 µV) as compared to the first run, but the difference was not significant (3.55 µV, $p = .084$). Differences

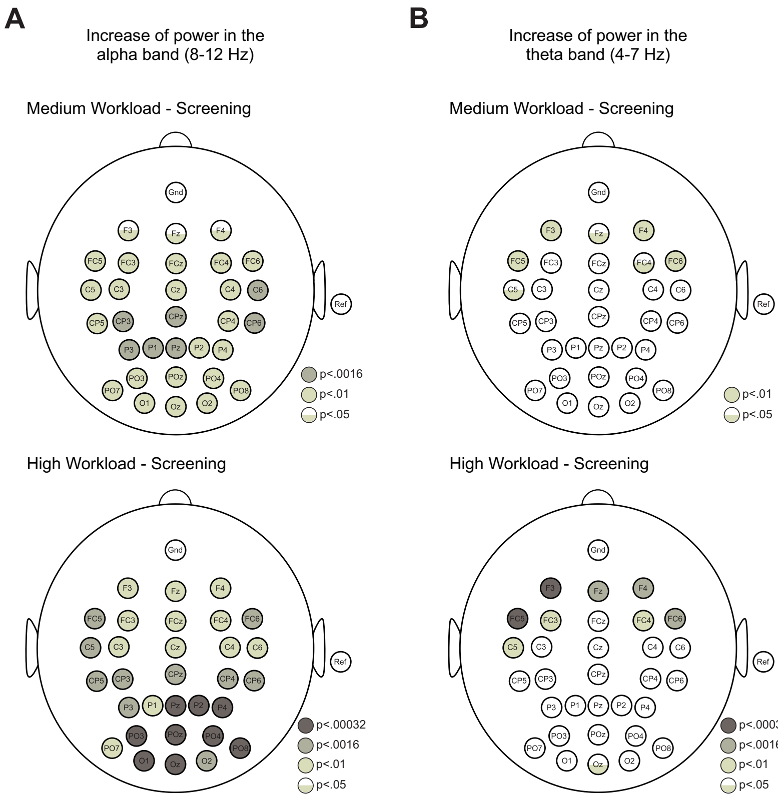

Fig. 6. Differences of power in the alpha (A) and theta band (B) at individual electrode sites. Significance values of the power differences are shown for the medium and high workload condition compared to the screening run.

between the conditions were significant for the first run ($p < .05$), but not for the last run. There was no significant effect of workload or time on P300 latency at Pz.

A 2 × 2 repeated measures ANOVA revealed a main effect of time for activity in the alpha band, $F_{(1, 19)} = 19.62$, $p < .001$, with an increase in activity in the last as compared to the first run but no significant effect of workload, $F_{(1, 19)} = .24$, n.s. No significant effects of workload or time were found for activity in the theta range at Fz.

3.3.1. *Spelling Only condition*

For the Spelling Only condition, a repeated measures ANOVA with runs (10) as factor revealed a main effect of time on alpha power at Pz, $F_{(4.14, 78.69)} = 4.99$, Greenhouse–Geisser corrected, $p < .01$. Post hoc tests revealed that alpha power was significantly higher in run 8 compared to run 1 ($p < .01$) and higher in run 6 compared to 2, and in run 4 compared to 2 ($p < .05$). A linear trend could be observed and was confirmed by a linear regression analysis. Time (run number) significantly predicted alpha power at Pz, $b = .115$, $t(199) = 2.18$, $p < .05$. Time explained a significant proportion of variance in alpha power at Pz, $R^2 = .024$, $F_{(1, 199)} = 4.77$, $p < .05$.

Repeated measures ANOVAs (10) revealed no main effects of time on P300 amplitude, $F_{(9, 171)} = 1.05$, $p = .399$, P300 latency, $F_{(9, 171)} = 1.28$, $p = .278$, or theta power at Fz, $F_{(4.52, 85.93)} = 2.08$, Greenhouse–Geisser corrected, $p = .082$.

3.3.2. *Explorative analyses*

To explore differences in alpha and theta power between the first and last runs of the medium and high workload condition at individual electrodes, multiple *t*-tests were conducted. Fig. 7 displays the level of significance for individual electrodes. The three electrodes with the lowest *p*-values in the high workload condition were CPz ($p = 1.8 \times 10^{-5}$), Pz (2.6×10^{-5}) and P1 (3.4×10^{-5}). For the medium workload condition a general increase in activity in the alpha band could be observed, but it did not reach significance at the adjusted level. The three electrodes with the lowest *p*-values were Pz ($p = .004$), P2 and CPz ($p = .005$).

Differences in the theta band (4–7 Hz) did not reach significance at the adjusted levels of significance. For the high workload condition an increase in activity for the last as compared to the first run was found at Fz, FC5, FC6, C5, CP5, P3, O1, O2 and PO8 ($p < .05$, not adjusted for multiple comparisons). A significant increase in activity in the last run compared to the first run of the medium workload condition was only found at electrode C5 ($p < .05$).

4. Discussion

We succeeded in the experimental manipulation of mental workload to induce changes in behavioral and electrophysiological indicators of performance during prolonged operation of a P300 BCI. As an indicator of high mental workload, a reduced P300 amplitude was found. The effects of the prolonged operation were evident in the time and frequency domain of the EEG. An increased activity in the alpha band was observed for the last run as compared to the first run for both, the medium and high workload condition.

The amplitude of the P300 was significantly smaller for the last run of the medium workload condition as compared to the first.

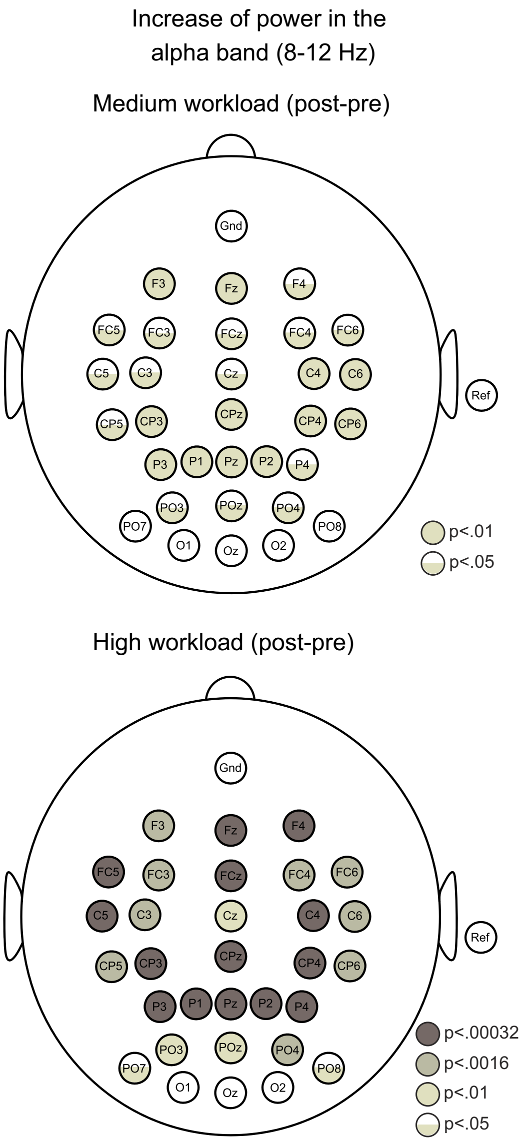

Fig. 7. Differences of power in the alpha band (8–12 Hz) at individual electrode positions. Significance values of the power differences are shown for the last run compared to the first run of the high and medium workload conditions.

The study also demonstrated that users were able to maintain a satisfactory level of performance with the P300 BCI despite long operation and constant auditory distraction.

4.1. Effects of the manipulation of mental workload

The behavioral data suggests that the experimental manipulation succeeded since it significantly affected performance with the BCI. Participants spelled better in the medium workload condition than in the high workload condition.

An accuracy of 70% correct selections was defined as the threshold value necessary to achieve satisfactory communication with a BCI (Kübler, Neumann, Kaiser, Kotchoubey, Hinterberger, & Birbaumer, 2001). The average accuracy of 80% achieved in the medium workload condition is above this level, despite constant distraction through background noise. In the high workload condition, accuracy dropped below this value (65%). Thus, mental workload was too high for the participants to perform at a satisfactory level. Accordingly, subjective workload as rated with the NASA-TLX was significantly higher than in the medium workload condition. Both ratings were substantially higher than ratings in a previous study in which participants used solely the visual speller without an additional task (Käthner et al., 2013). The multiple choice questionnaire, which was administered after every run, served as an index of compliance and task performance. Participants answered more questions correct in the high as compared to the medium workload condition, suggesting that task compliance was high and the manipulation successful. In addition, the fact that the number of correctly guessed answers did not differ significantly from chance level, indicates suitability of this instrument to assess (secondary) task performance.

As expected, P300 amplitude was significantly reduced in the high workload condition as compared to the medium workload condition and no significant differences in latency were found. This result confirms previous studies that reported also a decreased P300 amplitude with higher workload (Allison & Polich, 2007; Miller et al., 2011; Ullsperger et al., 2001; for a review see Kok, 2001) and again indicates that cognitive demands during task processing influence P300 amplitude. Although we analyzed P300 separately from changes in the frequency bands, there is generally a strong connection between the event-related potentials and oscillatory activity in specific frequency bands. P300 consists primarily of phase-locked delta and theta-range synchronized oscillations (Başar-Eroglu, Başar, Demiralp, & Schürmann, 1992; Spencer & Polich, 1999). Başar-Eroglu et al. (1992) observed diffuse delta increase and prolonged activation in the theta band in response to rare tones in an oddball paradigm. Further, Yordanova, Kolev, and Polich (2001) demonstrated strong relationships between event-related alpha power suppression (event-related desynchronization, ERD) and P300 latency and amplitude in auditory oddball tasks. ERD onset was negatively associated with P300 amplitude and positively with P300 latency. The authors also found that P300 preceded ERD indicating that the underlying cognitive processes are distinct, but that the internal processes underlying P300 influence (guide or modify) those underlying ERD.

Unlike hypothesized, there were no significant differences in activity in the alpha and theta bands between the medium and high workload conditions. However, the explorative analysis revealed that alpha power at Pz and theta power at Fz were increased in both workload conditions compared to the screening run, in which no additional workload was induced. The increase in alpha power with increasing task demands was unexpected, but had previously been observed in the study by Kohlmorgen et al. (2007), who induced workload by means of a mental calculation and an auditory task during a real-life driving condition. The authors explained their findings with the nature of their workload inducing tasks, which was not visual in contrast to the secondary tasks used in many studies. An increase of alpha activity with increasing task demands, especially during auditory stimulation had previously been reported (Galin, Johnstone, & Herron, 1978; Legewie, Simonova, & Creutzfeldt, 1969; Markand, 1990). These findings are descriptive and do not allow conclusions on the functionality of alpha oscillations. A possible functional interpretation is the alpha inhibition hypothesis (Klimesch, Doppelmayr, Schwaiger, Auinger, & Winkler, 1999; Klimesch, Sauseng, & Hanslmayr, 2007 for a review). According to this theory, low alpha activity reflects active neuronal processing, whereas high alpha activity indicates the inhibition of task-irrelevant brain regions. In our study, the secondary, workload inducing task was either to ignore two simultaneously presented stories or listen to both stories to recall their content later on. In line with the inhibition theory, top-down inhibition of the brain regions for auditory processing in the ignore condition could have led to the increase in alpha power, In the high work load condition that required divided attention, participants had to retain information in working memory. Klimesch et al. (1999) found that alpha activity was increased during encoding and retention of a working memory task and argued that the increase in alpha power reflects inhibitory top-down control to block retrieval of information. This could also be the case for the high workload condition of our study. However, Palva and Palva (2007) suggest that the working memory related alpha oscillations represent active processing of the frontoparietal network involved in sustaining the neuronal representations of memorized items. A claim that is supported by the positive correlation of alpha activity and working memory load and task difficulty (Jensen, Gelfand, Kounios, & Lisman, 2002; Sauseng et al., 2005). The mixed results indicate that the empirical data on the functional role of alpha band oscillations is not yet conclusive.

The explorative analysis of our study revealed differences in alpha power at multiple, widespread electrode sites for the workload conditions compared to the screening run, while for theta power differences were only found at frontal and frontocentral electrode sites. These topographic findings are in line with previous findings that show an increase of frontal theta with increasing workload (Gevins et al., 1998; Gundel & Wilson, 1992; Holm et al., 2009; Mecklinger et al., 1992). Further, Jensen and Tesche (2002) found an increase of frontal theta with increasing amount of encoded information and Sarnthein, Petsche, Rappelsberger, Shaw, and von Stein (1998) reported prefrontal to left temporo-parietal theta coupling especially for retention of verbal information. Depending on the task, the cognitive processes involved in working memory vary, but usually entail several processes such as encoding, storage and retrieval of information, attentional control, interfacing with long-term memory, multi modal integration and others (Sauseng, Griesmayr, Freunberger, & Klimesch, 2010). Nevertheless, an increase of theta is consistently reported. These observations led Sauseng et al. (2010) to suggest that theta might be an integrative brain mechanism to coordinate the processes in several brain regions involved in working memory. In the workload conditions of our study working memory related processes such as attentional control, encoding and storage of information were involved and might be indicated by the increase in frontal theta.

In the context of BCIs, it was recently shown in Mak et al. (2012) that an increase in theta power was associated with a decrease in P300 BCI performance, which is also the case for our study since performance decreased with higher mental load and theta increased.

Apart from changes in the frequency bands reported in this paper, changes could also occur in other frequency bands, or in particular sub bands (e.g. lower or upper alpha) and should be taken into account for workload detection algorithms. Therefore, we provide information for frequency bands not described in this paper in supplementary Fig. 1.

Supplementary Fig. I related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2014.07.014.

In this section, we discussed those processes modulating alpha and theta band activity with regard to mental workload that are under volitional control. It has to be noted, however, that tonic changes that occur, for instance as a consequence of fatigue, also play a role. This holds especially true for the explorative analyses, because the averaged effects from several runs were compared to the screening run that was performed in the beginning.

4.2. *Effects of prolonged BCI operation*

In accordance with the hypothesized effects, performance decreased over the course of the experiment. During the last run of the medium and high workload conditions, spelling accuracy was significantly lower than in the first. Further, subjective ratings of fatigue were significantly higher at the end of the experiment as compared to the beginning. Likewise, the P300 amplitude was reduced during the last as compared to the first run of the medium workload condition and the increase of power in the alpha band was significant in the high and medium workload conditions. An explorative analysis revealed a general increase of alpha power at multiple frontal, central and parietal electrode positions with strongest effects around parietal and central-parietal electrode sites. While for the first four runs of the high workload condition spelling accuracy was just below the critical value of 70%, it dropped below 60% in the last run. Considering the behavioral data, it is likely that the increase of activity in the alpha band indicates an increase of fatigue and a drop in the level of arousal and subsequent attention deficits. This interpretation is in line with the following findings from previous studies. If a person gets sleepier the activity in the alpha band typically decreases and eventually disappears (Santamaria & Chiappa, 1987). However, this holds only true for an eyes closed condition. If eyes are open, activity in the alpha band increases globally with increasing sleepiness (Åkerstedt, Torsvall, & Gillberg, 1985; Daniel, 1967; Stampi et al., 1995; Torsvall & Åkerstedt, 1987). Further, O'Connell et al. (2009) found that increasing activity in the alpha band was the strongest electrophysiological predictor of lapsing attention during the vigilance task used in their study. However, in contrast, Braboszcz and Delorme (2010) found a decrease in alpha power during periods of self-reported mind wandering, a state that constitutes low-alertness. Klimesch (1999) pointed out that the increase of alpha activity with increasing sleepiness is especially apparent in the lower alpha band. Interestingly, this is only the case if participants are not allowed to fall asleep and thus, the increase in lower alpha might indicate the increased effort of study participants to stay alert and awake. On the other hand, changes in upper alpha are probably task-induced and associated to storage processes during retention (Schack, Klimesch, & Sauseng, 2005).

Along with the changes in the alpha band, widespread increase of theta activity is seen in sleep deprived persons and during sustained wakefulness (Borbély et al., 1981; Cajochen, Brunner, Krauchi, Graw, & WirzJustice, 1995). The explorative analysis of the present study showed that theta was also increased at multiple widespread scalp positions (note that this was only observed at a level of significance not adjusted for multiple comparisons). Thus it is likely that the increase of theta, observed in the present study, represents an increase of fatigue.

As for mental workload, effects of time/fatigue could be apparent in frequency bands not reported in this paper, therefore, we provide information for other bands in supplementary Fig. 2.

Supplementary Fig. II related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2014.07.014.

The Spelling Only condition allowed to identify the changes in spelling accuracy, P300 amplitude and latency, alpha and theta power that occurred over the ten runs without the direct influence of a secondary task. Since the Spelling Only condition always followed the dual task conditions, spillover effects cannot be excluded. A main effect of time was revealed for spelling accuracy and alpha power at Pz. The performance with the BCI without auditory distraction does not follow a linear trend. It is generally high, but substantially varies around the mean accuracy of 78% (range 70–91%). The high variance within each run can be explained by the low number of letters to be spelled (4). Spelling accuracy is significantly higher in the beginning (runs 2 and 3: ≥ 90%) than toward the end (run 8: 70%), but is again high in the last run. Participants probably increased their mental effort, when they realized that the experiment was almost finished.

4.3. Toward a BCI that adapts to the mental state of the user

Ultimately, BCIs are intended as assistive technology to be used more or less independently by severely paralyzed patients. In this study, a high average performance of healthy users even during constant distraction was demonstrated. This is encouraging for BCI use in a home environment, where distraction is unavoidable.

However, classification accuracies are usually lower for patients than healthy users and in some the required pattern of EEG activity cannot be classified by the BCI (Kübler & Birbaumer, 2008; Mak et al., 2011; Nijboer et al., 2008). Countermeasures are necessary to overcome the so-called BCI inefficiency (Kübler, Blankertz, Müller, & Neuper, 2011). Different solutions were proposed to solve this problem. For instance, Kaufmann et al. (2013) have shown that changes in the stimulus material can boost performance for individual patients with neurodegenerative disease. Another approach may be to use a BCI that adapts to the mental state of the user. Thus, a BCI is desirable that automatically detects high workload and fatigue and either adapts the stimulation parameters or pauses the system, if voluntary selections are no longer possible. The current study demonstrates that ERPs and changes in the alpha and theta frequency bands are suitable candidates for the automatic detection of workload during operation of a P300 BCI.

Further, the automatic detection of mental states with EEG is of interest also for other user groups. A major advantage of the EEG over other functional neuroimaging methods is its portability. Recently it was demonstrated that the acquisition of good EEG signals is possible with a low cost mobile EEG, even when users are walking outdoors (Debener, Minow, Emkes, Gandras, & De Vos, 2012). Such developments increase the likelihood that the detection of mental states with the EEG will be possible during real life situations – a goal that has been pursued for decades (Brookings et al., 1996; Gevins et al., 1995; Kramer, 1991; Lindholm, Cheatham, Koriath, & Longridge, 1984; Sirevaag et al., 1993).

4.4. Limitations of the study

The study reported electrophysiological findings on the group level for fixed frequency bands. Previous studies demonstrated that alpha frequency not only varies with task demands, but is also strongly influenced by individual characteristics such as age and memory performance (Klimesch, Schimke, & Pfurtscheller, 1993; Niedermeyer, 1993), albeit the results require validation on the single subject level.

While the study succeeded in the manipulation of mental workload, the study design limits comparisons of the high and medium workload with baseline conditions (spelling without secondary task). Runs without auditory tasks, which were equal in length to the workload conditions, were not included to keep the total duration of the experiment at an acceptable level. Nevertheless, as an explorative analysis, the workload conditions were compared to the screening run and the Spelling Only condition. When interpreting the results of this analysis, one has to be aware of the limited comparability of these conditions. In particular, it is important to note that the Spelling Only condition always started after the spelling of 20 letters, thus, it cannot be ruled out that concentration had dropped. On the other hand, concentration was probably high during the screening run, which was performed before all online spelling runs.

5. Conclusions

The study demonstrates that satisfactory accuracies can be achieved by healthy participants with the P300 speller despite constant distraction and prolonged operation. This is promising for the use of BCIs in a home environment where distraction is inevitable. To improve usability for the target user group of severely paralyzed patients, it was suggested to implement a BCI that adapts to the mental state of the user. As a further step in this direction, the current study identified behavioral and electrophysiological changes that could serve as indicators of high workload or fatigue. Our results confirm that both, the frequency and time domains of the EEG contain valuable information that could be used for the automatic detection of workload and/or fatigue during operation of a P300 BCI.

Acknowledgements

The study was funded by the European ICT Program Project FP7-288566 and supported by Deutsche Forschungsgemeinschaft (DFG) RTG 1252/1. This paper only reflects the authors' views and funding agencies are not liable for any use that may be made of the information contained herein.

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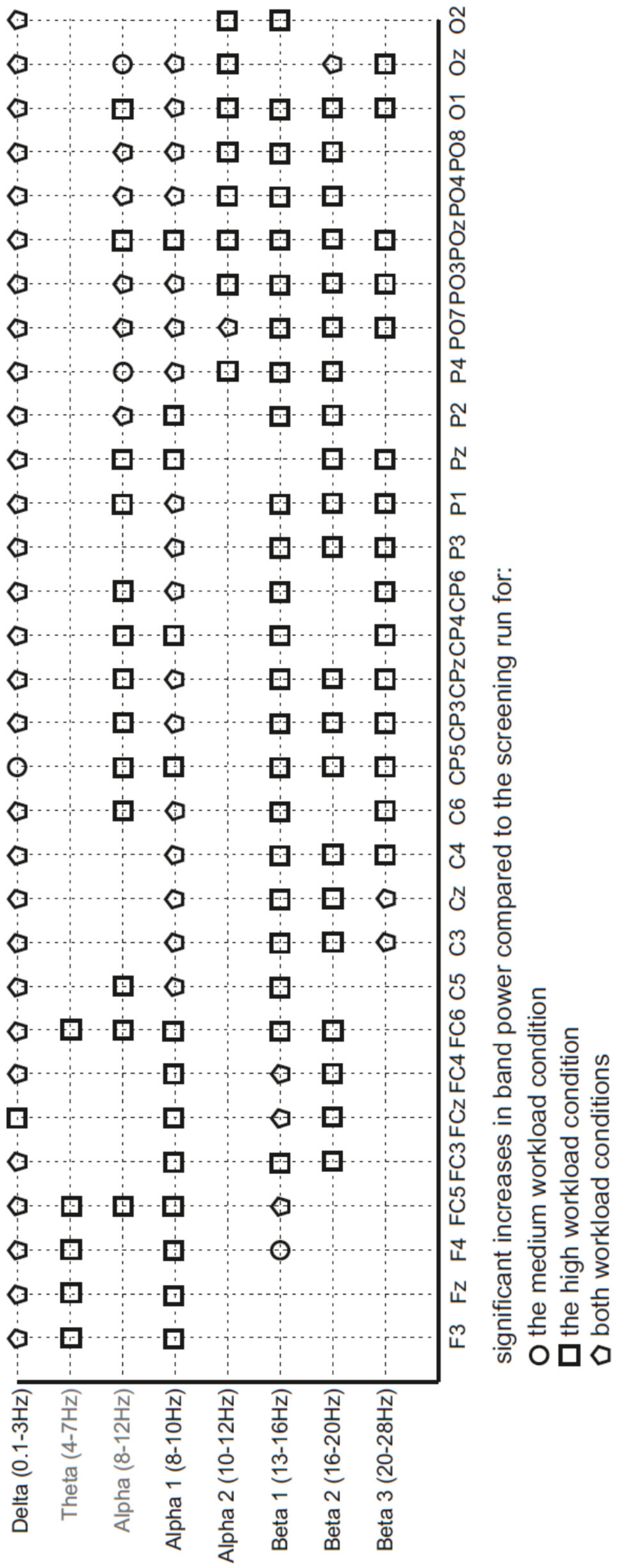
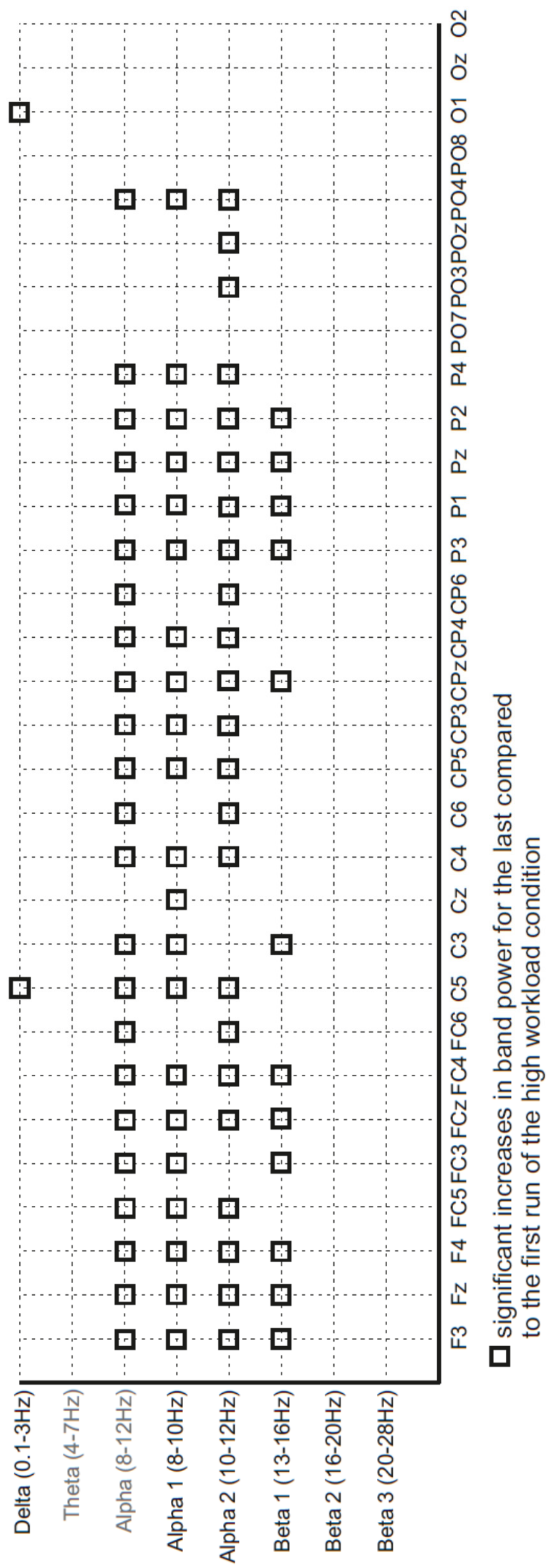
Supplementary Material



Supplementary Fig. I. Increases in band power for the workload conditions compared to the screening run. The level of significance of the *t*-tests was adjusted for multiple comparisons (Bonferroni correction) for individual frequency bands. Differences for the alpha and theta band are reported in the paper (Fig. 6) and are depicted again to facilitate comparisons between frequency bands.

Supplementary Material



Supplementary Fig. II. Significant increases for the last compared to the first run of the high workload condition for selected frequency bands at individual electrode positions (*t*-tests corrected for multiple comparisons). No significant differences were found at individual electrode positions in the medium workload condition.

2.2 Käthner, I., Kübler, A., Halder, S. (2015). Rapid P300 brain-computer interface communication with a head-mounted display. *Frontiers in Neuroscience*

Abstract

Visual ERP (P300) based brain-computer interfaces (BCIs) allow for fast and reliable spelling and are intended as a muscle-independent communication channel for people with severe paralysis. However, they require the presentation of visual stimuli in the field of view of the user. A head-mounted display could allow convenient presentation of visual stimuli in situations, where mounting a conventional monitor might be difficult or not feasible (e.g., at a patient's bedside). To explore if similar accuracies can be achieved with a virtual reality (VR) headset compared to a conventional flat screen monitor, we conducted an experiment with 18 healthy participants. We also evaluated it with a person in the locked-in state (LIS) to verify that usage of the headset is possible for a severely paralyzed person. Healthy participants performed online spelling with three different display methods. In one condition a 5 × 5 letter matrix was presented on a conventional 22 inch TFT monitor. Two configurations of the VR headset were tested. In the first (glasses A), the same 5 × 5 matrix filled the field of view of the user. In the second (glasses B), single letters of the matrix filled the field of view of the user. The participant in the LIS tested the VR headset on three different occasions (glasses A condition only). For healthy participants, average online spelling accuracies were 94% (15.5 bits/min) using three flash sequences for spelling with the monitor and glasses A and 96% (16.2 bits/min) with glasses B. In one session, the participant in the LIS reached an online spelling accuracy of 100% (10 bits/min) using the glasses A condition. We also demonstrated that spelling with one flash sequence is possible with the VR headset for healthy users (mean: 32.1 bits/min, maximum reached by one user: 71.89 bits/min at 100% accuracy). We conclude that the VR headset allows for rapid P300 BCI communication in healthy users and may be a suitable display option for severely paralyzed persons.

Originally published in: Frontiers in Neuroscience, *9*: 207
doi: 10.3389/fnins.2015.00207

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 05 June 2015
doi: 10.3389/fnins.2015.00207

Rapid P300 brain-computer interface communication with a head-mounted display

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OPEN ACCESS

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Specialty section:
This article was submitted to Neuroprosthetics, a section of the journal Frontiers in Neuroscience

Received: *06 February 2015*
Accepted: *23 May 2015*
Published: *05 June 2015*

Citation:
Käthner I, Kübler A and Halder S (2015) Rapid P300 brain-computer interface communication with a head-mounted display. Front. Neurosci. 9:207. doi: 10.3389/fnins.2015.00207

Visual ERP (P300) based brain-computer interfaces (BCIs) allow for fast and reliable spelling and are intended as a muscle-independent communication channel for people with severe paralysis. However, they require the presentation of visual stimuli in the field of view of the user. A head-mounted display could allow convenient presentation of visual stimuli in situations, where mounting a conventional monitor might be difficult or not feasible (e.g., at a patient's bedside). To explore if similar accuracies can be achieved with a virtual reality (VR) headset compared to a conventional flat screen monitor, we conducted an experiment with 18 healthy participants. We also evaluated it with a person in the locked-in state (LIS) to verify that usage of the headset is possible for a severely paralyzed person. Healthy participants performed online spelling with three different display methods. In one condition a 5 × 5 letter matrix was presented on a conventional 22 inch TFT monitor. Two configurations of the VR headset were tested. In the first (glasses A), the same 5 × 5 matrix filled the field of view of the user. In the second (glasses B), single letters of the matrix filled the field of view of the user. The participant in the LIS tested the VR headset on three different occasions (glasses A condition only). For healthy participants, average online spelling accuracies were 94% (15.5 bits/min) using three flash sequences for spelling with the monitor and glasses A and 96% (16.2 bits/min) with glasses B. In one session, the participant in the LIS reached an online spelling accuracy of 100% (10 bits/min) using the glasses A condition. We also demonstrated that spelling with one flash sequence is possible with the VR headset for healthy users (mean: 32.1 bits/min, maximum reached by one user: 71.89 bits/min at 100% accuracy). We conclude that the VR headset allows for rapid P300 BCI communication in healthy users and may be a suitable display option for severely paralyzed persons.

Keywords: brain-computer interface, head-mounted display, rapid BCI, P300, locked-in state

Introduction

Brain-computer interfaces (BCIs) can serve as muscle-independent communication channel through the use of brain signals as control commands for output devices. Event related potentials (ERPs) extracted from the electroencephalogram (EEG) are commonly utilized as control signals (see Kleih et al., 2011; Mak et al., 2011 for reviews). In particular, the paradigm introduced by Farwell and Donchin (1988) is widely applied. It consists of a symbol matrix that is presented to the BCI users on a computer screen. During stimulation, rows and columns of the matrix are highlighted in random order and for spelling the users are asked to focus on the letter or symbol they want to select. The most prominent ERP that is elicited by this method is the P300. It is a positive voltage deflection in the EEG that peaks at about 250–500 ms after onset of a rare, but task relevant stimulus (Polich, 2007). In case of the BCI, the P300 occurs in response to the flashing of the letter the user focusses on. Thereby, the row and the column that contain the target letter elicit ERPs that can be classified and the target letter can be identified by the classifier as the symbol at the intersection of the target row and column. It was demonstrated that most healthy users are able to control a P300 based BCI with accuracies of 80% or higher within the first session (Guger et al., 2009), are able to operate it despite constant distraction and when pursuing the task for a long time (Käthner et al., 2014) and control complex applications such as web browsers (Halder et al., 2015). Severely restricted users (e.g., motor impairments caused by amyotrophic lateral sclerosis, ALS) are also able to gain control over P300 BCIs (Kübler and Birbaumer, 2008; Nijboer et al., 2008; Townsend et al., 2010). However, varying degrees of motor impairments and the different paradigms used yielded a wide range of accuracies (see review by Mak et al., 2011).

Naturally, all visual P300 BCI paradigms require the presentation of stimuli in the field of view of the user. In some situations it is difficult to mount a display such that the user can see all the symbols of the matrix. This holds true especially for a hospital or home environment, where the end user is lying in a bed or sitting in a wheelchair and head movements are restricted due to paralysis. For these situations, we tested whether similar accuracies can be achieved with a virtual reality headset (head-mounted display, HMD) compared to a conventional TFT monitor. First, we tested the virtual reality (VR) headset with healthy users and in a second proof-of-principle step with a person in the locked-in state (LIS) to verify that usage of the VR headset is possible for severely paralyzed persons.

It was shown that similar and satisfactory accuracies (76–88%) can be achieved with a see-through HMD as compared to an LCD monitor (Takano et al., 2011). In their study, participants used a TV control panel with 11 symbols in the matrix and a 2 × 2 light control panel for environmental control. However, speed of selections was relatively slow (15 sequences per selection). Therefore, we aimed at improving speed by using a state of the art stimulation method. Recently, Kaufmann et al. (2011, 2013) showed that P300 BCI performance can be improved by means of face stimuli superimposed on characters of a BCI matrix for flashing, instead of flashing the symbols. Additional ERPs involved in face processing, namely the N170 and the N400f, were elicited as compared to conventional flashing and in some participants, including severely paralyzed end-users, the number of flash sequences needed for correct letter selections could be reduced to one sequence. The N400f is an enhanced negativity that can be observed at parietal and central electrode sites between 300 and 500 ms post stimulus, which is larger for familiar as compared to unfamiliar faces. Thus, it is assumed to be an indicator of face recognition (Eimer, 2000). The earlier occurring N170 component (usually peaking around 170 ms, but latencies up to 240 ms were reported) is most prominent over posterior lateral electrode sites (Bentin et al., 1996; Rossion et al., 1999; Bentin and Deouell, 2000; Joyce and Rossion, 2005; Luo et al., 2010). It is specifically evoked by faces or face components, such as isolated eyes, and not modulated by face familiarity (Bentin et al., 1996; Eimer, 2000). Hence, it is likely that this component represents processes involved in the perception of face specific components (Eimer, 2000). The vertex positive potential (VPP), which was primarily reported in earlier studies as a face specific component, peaks in the same time frame as the N170 over frontal and central electrode sites (Jeffreys, 1989, for a review Jeffreys, 1996). Joyce and Rossion (2005) provided strong evidence that the VPP is another manifestation of the brain process that the N170 represents. In our study, the VR headset, did not allow for the presentation of high resolution images. Since Sagiv and Bentin (2001) demonstrated that even a schematic face can trigger the N170, we overlaid rows and columns of the matrix with stylized representations of a smiling humanoid face (smileys) during stimulation. In a recently published study, Chen et al. (2015) found that similar ERPs were elicited and similar accuracies achieved with smileys as compared to face stimuli applied in a P300 BCI. Thomas et al. (2014) also used smileys as stimuli for a P300 BCI, but did not investigate their specific effects.

For both, spelling with the monitor and the VR headset, a 5 × 5 letter matrix was presented to the study participants. We tested two configurations of the VR headset with healthy participants. In the first, it was configured such that the matrix filled the field of view of the users. This condition is similar to the display on the TFT monitor, where the matrix is also fixed. With this configuration of the headset, we also tested if online spelling with one flash sequence (single trial analysis of EEG) is possible. This configuration could serve persons with severe paralysis as an alternative BCI display method. In the second VR headset configuration, matrix size was increased such that only one letter filled the field of view of the users. The users had to move their heads to focus on individual letters. For this, a built-in 3-axis gyroscope tracks the head orientation of the user. Although potential applications for end users with residual control over head movements could be imagined, we mainly aimed at exploring the possibilities of the headset with this configuration and only tested it with healthy participants; clearly, this approach is not suitable for end-users with severe motor impairment. This condition constitutes a "single stimulus paradigm," because only the targets are seen (Polich et al., 1994). It is a variation of the classic oddball paradigm that consists of targets and non-targets, the non-targets are omitted in the single stimulus paradigm (Polich et al., 1994). The single stimulus paradigm yielded similar ERP amplitudes compared to the oddball paradigm for auditory (Polich et al., 1994; Mertens and Polich, 1997) and visual stimuli (Wetter et al., 2004).

In our study we aimed at exploring if similar or higher accuracies can be achieved with the single stimulus paradigm. Because single stimuli were substantially larger and thus, more salient as compared to the other conditions and targets were presented in the center of view, we expected P300 amplitudes to be larger.

Methods

Participants and Data Acquisition

Eighteen healthy participants took part in the study (10 female, 25 ± 3.9 years, range: 21–34). They received 8€ per hour as compensation. In addition, one person participated diagnosed with amyotrophic lateral sclerosis (ALS). She was 80 years of age, in the locked-in state (LIS) and communicated with horizontal eye movements. She was artificially ventilated and fed and had an ALS-functional rating scale score of 0 (= worst possible). The study was carried out in accordance with the guidelines of the Declaration of Helsinki and all participants gave informed consent prior to the start of the experiment.

Data was recorded with eight active electrodes positioned at Fz, Cz, P3, P4, PO7, POz, PO8, Oz, and mounted in an elastic fabric cap. The reference electrode was attached to the right earlobe and the ground was positioned at FPz. The data was digitized at 256 Hz and amplified with a g.USBamp amplifier (g.tec GmbH, Austria). A low pass filter of 30 Hz, a high pass filter of 0.1 Hz and a notch filter around 50 Hz were applied. Stimulus presentation and data acquisition were controlled by the BCI2000 software framework (Schalk et al., 2004) with a Hewlett-Packard ProBook 6460b (dual-core CPU, 4 GB of RAM, 64-bit Windows 7). Depending on the experimental condition, stimuli were either presented on an external 22 inch TFT display or with a VR headset (Oculus Development Kit 1, Oculus VR, Inc., USA). The VR headset featured a 7 inch LCD display positioned behind two lenses that allows for a field of view of 90° horizontal. The resolution of the LCD was 1280 × 800 pixel and, thus, approximately 640 × 800 pixel per eye. A combination of 3-axis gyroscope, magnetometers and accelerometers enabled head orientation tracking. The whole headset weighted approximately 380 g.

Procedure

All healthy participants performed the experimental protocol outlined below, which consisted of online spelling with a BCI using three different display methods. The tasks were the same for all display methods.

We used an altered version of the classic P300 speller paradigm introduced by Farwell and Donchin (1988). A 5 × 5 matrix was displayed consisting of all letters of the alphabet (except Z) instead of a 6 × 6 matrix due to the limited resolution of the VR headset. Kaufmann et al. (2011, 2013) could show that flashing characters with famous faces can improve BCI classification accuracy, because additional face specific ERPs are elicited. Rows and columns of the matrix were overlaid with stylized representations of a smiling humanoid face (smileys) during stimulation. Rows and columns were highlighted in random order. To select a letter, participants were asked to focus on that letter and silently count whenever it was highlighted (overlaid with smileys). Stimulus duration was set to 62.5 ms and the inter-stimulus interval to 125 ms. There was a pause of 10 s between letter selections.

Participants had to perform two screening runs in which they had to spell the words SONNE (engl. "sun") and BLUME (engl. "flower"). In these runs each row and column was highlighted 10 times. The data of these screening runs was used to obtain the classification weights employing stepwise linear discriminant analysis (SWLDA, see Section Online Signal Classification). These were subsequently used for online spelling. In two runs, they spelled the words LUFTSCHLOSS (engl. "castle in the air") and SOMMERNACHTSTRAUM (engl. "summer night's dream"). The word to spell was displayed in a line above the matrix with the current letter in parenthesis behind the word to spell. Participants were also instructed verbally about the word and letter to spell. During online spelling each row and column was highlighted three times only. Feedback of the selected letters was presented in a row above the matrix.

Three experimental conditions (different display methods) were tested. In the first condition, stimuli were presented on a 22 inch TFT monitor. In the second and third conditions, stimuli were presented with the VR headset. The field of view was configured to either show the whole matrix (glasses A condition) or to display only a part of the matrix (glasses B condition; see **Figure 1**). In the glasses B condition individual letters filled the field of view of the user. Head movements were required to focus on the current letter to spell and/or look at the feedback of the selected letter, which was displayed in a line above the matrix. Additionally, feedback was provided verbally by the investigator in this condition. To control for order effects, the order of the display methods was alternated. To one third of the participants ($n = 6$) the stimuli were first presented on the external monitor,

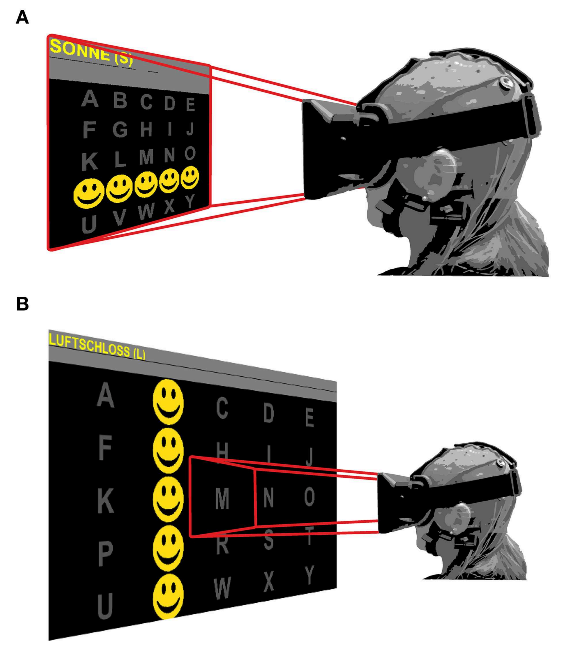

FIGURE 1 | Field of view for the glasses (A) and glasses (B) condition. In **(A)** the display is fixed and the user sees the whole matrix, independent of his/her viewing direction. In **(B)** the user sees only a limited portion of the matrix (one letter) of the matrix and has to move his head to focus on a particular letter. Rows and columns are flashed with yellow smileys during stimulation.

followed by the glasses B (single stimulus) and the glasses A (oddball) condition, while the order for the second group ($n = 6$) was: glasses B, glasses A, monitor and for the third group ($n = 6$): glasses A, monitor, glasses B.

After the glasses A condition, all participants performed an additional online spelling task, copy spelling the word SOMMERNACHTSTRAUM, with a reduced pause between letter selections (2 s) and each row and column was only overlaid once.

Spontaneous remarks of the participants concerning the usability of the display methods were noted.

For the participant in LIS, we adapted the protocol to her abilities. In separate sessions we tried to establish BCI control with three different display methods (a 32 inch LCD flatscreen TV, a 22 inch TFT computer monitor, and the VR headset). The protocol always consisted of screening runs (spelling of words with 5 or 6 characters each) used to obtain classification weights that were applied during subsequent online spelling of 15–29 characters. We either asked her to copy spell (CS) a particular word or she could spell a word of her choice (free spelling, FS). In the latter case, we asked her afterwards which word she had tried to write. She indicated the letters she intended to write in a partner assisted scanning approach with a conventional letter board.

Stimulation parameters were the same as for the healthy participants, with the exception that for the screening runs and online spelling, 10 flash sequences were used. The participant had a limited attention span and indicated via eye movements when she wanted to stop spelling. The participant was naïve to BCI, when we first visited her. Since the glasses B condition required head movements, only the glasses A condition was tested. We performed a total of eight sessions. The different paradigms used in the individual sessions and number of letters for online spelling are listed in **Table 1**. During all sessions except one, the participant was seated in her wheelchair. In session five, she was in a lying but elevated position in her bed. At the time of our measurements she used the 32 inch flat screen monitor on a daily basis to watch TV. The position of the monitor was kept constant across sessions in front of her wheelchair in her field of view (about 2 m distance to her head). The 22 inch monitor was positioned on a table with a distance of approximately 60 cm to her eyes. The VR headset was attached to her head with the elastic fabric bands provided by the manufacturer. In every session (for all display methods), we made sure that she could see all elements of the matrix and moved/adjusted the displays if necessary.

A deterioration of the health status of the participant prevented us from conducting further sessions. Damage to the cornea was diagnosed, requiring the eyes to be sealed shut for long periods throughout the day and night and additionally the participant's ability to move the eyes decreased further.

Online Signal Classification

A multiple regression algorithm was used for online classification derived by a stepwise linear discriminant analysis (SWLDA). This is an established method that is widely used in BCI studies. In a study comparing SWLDA with other linear and non-linear classification algorithms, the authors concluded that SWLDA provides the best characteristics for practical P300 Speller classification (Krusienski et al., 2006). Details of the analysis are described by Krusienski et al. (2008). The data was segmented into post stimulus epochs of 800 ms and then moving average filtered and decimated, corresponding to a sampling rate of 20 Hz. SWLDA then determined features from voltage values from each of the eight electrodes. For every participant, the features and feature coefficient were determined with Matlab (The MathWorks, version R2012b) using the SWLDA algorithm implemented in the P300-GUI (part of the BCI2000 software). The maximum number of features to be included was set to 60. After the parameters had been determined, based on the data acquired in the screening runs, they were used for online classification during BCI operation.

Effectiveness and Efficiency Metrics

The online spelling accuracy was calculated as the number of correctly spelled letters divided by all letters to be spelled. The accuracy was also calculated offline for one, two, and three flash sequences for all experimental conditions.

As a measure of the efficiency of the system the information transfer rate was calculated (Shannon and Weaver, 1964). Firstly, the bitrate was computed with the following formula

$$B = \log_2 N + P \log_2 P + (1 - P) \log_2 \left(\frac{1 - P}{N - 1} \right).$$

where N represents the number of possible targets (25 in case of the 5×5 matrix) and P is the probability of correct classification (average spelling accuracy). In a second step, the bitrate is multiplied by the average number of selection per minute to obtain the information transfer rate in bits/min.

Further, the correctly selected letters per minute were calculated as a practical performance indicator that can be easily interpreted.

Offline Data Analysis

Statistical analysis was performed with SPSS 19. To reveal the effects on spelling performance, we performed a repeated measures ANOVA with the factors "condition" (monitor, glasses A, glasses B) and "number of flash sequences" (one, two, three). To explore if the order of presentation had an influence on spelling performance, we conducted a second repeated measures ANOVA with the factors "order of presentation" (first, second, third) and "number of flash sequences" (one, two, three). For significant main effects, *post-hoc t*-tests were calculated for pairwise comparisons (Bonferroni corrected).

The EEG was analyzed with the EEGLab toolbox (version 10.2.2.4b; Delorme and Makeig, 2004) and the ERPLab plugin (Lopez-Calderon and Luck, 2014) implemented in Matlab (version R2012b). The EEG data was segmented into epochs of 800 ms starting at the onset of a stimulus and baseline corrected with a pre-stimulus interval of 200 ms. Averages were calculated for targets and non-targets. In case of the glasses B condition, flashes were the targets and non-flashes the non-targets. In the

TABLE 1 | Overview of sessions performed by the participant in LIS.

Session	Display method	Flash image	Letters spelled to train classifier	Number of letters spelled with feedback		
					Spelled with improved classification	Total number of letters spelled with feedback
1°	32″ LCD TV	Einstein face	BRAIN	7 (CS)	5 (CS) 6 (CS)	18
2	32″ LCD TV	Einstein face	BRAIN	5 (CS)	10 (FS)	15
3	VR Headset (Glasses A)	Smiley	SONNE ERWIN	6 (CS) 4 (FS) 5 (FS)		15
4.1	22″ TFT monitor	Smiley	SONNE ERWIN BLUME	No online spelling		n/a
4.2	VR Headset (Glasses A)	Smiley	SONNE ERWIN	6 (CS)	10 (FS)	16
5*	VR Headset (Glasses A)	Smiley	SONNE ERWIN	6 (CS) 6 (CS) 6 (FS)		18
6	22″ TFT monitor	Smiley	SONNE BLUME	5 (CS)	5 (FS) 11 (FS) 3 (FS)	24
7	22″ TFT monitor	Smiley	SONNE BLUME	4 (CS) 8 (FS) 12 (FS) 5 (FS)		29
8	22″ TFT monitor	Smiley	SONNE BLUME	5 (CS)	6 (FS) 6 (FS)	17

°16 electrodes used instead of 8.
**Problems with artificial ventilation.*
The category "Number of letters spelled with feedback" is separated into three columns. The rightmost column lists the total number of letters spelled with feedback for each session. The two columns to the left of it provide more detailed information. Each number in these two columns indicates the length of one word that was spelled. Words were either spelled in copy spelling (CS) or free spelling mode (FS). In some cases, letters spelled with feedback were added to train the SWLDA to improve classification for spelling of the subsequent letters. Thus, the number of letters spelled with improved classification, are listed in the middle column.

periphery of the headset the flashing of the neighboring non-target letters could be noticed. For the healthy participants this procedure resulted in 168 target and 672 non-target trials per condition per participant. Grand average ERP waveforms were calculated for each condition (display method).

We calculated R^2 plots as an estimation of the class discriminative information for specific time frames. On the basis of the grand-average ERP waveforms and the R^2 plots, we chose PO7 and PO8 for the analysis of the N170 component (150–300 ms) and Fz and Cz for the analysis of the VPP (150–300 ms). The P300 was determined in the timeframe between 200 and 400 ms at electrodes POz and Oz. In addition, we analyzed the later frontal positivity in the time frame between 350 and 550 ms at Cz, and refer to this component as late positive potential (LPP) to distinguish it from the earlier parieto-occipital P300 component. We analyzed the peak amplitudes in the given timeframes and determined the peak latencies (from stimulus onset to the maximum or minimum amplitude). To compare amplitudes between display modalities repeated measures ANOVAs were conducted with condition (three levels: monitor, glasses A, glasses B) and electrode site as within-subject factors for each ERP component. If appropriate, p-values were corrected with Greenhouse-Geisser correction. *Post-hoc* t-tests were performed and Bonferroni corrected. Due to the longer response time of the VR headset as compared to the monitor, which is in the range between 30 and 50 ms (LaValle, 2013), we refrained from a statistical analyses of the latencies and only report the observed values.

Results

Performance of Healthy Participants

Average accuracies for spelling with the three display modalities are depicted in **Figure 2** for healthy participants. During online spelling with three flash sequences, participants achieved on average 94% (15.5 bits/min) correctly selected letters with both the monitor (±5.3) and the glasses A condition (±8.8%) and 96% (16.2 bits/min) in the glasses B condition (±5.8%). Data of individual participants is listed for all conditions in **Supplementary Table 1**. The repeated measures ANOVA revealed a main effect of "flash sequence" $F_{(1.22,\ 20.70)} = 97.72$ Greenhouse-Geisser corrected (GG), $p < 0.001$ but no main effect of "condition" on spelling performance $F_{(2,\ 34)} = 0.11$, $p = 0.899$ and no significant interaction [$F_{(1.98,\ 33.71)} = 0.397$, $p = 0.673$]. The *post-hoc* comparisons for number of flash sequences were all significant ($p < 0.001$).

During online spelling with one flash sequence (only performed for the glasses A condition), participants achieved on average 64% (±24.4%) correctly selected letters (32.1 bits/min). This equals 9.93 correct symbol selections per minute. Ten of the 18 participants achieved accuracies higher than 70% and the maximum bitrate (100% spelling accuracy) achieved by one participant was 71.89 bits/min.

Figure 3 depicts the average accuracies achieved by the users by order of presentation. The repeated measures ANOVA revealed a main effect of "number of flash sequences" $F_{(1.22,\ 20.70)} = 97.72$, $p < 0.001$ GG corrected, but no main effect of "order of presentation" on spelling accuracy $F_{(2,\ 34)} = 1.44$, $p = 0.252$. The "order of presentation" × "number of flash sequences" interaction was significant [$F_{(2.09,\ 35.67)} = 4.16$, $p = 0.022$, GG corrected). For one flash sequence, performance was higher for the condition that was presented second (79%) compared to the condition that was presented first (67%; $p = 0.020$).

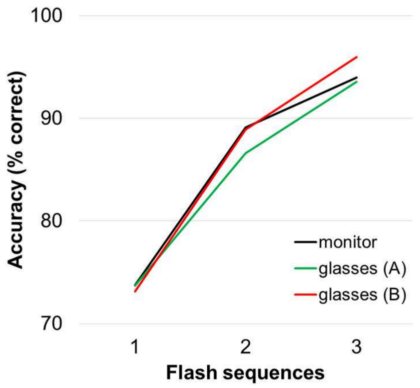

FIGURE 2 | Average accuracies for the three display methods. Accuracies were calculated offline (for three flash sequences the values are equal to those achieved during online spelling).

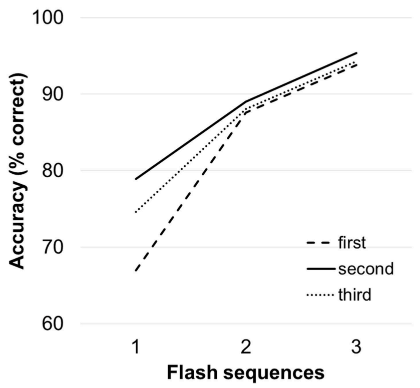

FIGURE 3 | Average accuracies as a function of order of presentation (first, second, third) independent of the display method. Accuracies were calculated offline (for three sequences these values are equal to the accuracies achieved during online spelling).

Remarks of Users Concerning the Usability of the Display Methods

A total of five participants commented on the usability of the different display methods. After having first used the VR headset (glasses A) followed by the monitor, one user stated that he found it more difficult to focus on the target letter in the monitor condition and said that his eyes were "drifting away." Nevertheless, spelling accuracy was 92% for this user in the monitor condition. Four users indicated negative aspects of using the VR headset. Two comments concerned the display quality/resolution of the headset, which one user described as "pixelated" and another noted that the letters in the margins of the matrix were "a bit out of focus." The other two comments concerned the wearing comfort of the headset, one participant speculated that it might be "heavy if wearing it for a longer time" and one said that it was "a bit warm underneath the headset."

Performance of the Participant in LIS

The accuracies achieved during online spelling (with feedback) with different display methods in individual sessions are depicted in **Figure 4** (see **Table 1** for the number of letters that were spelled and details on the paradigm used). In session 4, no online spelling was performed with the 22" monitor because only 10% classification accuracy were achieved with the 10 letters acquired during the screening runs, this value only increased to 27% with additional five letters. In the same session, classification accuracy with the VR headset was 70% (for the same 10 letters that had to be copied in the screening runs with the 22" monitor) and thus, online spelling was performed with the VR headset. In session 5, problems with the artificial ventilation occurred that could have influenced the results.

EEG Data

Figure 5 displays the ERP waveforms for healthy participants for all electrodes and the monitor and glasses A condition. **Figure 6** displays the ERP waveforms for the glasses B condition and again includes the waveforms of the glasses A condition to facilitate comparison. Amplitudes and latencies for the VPP, N170, and P300 and LPP components are listed in **Table 2**. **Figure 7** shows the R^2 plots for the three conditions. It is apparent that most class discriminant information is in the time frame between 200 and 500 ms post stimulus onset independent of the condition. The distribution of the class discriminant information within this timeframe is very similar for the monitor and glasses A condition. However, the magnitude of the class discriminant information varies between the conditions for certain channels and time frames. The N170 component at PO7 and PO8 and the P300 at POz and Oz has higher discriminative values for the glasses A condition compared to the monitor. For the glasses B condition, the high magnitude of the VPP and LPP at Cz is apparent compared to the other two conditions.

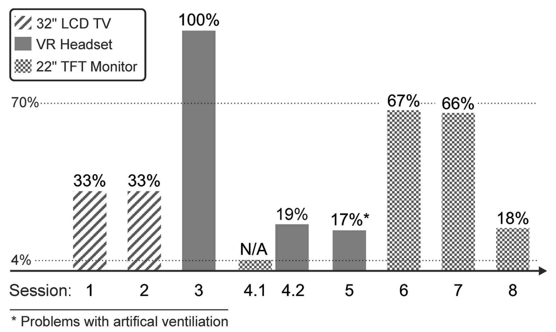

FIGURE 4 | Average accuracies achieved by the participants with LIS during online spelling in individual sessions. Please note that the letters spelled varied between 15 and 29 for individual sessions. In session 4.1 no online spelling was performed with the 22" monitor due to the low classification accuracy achieved with the screening runs (see Section Remarks of Users Concerning the Usability of the Display Methods).The first dotted horizontal line indicates the chance level (4%) and the second horizontal line the threshold level that has been defined for satisfactory communication (70%).

For the VPP, the ANOVA revealed main effects of condition [$F_{(2, 34)} = 22.58$, $p < 0.001$] and electrode site [$F_{(1, 17)} = 11.01$, $p = 0.004$] and a significant condition × electrode site interaction [$F_{(1.39, 25.51)} = 6.11$, $p = 0.014$, Greenhouse-Geisser corrected]. The VPP was significantly larger for the glasses B condition as compared to the glasses A condition ($p < 0.001$) and to the monitor ($p < 0.001$). It was significantly larger at Cz as compared to Fz ($p = 0.004$). At electrode Fz the amplitude was larger for the glasses B (4.86 µV) as compared to the glasses A condition (2.44 µV, $p < 0.001$) and to the monitor (2.40 µV, $p < 0.001$). Similarly, at electrode Cz it was larger for the glasses B condition (6.16 µV) as compared to glasses A (2.97 µV, $p < 0.001$) and the monitor (2.70 µV, $p < 0.001$).

For the N170 amplitude, the ANOVA yielded no significant results, neither a main effect of condition [$F_{(1.42, 24.19)} = 0.99$, $p = 0.382$, Greenhouse-Geisser corrected] nor of electrode

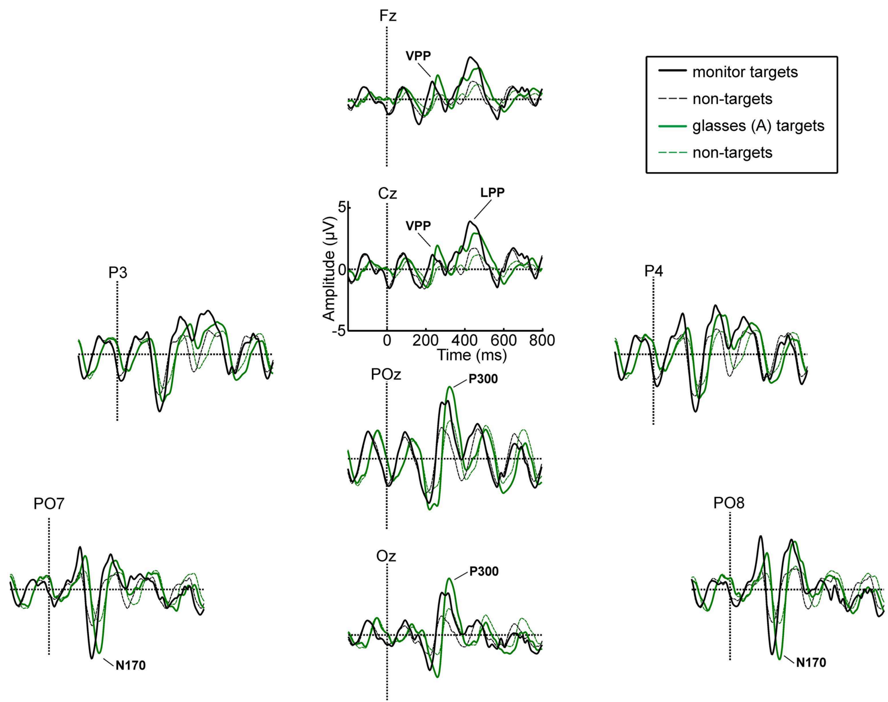

FIGURE 5 | Grand average ERP waveforms for targets and non-targets for the monitor and glasses A condition.

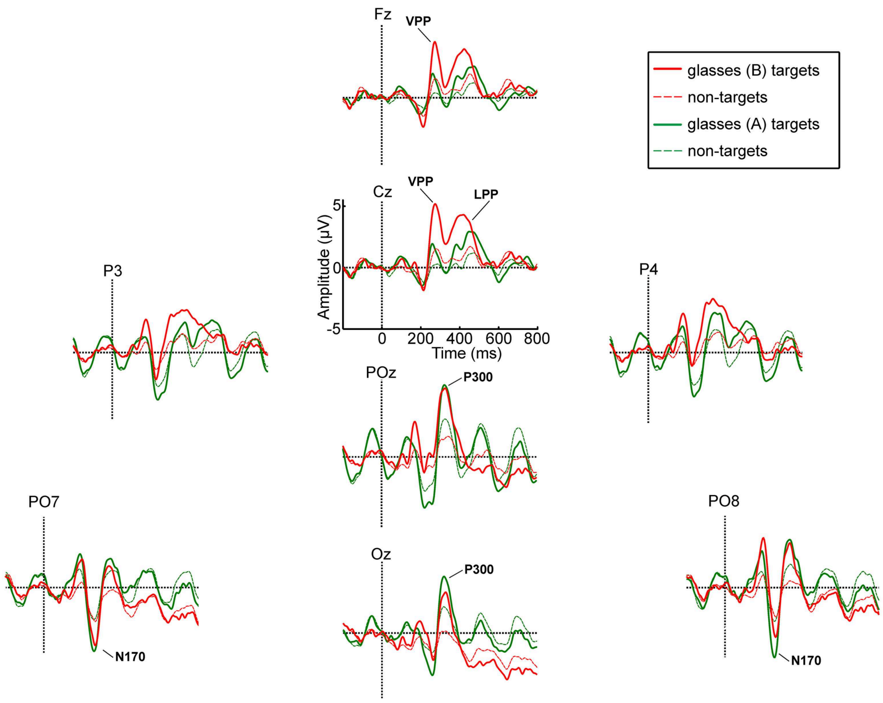

FIGURE 6 | Grand average ERP waveforms for targets and non-targets for the glasses A and glasses B condition.

TABLE 2 | Mean amplitude and latency values and standard deviations for the VPP, N170, and P300 components at selected electrode positions.

		VPP		N170		P300		LPP
		Fz	Cz	PO7	PO8	POz	Oz	Cz
Monitor	*Amplitude* (μV)	2.40 (±2.15)	2.70 (±2.14)	6.12 (±3.12)	5.28 (±2.92)	6.26 (±3.22)	5.24 (±3.26)	4.92 (±2.59)
	Latency (ms)	229.24 (±37.49)	221.68 (±38.16)	225.04 (±12.95)	221.39 (±12.29)	302.26 (±34.34)	295.89 (±41.34)	430.36 (±46.30)
Glasses A	*Amplitude* (μV)	2.44 (±1.84)	2.97 (±2.08)	6.02 (±3.97)	6.18 (±4.35)	6.69 (±3.70)	5.48 (±2.62)	4.13 (±2.45)
	Latency (ms)	250.06 (±28.86)	240.55 (±35.73)	256.35 (±20.62)	251.29 (±23.57)	322.13 (±40.61)	315.44 (±32.79)	451.67 (±45.84)
Glasses B	*Amplitude* (μV)	4.86 (±2.92)	6.16 (±3.11)	5.39 (±4.19)	4.58 (±4.82)	6.99 (±2.79)	5.09 (±2.43)	5.61 (±3.32)
	Latency (ms)	256.93 (±39.97)	262.39 (±32.18)	256.95 (±20.41)	247.39 (±37.87)	293.21 (±53.04)	292.57 (±51.49)	417.89 (±45.34)

Please note that the VR headset has a delayed response time (30–50ms) that one should be aware of when comparing latencies between the display conditions.

site [$F_{(1, 17)} = 1.46$, $p = 0.243$] nor a significant interaction [$F_{(2, 34)} = 1.51$, $p = 0.236$].

For the P300, no significant main effect of condition [$F_{(2, 34)} = 0.12$, $p = 0.891$] was found, but a significant main effect of electrode site [$F_{(1, 17)} = 13.28$, $p = 0.002$]. The amplitude was significantly larger at POz as compared to Oz ($p = 0.002$). The interaction between condition and electrode site was not significant [$F_{(1.38; 23, 38)} = 2.07$, $p = 0.159$, Greenhouse-Geisser corrected].

The amplitude of the LPP was not significantly different for the three display modalities as revealed by the ANOVA [$F_{(2, 34)} = 2.09$, $p = 0.139$].

Figure 8 depicts the averaged ERP waveforms for the participant with LIS in session 3. In this session she achieved 100% spelling accuracy with the VR headset (glasses A).

Discussion

Performance of Healthy Users

It could be shown that the average accuracies achieved during online spelling by the healthy participants did not differ for the VR headset and a conventional 22” TFT monitor. An accuracy of 94% (16 bits/min) was achieved with only three flash sequences during online spelling. An accuracy of 70% was previously

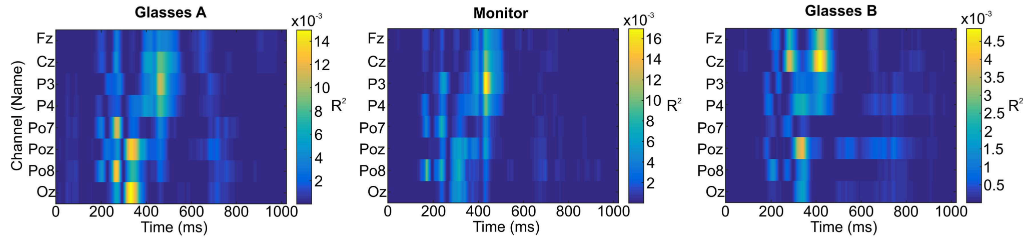

FIGURE 7 | R^2 plots for the glasses A condition, the monitor and the glasses B condition.

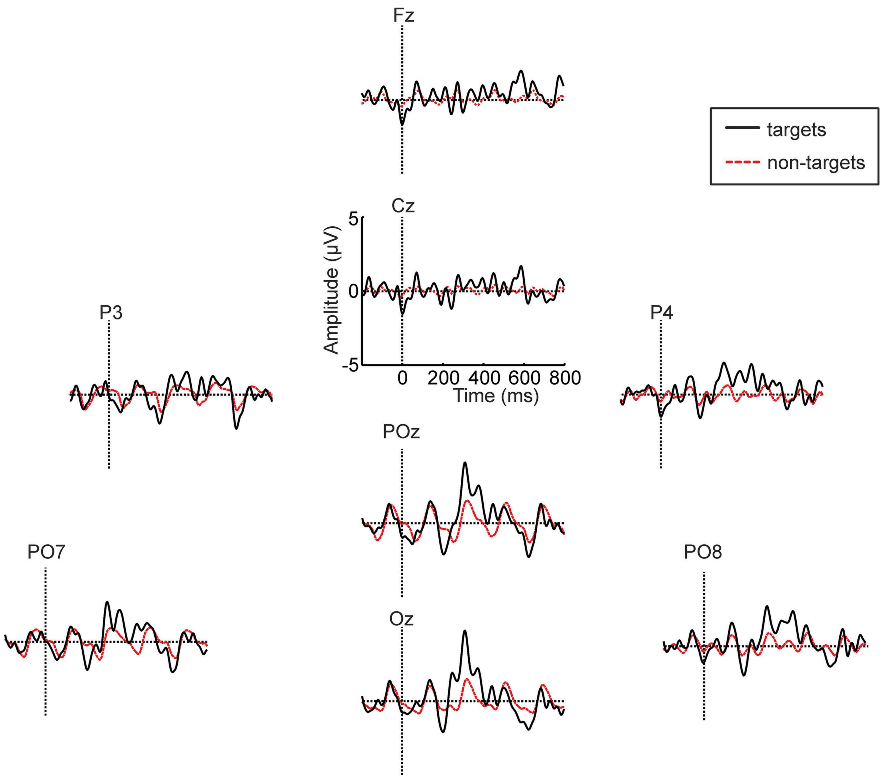

FIGURE 8 | Averaged ERP waveforms for the participant with LIS in session 3 (glasses A condition). The data of the copy spelling and the two free spelling runs were combined for the analysis.

defined as a criterion level for satisfactory BCI performance (Kübler et al., 2001). Offline classification revealed that average accuracies were above this value with only one flash sequence (single trial analysis of EEG). Thus, speed of selection could be substantially improved compared to the study by Takano et al. (2011). The authors used a P300 BCI matrix displayed with a see-through head-mounted display or an LCD monitor to control a light and a TV. They reported average online accuracies ranging from 76 to 88% with 15 flash sequences and at least 6 flash sequences were needed to reach ≥70% accuracy (offline analysis).

We could further show that online spelling with one flash sequence is feasible with the VR headset. Healthy participants achieved 64% (32.1 bits/min) in this condition during copy spelling of 18 letters. About half of the participants achieved a level needed for satisfactory spelling (>70% accuracy).

In contrast to previous studies we did not flash the characters of the matrix directly, instead rows and columns were overlaid with smileys. Kaufmann et al. (2011, 2013) showed that flashing characters with famous faces significantly improved classification performance. Here, we demonstrated that similar speed of communication and classification accuracies as reported in the studies by Kaufmann et al. can be achieved by applying simple smileys as stimulus material. About three flash sequences were needed in their study to achieve 100% classifier accuracy as compared to five for the classic flashing paradigm. A systematic comparison of monochromatic face stimuli and smileys was recently published by Chen et al. (2015). Participants of their study achieved similar accuracies and bitrates for smileys (94%, 33.3 bits/min) and human face stimuli (96%, 35.9 bits/min). Further, they did not find significant differences in face specific ERP components between the different stimuli types. This demonstrates that smileys can be an adequate stimulus to achieve state of the art ERP-BCI performance.

Most ERP-BCI studies highlight the rows or columns by flashing the characters directly (e.g., Farwell and Donchin, 1988; Sellers and Donchin, 2006; Sellers et al., 2006, 2010; Nijboer et al., 2008; Guger et al., 2009).

To our knowledge Lenhardt et al. (2008) reported the highest bitrates achieved with a non-invasive ERP speller to date using the classic flashing paradigm in which the symbols are highlighted directly. For calculation of the information transfer rate, the authors did not take the pause between letter selections into account. However, they report accurate symbol selections per minute (SPM) for both online and offline performance. Participants in their study had to copy spell 22 letters using a P300 BCI with a dynamic stopping method (number of stimulus repetitions were optimized based on different thresholds). In the best setting 4.41 letters were correctly selected per minute. In our study, 9.93 letters could be correctly selected per minute, making it a fast and competitive non-invasive ERP based BCI. Whether this rate can be maintained during sustained spelling with the BCI remains subject of further research.

The peak information transfer rate of 71.89 bits/min (100% spelling accuracy during spelling of 18 letters) achieved by one subject in the glasses A condition is in the range of invasive BCIs. In the study by Brunner et al. (2011) the intracranial EEG was recorded with Electrocorticography (ECoG,). For spelling of 43 letters an information transfer rate of 69 bits/min (86% correctly selected letters) was achieved by the participant of the study. Speier et al. (2013) reported ITRs of 49.47 bits/min and 27.05 bits/min respectively, achieved by the two epilepsy patients that participated in their study.

Although speed of communication with an ERP BCI can already be quite high using salient stimulus material, it can be optimized further. In a proof-of-principle study, Kaufmann and Kübler (2014) demonstrated that it is possible to double the spelling speed by modifying the paradigm. Two very distinct types of stimuli were superimposed on different characters simultaneously during flashing. The offline analysis revealed that about half of the participants could improve their performance compared to a single stimulus (face) paradigm and two users could achieve information transfer rates of 150 bits/min.

Performance in the Glasses B (Single Stimulus) Condition

Participants achieved high accuracies (96%) during online spelling with the glasses B condition. In this condition, only the target letters were in the field of view of the user. Therefore, it constitutes a "single stimulus paradigm" (Polich et al., 1994). Although this display method did not yield higher accuracies as compared to the other two "oddball conditions" (glasses A and monitor), probably due to a ceiling effect, it might be an alternative display option for healthy users. In this condition, individual stimuli are particularly large and hard to ignore and therefore less mental effort is required for their recognition. This configuration of the VR headset cannot be used by persons with severe paralysis and unable to move their heads. However, for users with severe paralysis, but able to move their heads, the possibility to infer the head position with the VR headset could be advantageous. For instance, it could be used to display different matrices depending on the direction of view of the user and thus, speed of communication could be improved. Additionally, BCI controlled applications could be displayed in addition to the BCI matrix in different locations of the user's field of view that currently need two screens, such as the web browser proposed by Halder et al. (2015).

Performance of the Participant in LIS

Online spelling accuracy varied substantially for different display methods and sessions. There are many factors that can negatively influence BCI performance, particularly during home use by a participant with LIS: e.g., artificial ventilation, fluctuations in health condition, noisy and distracting environment, side effects of medication. Nevertheless, the participant was able to spell 15 letters with an online accuracy of 100% during one session, demonstrating that an 80 year old person in the locked-in state is able to use the VR headset to control an ERP BCI. In another session, a classifier performance of 70% was achieved with the VR headset, although in the same session classifier accuracy with a conventional monitor was only 10%. Taking into account all sessions and accuracies achieved with the different display methods, one can state that similar accuracies can be achieved with the VR headset as compared to conventional display methods (large screen TV, flatscreen monitor). Thus, we propose the VR headset as a display option for situations in which mounting a conventional monitor might be difficult or not feasible. Nevertheless, the tested VR headset has several disadvantages, which are discussed in the next section.

Usability of the Different Display Methods

Unlike a conventional monitor, the VR headset (Glasses A condition) has the advantage of always displaying the speller matrix in the field of view of the user. A disadvantage is that communication is no longer possible via eye movements once the user is wearing the VR headset. We made sure that the participant felt comfortable wearing the headset by lifting it after every word spelled. If using the headset for a longer period of time, it would visually isolate the user from his or her environment. Further, healthy participants pointed out that it might be uncomfortable to wear for longer periods of time due to its weight and because it might get warm underneath the headset. An additional disadvantage is that the resolution of the VR headset is low. Therefore, the tested version of the VR headset might be particularly suited for initial communication attempts with a BCI for severely paralyzed persons if mounting a monitor is difficult. For long term use of a P300 BCI, displaying stimuli on a conventional monitor is probably advantageous for social-interactive reasons.

Usability of head-mounted displays will likely be improved in the near future (e.g., reduced weight, higher screen resolution, high quality see-through displays) and therefore become an even more promising display option for BCI use. Further, the combination of a BCI and a virtual environment presented via a HMD (as explored by Leeb et al., 2006) might be of particular interest for persons who are severely paralyzed to gain a higher quality of life.

ERP Waveforms

In the present study, we did not systematically investigate the effects of the stimulus material (smileys) on ERP waveforms. The lack of a control conditions such as flashing rows and columns with the face stimuli proposed by Kaufmann et al. (2011, 2013) or highlighting the rows and columns directly, does not allow us to draw definite conclusions on the effects of stimulus material on ERP waveforms. However, we investigated whether the face specific ERPs reported by Kaufmann et al. (2011, 2013), namely the N170 and the N400f were also apparent in our study using smileys as stimulus material.

In the grand-average ERP waveforms, the most pronounced negative deflection is apparent at electrode positions PO7 and PO8 for all display methods. Although the mean latencies for the monitor condition at PO7 (225 ms) and PO8 (221) are substantially later (∼50 ms) than the values usually reported in studies of face perception (e.g., Bentin et al., 1996; Eimer, 2000), we argue that they are not atypical and this negativity is the N170 component. First of all, even longer latencies were observed for a face specific negative component by Luo et al. (2010) in a rapid serial visual presentation (RSVP) task in response to faces with different emotional expressions (240 ms) and by Chen et al. (2015), who compared the ERPs elicited by faces and smileys using a P300 based BCI (252 ms). Secondly, in the same timeframe as the N170 component, a vertex positive potential (VPP) was apparent at electrode positions Cz and Fz in our study. Thus, the N170 at parieto-occipital electrode sites and the VPP at fronto-central electrode sites were apparent at the expected sites. As stated in the introduction, Joyce and Rossion (2005) provided strong evidence that they are manifestations of the same neural generator. No clear N400f component was apparent at central and parietal electrode sites in our study. Since the component is linked to processes involved in the recognition of familiar faces, this potential was not expected (Eimer, 2000). Hence, we focused on the analysis of the N170 and VPP components.

The ANOVA did not reveal a significant difference between the amplitudes of the N170 between the three display modalities, but the amplitude of the VPP was significantly larger for the glasses B condition as compared to the other two conditions. The glasses B condition differed from the other two conditions twofold: firstly, only the targets were seen (single stimulus, rather than conventional target/non-target oddball condition) and secondly, individual stimuli filled the field of view of the user, thus, stimulus size was substantially larger. Hence, it is easier to focus on the targets and they are more salient. To our knowledge, no studies reported on manipulating the size or discriminability of smileys/stimuli in a P300 BCI task, but several basic studies point in the direction that the positive component in the timeframe of the VPP (150–250 ms) can be manipulated by stimulus properties, with higher stimulus intensity eliciting a higher P200 (Picton et al., 1974; Vesco et al., 1993; Sugg and Polich, 1995; Covington and Polich, 1996). The majority of these studies manipulated stimulus intensity in the auditory domain.

The P300 was largest for the glasses B condition, but unlike hypothesized, it was not significantly larger as compared to the other two conditions. Whether larger stimuli in a visual "single stimulus" paradigm elicit larger P300 amplitudes has not yet been systematically investigated. Li et al. (2011, 2014) investigated the effect of screen size and stimulus luminosity with a P300 BCI and found that a computer monitor elicited a larger P300 as compared to a cell phone display and reported a higher P300 with increased luminosity of the stimuli, the latter effect, however, was not significant. Similar P300 amplitudes were elicited by a visual oddball and a visual "single stimulus" paradigm (Mertens and Polich, 1997).

We conclude that a systematic study is needed to investigate the effects of using a "single stimulus" paradigm and determining the effect of stimulus size on ERP waveforms with a P300 BCI.

General Remarks

We found a significant interaction of "order of presentation" and "number of flash sequences." This demonstrates that the order of presentation (of different display methods) can have an influence on spelling accuracy with a BCI, particularly for few stimulus repetitions. Therefore, it is crucial to control for order effects, when comparing different experimental conditions. Because we controlled for order effects and did not find a main effect of display method, the finding suggests that participants performed particularly well with the BCI after they have gained control over it (after the first condition) independent of display method.

Conclusions

Healthy users achieved very high spelling accuracies (>90%) with a VR headset (head-mounted display), similar to those achieved with a conventional monitor used to display a P300 BCI matrix. A person in the locked in state was able to gain control over the BCI (100% in one session) using the VR headset. Therefore, we propose it as a display option for severely paralyzed persons for situation in which mounting a conventional monitor is not feasible.

We also demonstrated that rapid BCI communication is possible with only one flash sequence (single trial analysis of EEG) using the VR headset in some but not all subjects. With 9.91 correctly spelled letters per minute it constitutes a fast and competitive ERP BCI.

Acknowledgments

The authors are very grateful to Johanna Räderscheidt for her help with data acquisition and to the participant with LIS for her patience. The study was funded by the European Community for research, technological development and demonstration activities under the Seventh Framework Program (FP7, 2007-13), project grant agreement number 288566 (BackHome). The senior author (SH) has received funding as International Research Fellow of the Japan Society for the Promotion of Science and the Alexander von Humboldt Foundation. This paper reflects only the authors' views and funding agencies are not liable for any use that may be made of the information contained herein.

Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnins.2015.00207/abstract

Supplementary Table 1 | Performance for each participant and for all conditions listed by the number of flash sequences. Online spelling with one flash sequence was only tested for the glasses A condition.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary Material

Supplementary Table 1. Performance for each participant and for all conditions listed by the number of flash sequences. Online spelling with one flash sequence was only tested for the glasses A condition.

	One flash sequence (online)	One flash sequence (offline)			Two flash sequences (offline)			Three flash sequences (online)		
Participant	Glasses A	Glasses A	Monitor	Glasses B	Glasses A	Monitor	Glasses B	Glasses A	Monitor	Glasses B
1	96	86	64	96	93	96	100	96	96	100
2	76	82	57	61	93	75	75	96	82	89
3	71	96	79	96	96	96	100	100	100	100
4	82	64	50	75	86	89	89	89	89	100
5	59	75	50	79	86	82	86	93	93	100
6	35	64	61	64	82	82	79	93	93	93
7	100	93	93	96	100	96	100	100	96	100
8	93	71	61	82	89	86	93	96	93	100
9	59	71	86	64	89	96	89	100	100	96
10	76	96	93	93	100	100	100	100	96	100
11	76	96	86	64	100	93	100	100	100	100
12	18	54	79	68	71	89	100	82	96	100
13	47	61	75	71	82	93	82	93	96	89
14	59	75	57	39	89	71	75	93	82	82
15	70	64	89	100	86	89	100	96	93	100
16	35	64	100	39	71	100	68	93	100	89
17	24	32	79	36	50	89	68	64	93	89
18	82	82	68	93	96	82	96	100	93	100
Mean	64,33	73,67	73,72	73,11	86,61	89,11	88,89	93,56	93,94	95,94
SD	24,36	16,87	15,70	20,77	12,57	8,21	11,74	8,75	5,33	5,83

2.3 Simon, N., Käthner, I., Ruf, C. A., Pasqualotto, E., Kübler, A., Halder, S. (2015). An auditory multiclass brain-computer interface with natural stimuli: Usability evaluation with healthy participants and a motor impaired end user. *Frontiers in Human Neuroscience*

Abstract

Brain-computer interfaces (BCIs) can serve as muscle independent communication aids. Persons, who are unable to control their eye muscles (e.g., in the completely locked-in state) or have severe visual impairments for other reasons, need BCI systems that do not rely on the visual modality. For this reason, BCIs that employ auditory stimuli were suggested. In this study, a multiclass BCI spelling system was implemented that uses animal voices with directional cues to code rows and columns of a letter matrix. To reveal possible training effects with the system, 11 healthy participants performed spelling tasks on 2 consecutive days. In a second step, the system was tested by a participant with amyotrophic lateral sclerosis (ALS) in two sessions. In the first session, healthy participants spelled with an average accuracy of 76% (3.29 bits/min) that increased to 90% (4.23 bits/min) on the second day. Spelling accuracy by the participant with ALS was 20% in the first and 47% in the second session. The results indicate a strong training effect for both the healthy participants and the participant with ALS. While healthy participants reached high accuracies in the first session and second session, accuracies for the participant with ALS were not sufficient for satisfactory communication in both sessions. More training sessions might be needed to improve spelling accuracies. The study demonstrated the feasibility of the auditory BCI with healthy users and stresses the importance of training with auditory multiclass BCIs, especially for potential end-users of BCI with disease.

Originally published in: Frontiers in Human Neuroscience, *8*: 1039
doi: 10.3389/fnhum.2014.01039

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 09 January 2015
doi: 10.3389/fnhum.2014.01039

An auditory multiclass brain-computer interface with natural stimuli: Usability evaluation with healthy participants and a motor impaired end user

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Brain-computer interfaces (BCIs) can serve as muscle independent communication aids. Persons, who are unable to control their eye muscles (e.g., in the completely locked-in state) or have severe visual impairments for other reasons, need BCI systems that do not rely on the visual modality. For this reason, BCIs that employ auditory stimuli were suggested. In this study, a multiclass BCI spelling system was implemented that uses animal voices with directional cues to code rows and columns of a letter matrix. To reveal possible training effects with the system, 11 healthy participants performed spelling tasks on 2 consecutive days. In a second step, the system was tested by a participant with amyotrophic lateral sclerosis (ALS) in two sessions. In the first session, healthy participants spelled with an average accuracy of 76% (3.29 bits/min) that increased to 90% (4.23 bits/min) on the second day. Spelling accuracy by the participant with ALS was 20% in the first and 47% in the second session. The results indicate a strong training effect for both the healthy participants and the participant with ALS. While healthy participants reached high accuracies in the first session and second session, accuracies for the participant with ALS were not sufficient for satisfactory communication in both sessions. More training sessions might be needed to improve spelling accuracies. The study demonstrated the feasibility of the auditory BCI with healthy users and stresses the importance of training with auditory multiclass BCIs, especially for potential end-users of BCI with disease.

Keywords: P300, EEG, auditory BCI, brain-computer interface, communication, ALS

INTRODUCTION

One of the main goals in the development of brain computer interfaces (BCIs) is the implementation of devices that can serve as communication aids for severely paralyzed persons Most common BCIs rely on visual stimulation and the patient's ability to control eye movements (Birbaumer and Cohen, 2007). However, neurological disorders, such as stroke or traumatic brain injury, and neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), can lead to a complete locked-in syndrome (CLIS). In this condition, control over all muscles (including eye muscles) is lost (Bauer et al., 1979). Since auditory information processing is not affected in persons with ALS (Murguialday et al., 2011) auditory BCI systems could be the key to communication in CLIS. In recent years there have been several approaches that focused on the auditory modality when developing new BCI systems.

Auditory paradigms using the modulation of slow cortical potentials (SCPs) and sensorimotor rhythms (SMRs) as input signal did not yield satisfactory results (Pham et al., 2005; Nijboer et al., 2008a). Only a minority of participants achieved classification accuracies above 70%, which was marked as a threshold for successful BCI communication (Kübler et al., 2001). Further, several studies implemented paradigms based on event-related potentials (ERPs) that allow for binary communication (Hill et al., 2004, 2005; Halder et al., 2010; Hill and Schoelkopf, 2012; Lopez-Gordo et al., 2012). While tests with healthy participants yielded satisfactory results, a spelling solution based on a binary choice paradigm would be slow and these paradigms have not been tested with target end users (Halder et al., 2010).

Therefore, we implemented and evaluated a multiclass BCI based on ERPs as control signals. A number of previous studies used a modification of the P300 speller introduced by Farwell and Donchin (1988), in which the rows and columns of a letter matrix are coded by tones (Sellers and Donchin, 2006; Furdea et al., 2009; Klobassa et al., 2009; Käthner et al., 2013). These studies are presented below along with other approaches that influenced the design of the paradigm presented in this paper.

Furdea et al. (2009) proposed an auditory P300 speller using a 5 × 5 letter matrix. The rows were coded by the spoken numbers 1 to 5, columns by the numbers 6 to 10. To choose a letter, participants first had to attend to the number representing the target row, and subsequently to the number coding the desired column. Out of 13 healthy participants, nine were able to write a word with accuracies of 70% or higher (mean 65%). The comparatively long stimulus duration of the spoken numbers (450 ms) yielded a mean information transfer rate (ITR) of 1.54 bits/min. In the evaluation of this paradigm with four persons with LIS caused by ALS, accuracies higher than chance level have been achieved, but the mean rate of correctly chosen letters was only 12% (Kübler et al., 2009).

Klobassa et al. (2009) used shorter (110 ms) and natural tones (e.g., the chime of a clock) to represent rows and columns of a 6 × 6 matrix. The authors reported mean online classification accuracies of 59%, and offline accuracies of 70%. Mean ITR was 1.86 bits/min. Further, there was a training effect resulting in higher classification accuracies after 11 sessions.

In recent years, it was proposed by Schreuder et al. (2010) to use additional spatial cues to improve auditory ERP based BCIs. In their study, five tones differing in pitch were presented using five speakers placed in front of the participants in a semi-circle. A predefined tone from a certain direction served as target. When averaging across 12 repetitions, binary classification rates of more than 90% and a bit rate of up to 17.39 bits/min was achieved. Mean classification accuracy dropped to 70% when tones were presented without spatial information. In a subsequent study, the paradigm was used for spelling (Schreuder et al., 2011). To choose a letter, participants had to focus attention on one of six different tones that were presented via six speakers placed in a circle around the participants. Each tone/direction represented one group of letters. After choosing one group by focusing attention to the corresponding tone, the single letters of this group were assigned to one tone/direction each. With this method, a maximum of 0.94 letters per minute could be selected. Mean classification accuracies of 77% and bit rates of 5.26 bits/min were achieved.

Directional cues were also used in the study by Höhne et al. (2011) that were presented via headphones. The columns of a 3 × 3 matrix were coded by directional cues (left, both, right speaker) and the rows by pitch (high middle, low), thereby creating 9 distinct tones. While on average 0.89 letters/minute could be chosen, with a mean ITR of 3.4 bits/min, participants described the artificial tones as unpleasant and they were often confused. Subsequently, natural stimuli (sung syllables) were implemented to improve classification performance (Höhne et al., 2012).

Käthner et al. (2013) also proposed a practical multiclass BCI with directional cues. A 5 × 5 letter matrix served as visual aid (visual support matrix). Rows and columns were represented by five artificial tones to allow for fast stimulus presentation. Using interaural time difference (ITD) and interaural level difference (ILD), directional cues were added to the tones to improve discriminability. Tones were presented via headphones to simplify the set-up. To select a letter, participants first had to attend to the tone that coded the column, and after a short break to the tone that coded the row. Different interstimulus intervals were tested. In the best case, an average classification accuracy of 66% with a bitrate of 2.05 bits/min was achieved.

STUDY AIMS

A major goal of the present study was to further improve the auditory P300 speller with directional cues proposed by Käthner et al. (2013). Since it was shown that the use of natural stimuli is advantageous (Höhne et al., 2012), natural tones were implemented to improve classification accuracies. The present paradigm was first tested with healthy participants and subsequently validated with a person diagnosed with ALS.

Since Klobassa et al. (2009) reported an increase in accuracy over several sessions using an auditory BCI, two sessions were performed to reveal a possible training effect that would be evident in better performance and possibly in a higher amplitude/shorter latency of the P300. Further, we investigated if the use of natural sounds can reduce the subjective workload compared to the previous study and if a positive influence of motivation and mood on performance and P300 characteristics could be found.

METHODS

PARTICIPANTS

Originally, 14 healthy participants were recruited for the study. One had to be excluded due to insufficient hearing and two due to technical problems during the measurements. Thus, 11 healthy subjects (8 female, mean age 24.27 years, $SD = 7.14$ years, 2 left handed) and one participant with ALS (female, age 66) were included in the study. Healthy subjects had no experience with auditory BCIs and no or little experience with other kinds of BCIs. They were compensated with course credits. All of them were students (nine of them students of psychology) with German as their mother tongue. Only healthy subjects with no history of neurological or psychological disorders, difficulties localizing sounds in space, and no general hearing problems were included in the study. To rule out hearing impairments, a test based on the Hughson-Westlake method (conforms to ISO 8253; Madsen Xeta Audiometer, GN Otometrics, Denmark) was conducted. All participants gave informed consent prior to the experiment. The study was approved by the Ethical Review Board of the Medical faculty of the University of Tübingen.

The participant with ALS had no experience with auditory BCIs. She was right handed and reported not to be musical. The disease was diagnosed at the age of 63 as being sporadic with bulbar onset. Her husband took care of her at home, where the experiments were conducted. At the time of the measurements, the patient was still able to talk, but difficult to understand. Her ability to move around was heavily restricted. To walk within the flat she relied on a walking frame, outside on a wheelchair. At the time of the first measurement the patient reached a score of 17.5 (ranging from 48, no impairment, to 0, locked in) on the ALS Functional Rating Scale-Revised (ALSFRS-R, Cedarbaum et al., 1999). This score had decreased to 16 at the time of the second measurement, 1 month later. Since the hearing threshold of the patient was very high, the volume of the stimuli was adjusted and it was ensured that she was able to perceive and discriminate correctly all the stimuli.

DATA ACQUISITION AND MATERIAL

Participants were seated in a comfortable chair, about 0.5–1 m from a 17″monitor. Data acquisition, processing, and storage were conducted on an IBM Thinkpad (Intel Core Duo 2.53 GHz, 1.89 GB RAM, Microsoft Windows XP SP3 Professional). Data acquisition and stimuli presentation was controlled by the BCI2000 software (Schalk et al., 2004) in combination with the Brain Vision Recorder (Version 1.2, Brain Products GmbH, Deutschland). Auditory stimuli were presented via circumaural headphones (Sennheiser 280 HD Pro) to minimize background noise.

The EEG was recorded using 28 active Ag/AgCl electrodes (Easycap GmbH, Germany) following the modified version of the international 10–20 system of the American Electroencephalographic Society (Sharbrough et al., 1991). Electrodes were placed at positions F3, Fz, F4, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4, CP6, P3, P1, Pz, P2, P4, PO7, PO3, POz, PO4, PO8, and Oz. Channels were referenced to the left mastoid and grounded to the right. Electrooculogram was recorded with four electrodes placed below and above the right eye and at the outer canthi of both eyes. Signals were amplified with a sampling rate of 500 Hz using a BrainAmp DC amplifier (Brain Products GmbH, Germany). Signals were filtered with a high pass of 0.1 Hz, a low pass of 30 Hz and a notch filter at 50 Hz. These were the same electrode positions and settings that were used in Käthner et al. (2013) to allow for a better comparison across studies.

LETTER MATRIX

During the measurement, the participants were facing a screen displaying a 5 × 5 letter matrix with the letters A to Y (see **Figure 1**). Since the study used an auditory paradigm the matrix only served as static visual aid. Each row and each column of the matrix was coded by one of five animal tones (shown in the visual support matrix). The numbers "1" and "2" in the top left corner of the matrix indicated the order of selection of rows and columns (during the experiment first the tones coding the rows were presented, then the tones coding the columns). The words that had to be written were presented in a row above the matrix, with the current letter presented in brackets. In a second row the letters selected during online spelling were fed back to the participants.

AUDITORY STIMULI

Rows and columns of the letter matrix were coded by five different tones. In a pre-study five groups of different tones were evaluated to determine the tones that were best discriminable. The groups included either five different white noise tones, five sine tones, five tones of everyday life (e.g., ticking of a clock) or one of two sets of animal voices. Ten subjects rated the discriminability of the tones for each of the five groups on a visual analog scale (VAS)—a 10 cm long horizontal line ranging from 0 to 10. The second group of animal tones (with the sounds of a duck, singing bird, frog, seagull, and a dove) achieved the best ratings of discriminability and was therefore chosen for the experiment. The sounds had been downloaded from the webpage http://www.soft-ware.net/animal-sounds and edited. Animal tones were cut to 150 ms length, using the interval in which the sound was best distinguishable. **Figure 2** shows the spectrograms of the sound files, illustrating the heterogeneous temporal structure. To better differentiate the tones via headphones, directional cues were added as described in Käthner et al. (2013). The simulated sound sources were left (duck), center-right (singing bird), center (frog), center-left (seagull), and right (dove). To remind participants of this scheme, the illustration shown in **Figure 3** was displayed on a sheet of paper that served as a reference base.

PROCEDURE

The study consisted of two measurements on consecutive days. To control for circadian effects (Wesensten et al., 1990) both measurements were conducted at the same time of day.

The measurements with the participant with ALS were conducted at her home. Due to a temporary worsening of the participant's state of health, the interval between the two measurements was 1 month.

Before the beginning of the measurements, the sounds were played to the participants a number of times to familiarize them with the task of identifying certain tones. Also the volume could be adjusted. Each tone had a length of 150 ms, followed by an inter stimulus interval (ISI) of 250 ms, thus the stimulus onset asynchrony (SOA) was 400 ms. The choice of the timing parameters was motivated by the results of previous studies which showed that the choice of stimulation speed is crucial for performance with auditory BCIs (Höhne and Tangermann, 2012; Käthner et al., 2013). Höhne and Tangermann (2012) tested SOAs between 50 and 1000 ms in a simple auditory oddball paradigm and found increasing P300 amplitudes with slower stimulation speed. With regard to ITR, SOAs between 87 and 200 ms were optimal for most healthy participants of the study. In their online study using a multiclass BCI paradigm Käthner et al. (2013) could confirm the finding that optimal stimulation parameters differed between participants. On average, the highest ITR was achieved in the condition with an ISI of 400 ms. In both studies, however, stimulus duration of the artificial tones (40 ms) was considerably shorter than the natural stimuli of the present study (150 ms). The stimulus duration probably also influences auditory BCI performance, but has not yet been systematically evaluated. As a tradeoff between speed and accuracy we decided for a SOA of 400 ms, although higher P300 amplitudes and accuracies might be achieved with slower stimulation.

For the selection of one letter, two steps were needed. In the first step, the tone representing the row containing the target letter had to be selected. While all five animal tones were presented 10 times each in pseudo randomized order, the participant had to focus attention on the target tone and count its appearance. After a pause of 1.92 s, the tones representing the columns were presented. Then the participants had to concentrate on the tone representing the column with the target letter. Between letter selections there was a pause of 12 s to focus on the next letter. The process of letter/word selection is illustrated in **Figure 1**. A recording of one exemplary trial is published as Supplementary Material.

Session 1

For the training of the classifier, participants completed three calibration runs in which they had to select the letters "AGMSY."

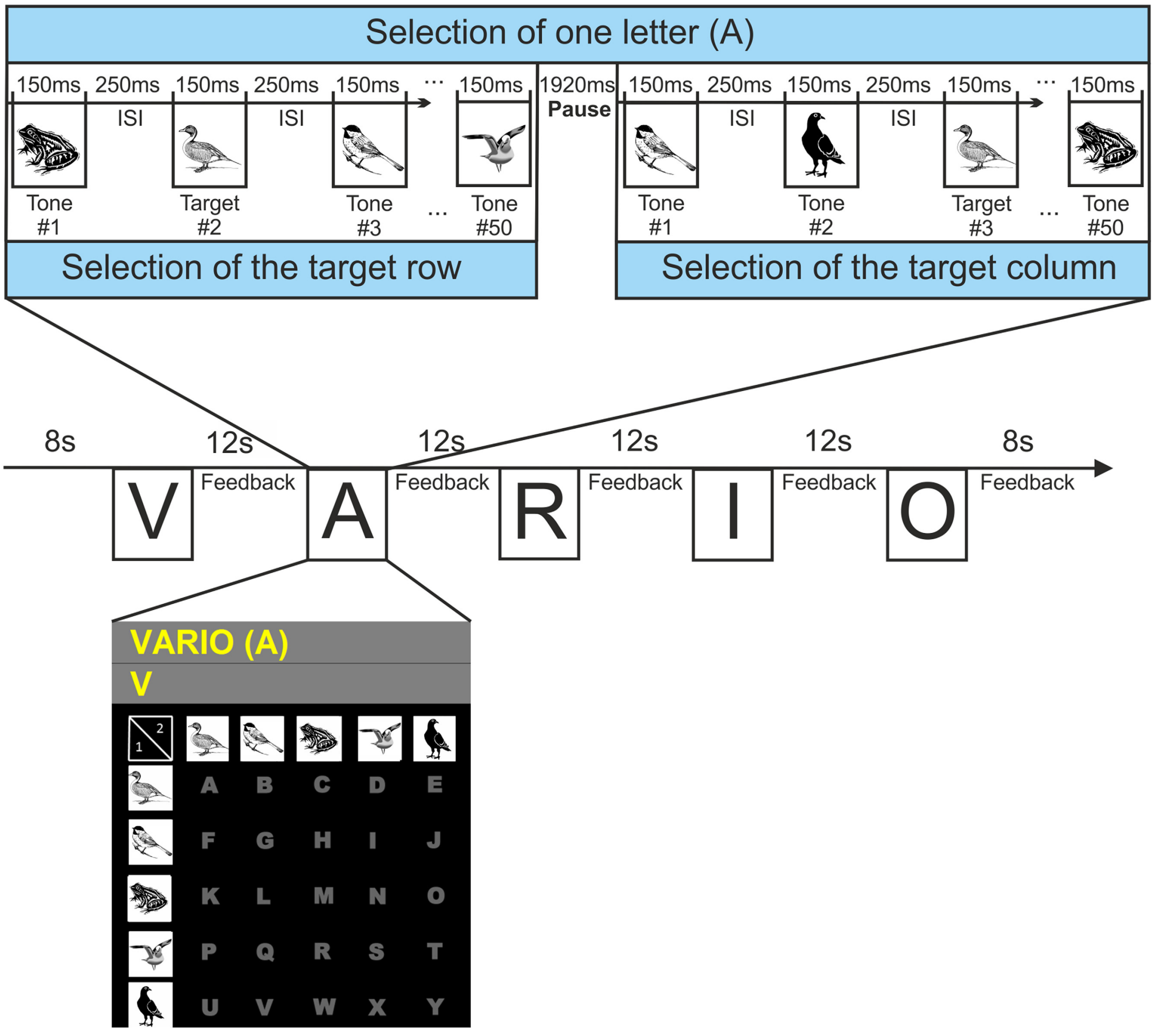

FIGURE 1 | Visualization of the tasks needed to spell a specific word. To select a particular letter (in this example the letter A), participants had to first focus attention on the tone coding the target row and in the second step, concentrate on the tone coding the target column (twice duck in the example). The tones were played in random order and the sequence of all tones was repeated a total of 10 times. The matrix was displayed to the participants during spelling. For copyright reasons the displayed animal illustrations differ from those used in the experiment.

Based on these runs, feature weights were calculated for the online classification. After training the classifier, nine words had to be written in an online copy spelling task during which feedback about the selected letters was provided (see **Table 1**). No feedback about the selected row (necessary sub-step for one letter selection) was provided. Each row and each column was represented once within each word to minimize possible confounds caused by specific tones or directions. The copy spelling was divided into three blocks with three words each and breaks between the blocks.

After the copy spelling tasks and a short break, participants completed a free spelling task. They were asked to think of a five letter word that they wanted to write. Before the actual spelling, they wrote the desired word on a piece of paper and revealed it only after they had completed the spelling.

The course of the measurement was the same for the participant with ALS, with the exception that she was allowed to take breaks between spelling of individual words. Since she was physically too exhausted to perform the free spelling, the session was stopped after the copy spelling.

Session 2

At the beginning of Session 2, the task was explained to the participants and they could listen to the tones again. For the healthy participants, there was no distinct calibration run in Session 2. Since no changes in the individual parameters of the

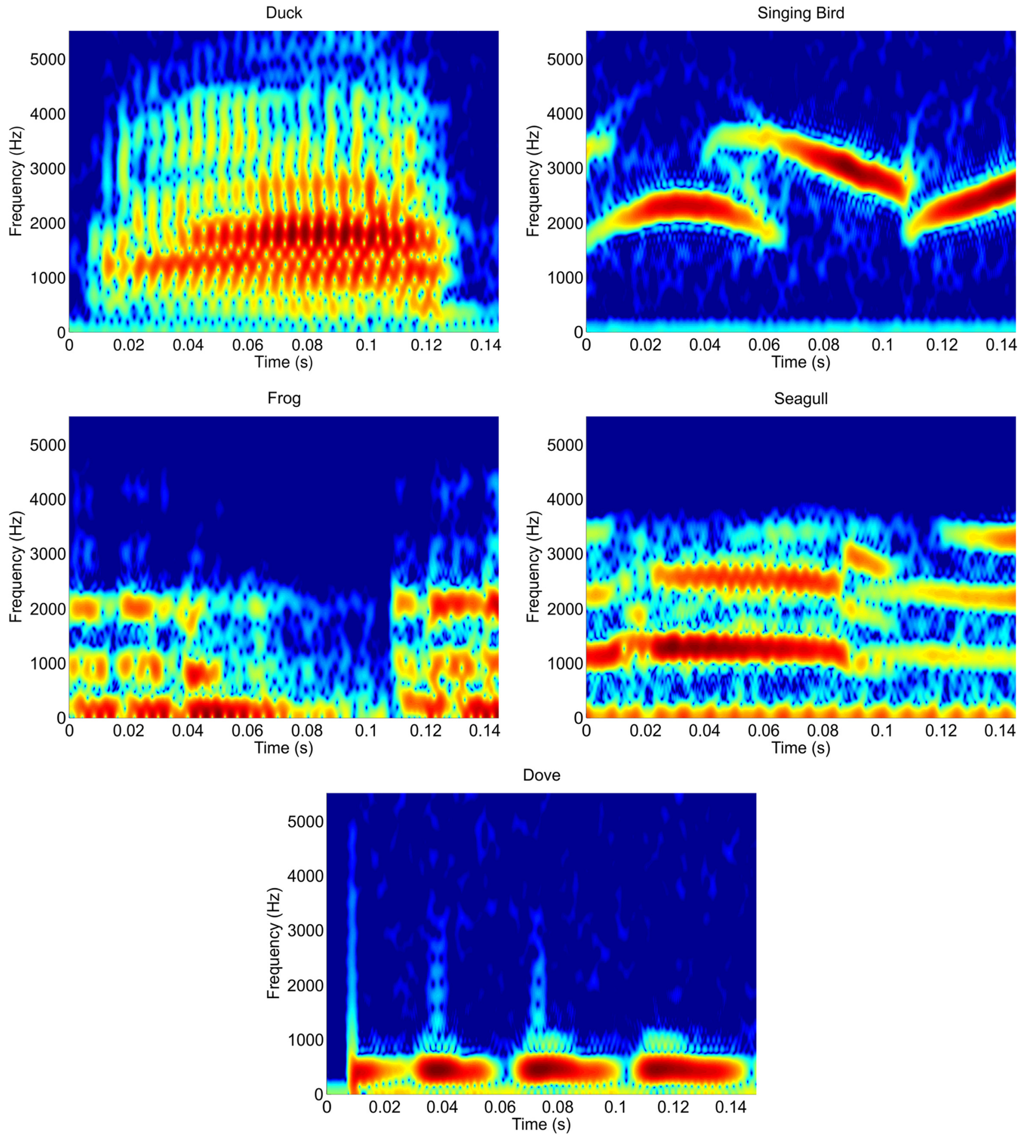

FIGURE 2 | Spectrograms of the auditory stimuli.

participants within 2 days were expected (Nijboer et al., 2008b), classification weights of Session 1 were applied. The procedure of the online copy spelling was the same as in the first session. In the subsequent free spelling task the participants had to spell the words BRAIN and POWER (no display of the words to spell).

Since the analysis of the data of the healthy participants revealed that the missing calibration run in Session 2 lead to a decline in accuracy, a distinct calibration run was conducted with the participant with ALS. As in Session 1, she completed three calibration runs followed by the copy spelling tasks.

QUESTIONNAIRES

At the beginning of the first session all participants completed a demographic questionnaire which also assessed the musicality of the participants as well as their experience with BCIs (and auditory BCIs in particular). Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Prior to each measurement, participants rated their mood and motivation on VAS. The 10 cm long lines of the VAS ranged from "0 = not motivated at all" to "10 = extremely motivated" and from "0 = extremely bad mood" to "10 = extremely good mood," respectively. For the assessment of general functioning

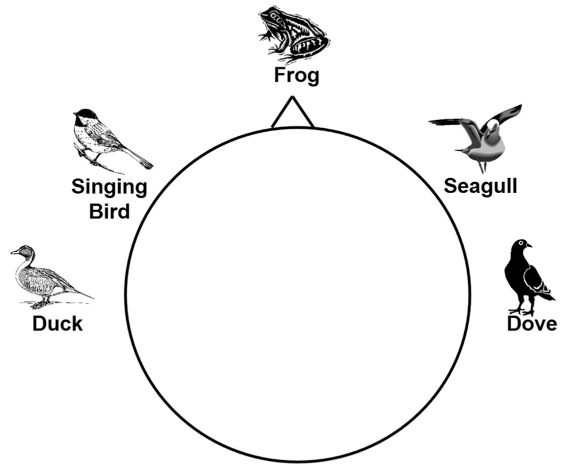

FIGURE 3 | Visualization of the simulated sound sources for the five animal voices that was presented to the participants during the experiment.

Table 1 | Blocks of letters that had to be spelled during the two sessions.

	Session 1 online	Session 2 online	Session 2 offline
Calibration	AGMSY AGMSY AGMSY	Classification weights of Session 1	VARIO GRUEN HUNGER
Letters to be spelled	15	15	16
Copy spelling	VARIO GRUEN HUNGER TUMBI RUBIO VALERI UMBIT PHLEX VIRAGO	VARIO GRUEN HUNGER TUMBI RUBIO VALERI UMBIT PHLEX VIRAGO	TUMBI RUBIO VALERI UMBIT PHLEX VIRAGO
Letters to be spelled	48	48	32
Free spelling	5 letter word of own choice	BRAIN POWER	BRAIN POWER
Letters to be spelled	5	10	10

the participant with ALS completed the ALS function rating scale (Cedarbaum et al., 1999) prior to each measurement session.

Subsequent to each training session participants completed an electronic version of the NASA Task Load Index (NASA-TLX, NASA Human Performance Research Group, 1987). The NASA-TLX measures the subjective workload during human machine interaction. On the basis of six subscales (Mental, Physical and Temporal Demands, Own Performance, Effort, and Frustration) a global value for the subjective workload is determined. Each of the six factors are first evaluated on a 21-point scale ranging from "very low" (0) to "very high" (100; for the factor Own Performance the scale ranged from "bad" to "good"). In a second step, pairwise comparisons of all the factors are used to determine to what degree each of the factors contributed to the overall workload of the task. This procedure yields a total value between 0 and 100, with 100 representing the highest subjective work load. The NASA-TLX is a validated, sensitive and reliable instrument for measuring the subjective workload (Rubio et al., 2004; Hart, 2006). Following the user-centered design (ISO 9241-210) it has been introduced as a measure of usability, specifically efficiency which relates accuracy to the costs involved in using the technology (Zickler et al., 2011; Kübler et al., 2014).

At the end of the second session, participants completed the System Usability Scale (SUS, Brooke, 1996). On the basis of 10 questions (concerning topics like complexity of the application, need of support and training) the subjective usability of a system is assessed. Questions are answered on a five point Likert scale ranging from "1 = Strongly disagree" to "10 = strongly agree." The completion of the SUS results in a total value between 0 and 100, with 100 representing the highest subjective usability. The SUS is a reliable instrument that correlates high with other measures of usability (Brooke, 1996).

Further, participants were asked to evaluate their experiences with the auditory P300 speller with a custom-made questionnaire. They responded to 13 statements on a five point Likert scale ranging from "1 = Agree" to "5 = Disagree." The questionnaire also offered space for suggestions on how to improve the system.

The participant with ALS was unable to write due to her disease, therefore, she answered the questions orally with the help of her husband.

ONLINE SIGNAL CLASSIFICATION

Classification weights were calculated in Matlab using stepwise linear discriminant analysis (SWLDA) implemented in the P300 GUI of the BCI2000 software. After the classification parameters had been determined, the EEG data were classified online using BCI2000. The usage of SWLDA is an established procedure in BCI studies and it was shown that this approach surpasses other classification techniques (Krusienski et al., 2006). It determines features from voltage values from each of the 28 electrodes that best discriminate the two classes (targets/non-targets). Firstly, the data was segmented into post stimulus epochs of 800 ms and then moving average filtered and decimated, corresponding to a sampling rate of 20 Hz. This procedure yielded 16 values per stimulus. From this data set, features were selected in a stepwise process. The feature that best predicted the target label using least square regression was added to the discriminant function (p-value $\leq$ 0.1). After adding another feature to the function, a backward stepwise discriminant analysis was performed to remove the features that were no longer significant ($p > 0.15$). This process was repeated until a maximum of 60 features was reached or no additional features met the inclusion/exclusion criteria (Krusienski et al., 2006).

OFFLINE DATA ANALYSIS

The EEG data was analyzed with Matlab (version R2012b) in combination with the EEGLab toolbox (version 10.2.2.4b; Delorme and Makeig, 2004). It was segmented using an epoch of 800 ms, starting at the onset of a stimulus and baseline corrected using a pre-stimulus interval of 200 ms. Averages and grand averages over all runs were calculated for each participant for targets and non-targets. Data was only analyzed for the copy spelling runs. Because the missing calibration run in Session 2 lead to a decline in online performance (see BCI Performance), the classifier was retrained offline using the first three words acquired during the copy-spelling runs of that session (VARIO, GRUEN, and HUNGER) and feature weights were applied for classification of the remaining words. Averages and grand averages were calculated for all nine words.

Statistical analysis of ERPs was restricted to Pz, where the P300 is prominent. The maximum positive peak between 250 and 560 ms was defined as P300. Topographies of differential ERP activity (targets minus non-targets) were calculated. For the participant with ALS, data was re-referenced offline using common average referencing, because of artifacts in the data, which were probably caused by technical issues with the reference electrode.

Classification accuracies were calculated as the number of correctly selected letters. Statistical analysis of the data was conducted with SPSS. All statistical analyses were only performed for accuracies achieved in the copy spelling runs. A Wilcoxon signed-rank test was conducted to reveal differences in the accuracies between the 2 days and to check for differences in the online and offline accuracies of the second day.

The error distribution for individual tones was analyzed and depicted in confusion matrices. Chi-square tests were calculated to check the distributions of errors and false positive selections for individual tones. Kendall's Tau was calculated to reveal statistical correlations between questionnaire values (mood, motivation), BCI performance and P300.

INFORMATION TRANSFER RATE

ITR was calculated with the formula originally proposed by Shannon and Weaver (1964) and suggested for BCI research by Wolpaw et al. (2000) for online and offline classification accuracies. The bits per minute (bits/min) were computed taking into account the 12 s pause between the selections of individual letters.

RESULTS

BCI PERFORMANCE

Classification accuracies and bitrates of all participants are listed in **Table 2**. Mean online classification accuracies (69.64 ± 13.64%) of Session 2 were significantly smaller than those calculated offline (90.18 ± 9.29%) using the first three copy spelling words from Session 2 to retrain the classifier ($Z = -2.67$, $p < 0.01$). Based on this finding we decided to use the offline results of Session 2 to investigate a possible training effect (see Limitations for a discussion). All reported analyses regarding Session 2 are related to offline results.

Classification accuracies in Session 2 (90.18%) were significantly higher than in Session 1 (76.73%; $Z = -1.99$, $p < 0.05$). Average bitrates were 3.29 bits/min in Session 1 and 4.23 bits/min in Session 2.

The participant with ALS reached an accuracy of 20% (± 9.67%) in the first session that rose to 47% (±20.05%) in the second session. This equals bitrates of 0.28 bits/min in session 1 and 1.35 bits/min in Session 2. The classification accuracy of the single words ranged from 0 to 33% in Session 1 and from 20 to 80% in Session 2.

Table 2 | Classification accuracies and bitrates of all healthy participants.

VP	Copy spelling				Free spelling			
	Mean accuracy		Bitrate		Mean accuracy		Bitrate	
	Session 1 (in %)	Session 2 (in %)	Session 1 (bits/min)	Session 2 (bits/min)	Session 1 (in %)	Session 2 (in %)	Session 1 (bits/min)	Session 2 (bits/min)
1	82	94	3.49	4.50	80	90	3.34	4.14
2	91	91	4.22	4.22	100	100	5.17	5.17
3	58	88	1.93	3.97	40	90	1.03	4.14
4	83	75	3.57	2.99	80	60	3.34	2.05
5	78	75	3.20	2.99	100	100	5.17	5.17
6	21	100	0.31	5.17	40	100	1.03	5.17
7	94	100	4.50	5.17	100	100	5.17	5.17
8	72	88	2.79	3.97	60	90	2.05	4.14
9	98	97	4.91	4.80	100	100	5.17	5.17
10	77	84	3.13	3.65	40	90	1.03	4.14
11	90	100	4.14	5.17	80	100	3.34	5.17
M	76.73	90.18	3.29	4.23	74.55	92.73	3.26	4.51
SD	21.63	9.27	1.30	0.81	25.44	11.91	1.76	0.96

The accuracies were calculated as the percentage of correct letter selections. Accuracies of Session 2 were calculated offline.

MULTICLASS ACCURACY

To reveal differences in classification accuracies of individual tones, confusion matrices for all 5 tones are shown in **Table 3** for healthy participants. In Session 1, 87% of multiclass decisions (row or column selected) were correct compared to 95% in Session 2. In Session 1, the number of total errors for individual tones ranged from 14 errors (dove) to 37 errors (duck). The distribution is a significant deviation from the number of errors that would be expected by chance (28.2 errors per tone; $\chi^2 = 13.29$, $p = 0.01$). For the multiclass error distribution of individual tones, chi-square tests did not yield significant results, however, a trend toward significance ($\chi^2 = 7.56$, $p = 0.056$) was revealed for the singing bird sound, where multiclass errors were lowest for duck, four errors, and highest for seagull, 14 errors. It can be inferred from **Table 3** that the lowest false positive rate was obtained for the duck sound (19 false positive selections) and the highest for the dove sound (45 false positive selections). A chi-square test revealed a significant deviation from the distribution of false positive selections that would be expected by chance (28.2 false positives per tone, $\chi^2 = 15.14$, $p = 0.004$). For the distribution of false positive selections for individual tones, a significant result was only obtained for the seagull sound ($\chi^2 = 8.93$, $p = 0.03$), which was most often wrongly selected if the singing bird was the target sound. The low number of errors in Session 2 does not allow to calculate chi-square values for error and false positive distributions.

ERP ANALYSIS

Figure 4A shows the average waveforms for targets and non-targets in Session 1 and 2 for the copy spelling task for the healthy participants. Neither peak amplitude of the P300 differed between Session 1 (6.66 ± 3.22 μV) and Session 2 (7.17 ± 2.75 μV; $Z = 0$, $p = 1$) nor was there a significant difference between P300 latencies of Session 1 and 2 (366.59 ± 78.59 ms, 359.59 ± 81.45 ms; $Z = -1.07$, $p = 0.286$). **Figure 4A** also depicts the grand average spatial distribution of the differential ERP activity (targets minus non-targets) for different time points.

Figure 4B shows the average waveforms and the spatial distribution of the differential ERP activity for the participant with ALS. Peak amplitude at Pz for Session 1 was 0.84 μV at 491.32 ms and 1.35 μV for Session 2 at 493.21 ms.

Table 3 | Confusion matrices for Session 1 and 2 for healthy participants.

Target	Selected					Accuracy (in %)
	Duck	Bird	Frog	Seagull	Dove	
SESSION 1						
Duck	**172**	8	6	8	15	82
Bird	4	**206**	6	14	12	85
Frog	6	10	**178**	4	11	85
Seagull	7	5	4	**175**	7	88
Dove	2	3	5	4	**184**	93
False positive (in %)	9.95	11.21	10.55	14.63	19.65	**87**
SESSION 2 (OFFLINE)						
Duck	**136**	1	2	2	2	95
Bird	3	**156**	0	3	3	95
Frog	4	1	**118**	5	4	89
Seagull	1	2	1	**127**	1	96
Dove	0	1	1	0	**130**	98
False positive (in %)	5.56	3.11	3.28	7.30	7.14	**95**

Classification accuracies of the single tones are shown in the right column, false positives in the bottom row, correct classifications (hits) are in printed in bold.

INFLUENCES OF MOTIVATION, MOOD, AND MUSICALITY

Healthy participants had a mean motivation score of 7.75 ($SD = 1.73$) in Session 1 and 7.70 ($SD = 1.55$) in session. The mean mood score was 6.59 ($SD = 1.21$) in Session 1 and 6.32 ($SD = 1.24$) in Session 2. In both sessions, there was no significant correlation of motivation and mood with classification accuracies, P300 amplitude and latency.

The participant with ALS indicated a motivation of 3.95 in Session 1, and 6.7 in Session 2. The indicated mood score was 6.45 in Session 1, and 8.75 in Session 2.

SUBJECTIVE WORKLOAD

The average score of the NASA-TLX for the healthy participants did not differ significantly between Session 1 (62.24 ± 10.54, range: 43.33–85.00) and Session 2 (69.42 ± 10.59, range: 46.33–83.00; −1.824, $p = 0.068$).

The participant with ALS had a general workload score of 69 in Session 1 and 23.33 after Session 2. The global workload in Session 1 was to a large degree due to the high physical strain as revealed by the subscale physical effort (after the weighting procedure the subscale contributed 32 of the 69 points).

SYSTEM USABILITY SCALE

The usability of the system was measured on the basis of the SUS. The global scores can range between 0 and 100, with 100 reflecting the highest usability. At the end of Session 2, answers of the healthy participants yielded individual SUS scores between 47.5 and 80, with a mean SUS score of 64.8 ($SD = 11.8$) across all healthy participants. **Figure 5** depicts the responses of the participants to the individual items of the scale.

The statements of the participant with ALS yielded a total SUS score of 82.5. She reported that for item 3 "I thought the system was easy to use" she only marked "3" (moderate agreement) because of the high technical effort that is necessary for the measurement. Apart from that she did not find it difficult to use the BCI speller.

POST-STUDY EVALUATION

In the post-study evaluation, 3 out of the 11 healthy participants stated the wish for longer pauses between the presentations of individual tones. Two participants stated that they had problems differentiating the duck and the dove tones. Five reported difficulties in the differentiation of the gull and the singing bird tone. One participant suggested to minimize the number of tone repetitions per row and column.

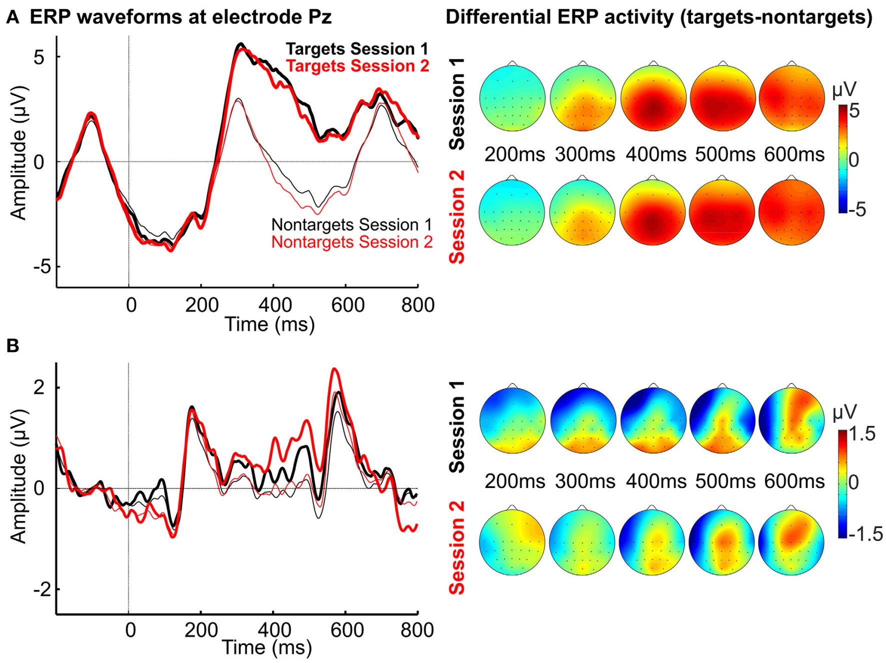

FIGURE 4 | (A) Average waveforms for targets (thick lines) and non-targets (thin lines) at Pz for healthy participants and scalp plots of differential ERP activity (targets minus non-targets) for different time points. **(B)** Average waveforms for targets (thick lines) and non-targets (thin lines) at Pz for the participant with ALS and scalp plots of differential ERP activity (targets minus non-targets) for different time points.

The participant with ALS suggested to simplify the technical effort that is currently necessary to use the speller. She also suggested to reduce the number of birds in the animal tones and to replace them by other animal voices.

DISCUSSION

With the proposed auditory multiclass BCI using natural stimuli and directional cues, high mean accuracies could be achieved by healthy participants. Accuracies increased from 76% in the first to 90% in the second session.

BCI PERFORMANCE

In the second session, healthy participants achieved average spelling accuracies of 90% and all participants achieved accuracies of more than 75% correctly selected letters. Thus, the BCI performance is higher than in the study by Klobassa et al. (2009), in which average accuracies of 70% were calculated offline for the last of 11 training sessions. In the study by Höhne et al. (2011) similarly high accuracies (90%) were achieved within one session, but with a paradigm that only allows to select from 9 different classes as opposed to 25 in the current study. In terms of selection speed, auditory BCIs still lag behind visual spellers, which report bitrates of up to 50.61 bits/min (Lenhardt et al., 2008) and 106 bits/min (Kaufmann and Kübler, 2014). The auditory speller of the current study allowed for only 1.11 selections per minute, but the bitrates of 3.29 bits/min for Session 1 and 4.23 bits/min for Session 2 are still among the highest reported for auditory BCIs (see Riccio et al., 2012 for a review). Bitrate could be optimized by reducing the pause between letter selections and reducing the number of sequences (fixed to 10 independent of individual performance in this study). Dynamic stopping methods allow for determining the optimal number of sequences and have been successfully applied in ERP spellers to improve spelling speed (e.g., Schreuder et al., 2011; Mainsah et al., 2014; for a comparison see Schreuder et al., 2013).

The average classification accuracies achieved by the participant with ALS (20 and 47%) were higher than chance (4%), but did not reach a sufficient level for communication (≥70%; Kübler et al., 2001). For the first session, the achieved accuracy is in the same range as reported by previous studies that tested an auditory multiclass BCI with motor impaired end users. Kübler et al. (2009) reported accuracies between 0 and 25% for the four study participants. Schreuder et al. (2013) tested the AMUSE paradigm (Schreuder et al., 2010) with a severely impaired end user and reported accuracies below chance level for the first and slightly above chance for the second session. However, spelling accuracy steadily improved up to the fourth session (39%). Thus, more training might also improve spelling accuracy with the present auditory multiclass BCI, in particular if testing the system with end users. It is promising that the participant of our study already achieved accuracies substantially above chance in the first two sessions. Only two sessions were conducted in the present study, but the participant with ALS communicated that she would have participated in further sessions, if her physical

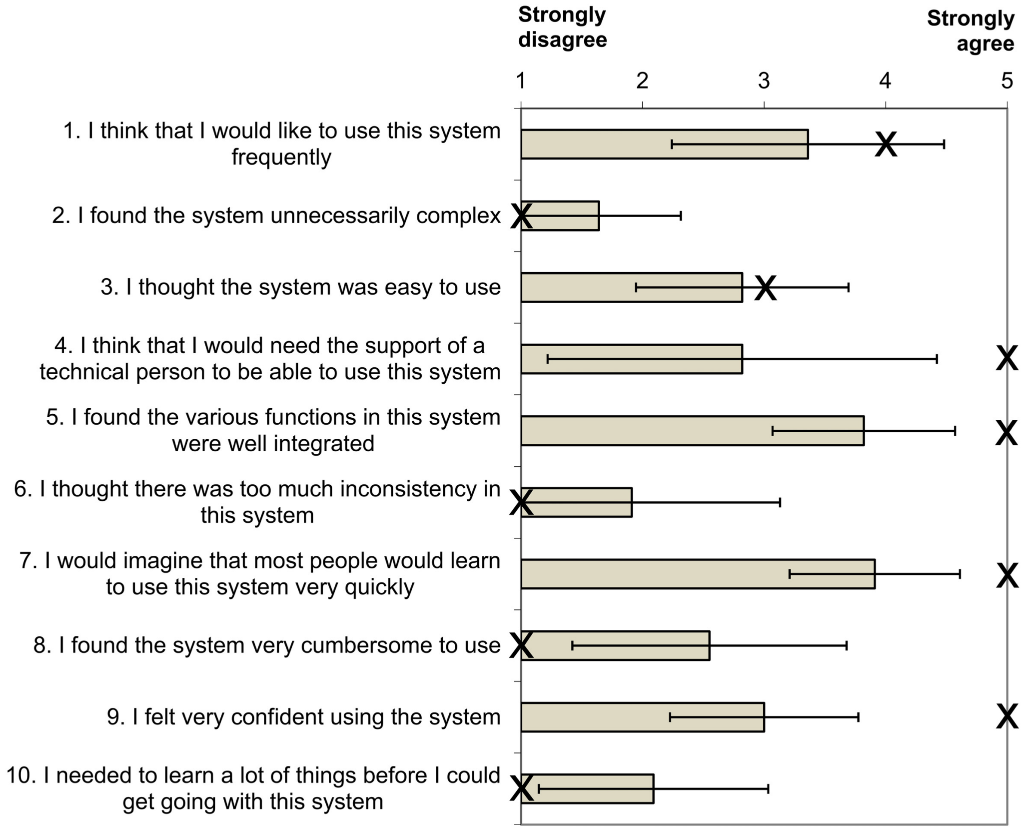

FIGURE 5 | Scores of the study participants for the items of the system usability scale (mean ± standard deviation). The answers of the participant with ALS are marked with an X.

condition would have allowed it and rated the overall usability as high.

There are a couple of not directly BCI related factors that could have negatively influenced the results. Among the medication that the participant took during the time of the study was Zopiclone, a hypnotic drug that has similar effects on the central nervous system as benzodiazepines, which were shown to directly influence vigilance and P300 amplitude (Engelhardt et al., 1992; Hayashi, 2000). Possibly better results could have been achieved in the second session if the time between measurements had only been a week as originally planned. Nevertheless, further modifications of the paradigm, the stimulus material or the classifier might be needed for end users to achieve higher accuracies even within the first two sessions.

TRAINING EFFECTS AND AUDITORY STIMULI

The significant increase in classification accuracies from the first to the second session indicates a training effect. The training effect is not reflected in P300 characteristics for the healthy participants. Since neither P300 amplitude nor latency differed significantly between Session 1 and 2, we assume that the training effect is not due to effects that would modulate the P300, such as increased attention or motivation. Possible explanations for this improvement from Session 1 to 2 are either task specific, i.e., adaptation to the task and BCI in general, or stimuli specific, i.e., an improved ability to discriminate the target tones. In the second session compared to the first session, especially the adaptation to the task might have a large influence. The second explanation (improved ability to discriminate the target tones), might be particularly valid for participants, who have difficulties discriminating the target tones initially. For the participant with ALS and increase in the amplitude of the P300 could be observed (from 0.84 to 1.35 μV). No statistically relevant increase in P300 amplitude could be found for the healthy participants, but a slight increase in the amplitude was apparent from Session 1 (6.66 μV) to 2 (7.17 μV). In any case, the results suggest that training should be conducted with auditory multiclass BCIs, especially when testing with end users is performed.

An important goal of this study was to further improve the speller described in Käthner et al. (2013) by replacing the artificial tones with natural stimuli, since several study participants had criticized the stimuli. Average classification accuracies improved from 66% (reported by Käthner et al., 2013) to 77% (first session of this study). This substantial improvement is also apparent in the increase of the bitrate from 2.76 to 3.29 bits/min (first session of this study). Although stimulus duration was shorter, P300 latency at Pz was higher in the study by Käthner et al. (2013; 487 ms) as compared to results of the current study (367 ms). This supports the assumption that the natural stimuli can be more easily discriminated than the artificial tones. The increase of performance for natural stimuli compared to artificial tones was also demonstrated by Höhne et al. (2012). Hence, we think that the increase of performance is mainly caused by the changes in the stimulus material and not by other factors that could also influence the results (see Limitations). While we tried to find a tradeoff between speed and accuracy for the stimulus timing parameters, they could be further optimized. Höhne and Tangermann (2012) demonstrated that individualized timing parameters could boost performance. Further, the effect of stimulus duration has not yet been systematically evaluated.

The multiclass accuracies are high in both sessions (87 and 95% correct), but false positive rates and errors are not equally distributed for the five tones in Session 1. Thus, some tones (with the highest false positive selection rate, i.e., dove, seagull) might be more distinct than others. An alternative explanation could be a general preference of participants to tones that are presented from the right (in our study dove, seagull). Several studies showed a right ear/left hemisphere advantage for vocal sounds using dichotic listening tasks, while a left ear/right hemisphere advantage was shown for musical sounds (for a review see Tervaniemi and Hugdahl, 2003). Whether there is an ear/hemisphere advantage for the particular sounds used in our study has yet to be shown. Another reason for false selections could be that some tones (e.g., singing bird and seagull) are more difficult to discriminate than others, therefore the combination of tones could still be optimized. Nevertheless, in Session 2 hardly any mistakes were made by the healthy participants, thus the tones are well suited for the paradigm and can possibly be better discriminated with training.

INFLUENCES OF MOOD AND MOTIVATION

No significant influences of self-reported motivation or mood on BCI performance were found in the current study. Whiles several studies reported a positive influence of motivation on BCI Performance (Nijboer et al., 2008a, 2010; Kleih et al., 2010), other studies could not replicate this finding (Käthner et al., 2013; Kleih and Kübler, 2013).

BCI USABILITY

Evaluation with the SUS revealed that usability of the system is already quite good, but could still be improved. Ratings of healthy participants indicate only moderate levels of self-confidence (question 9) and ease of use of the system (question 3). However, learnability was rated as high (question 7 and 10). The overall usability rating was very high for the participant with ALS, but in terms of ease of use she also rated the system as mediocre, due to the high technical effort that is necessary to operate the system. This finding is in line with evaluations by Zickler et al. (2011, 2013), who reported that a fast, reliable and simple setup of the EEG hardware and software is necessary, if the system is to be used in daily life.

In terms of subjective workload the switch from artificial tones to animal sounds did not result in a lower score of the NASA-TLX in this study, average value 62, as compared to Käthner et al. (2013), average value 57. The participant with ALS indicated a similar workload in the first session (69) of the present study. However, it was negatively influenced by physical strain experienced during the measurements. In the second session she indicated a much lower workload (23), whereas it was still relatively high for healthy subjects in the second session (69). Workload was estimated subjectively and due to of her physical condition, we expect that the task is more difficult for the participant with ALS. Her frame of reference, on the other hand also differs from that of healthy participants, thus this task might not be as difficult for her compared to other tasks that she performs on a regular basis. A high variance between sessions for motor impaired end users was also reported in the study by Holz et al. (2013), in which participants evaluated a sensorimotor rhythm based gaming application. Workload evaluations of auditory P300 BCIs are scarce. In the single case study by Schreuder et al. (2013), the severely motor impaired end user could not achieve control over the AMUSE paradigm (Schreuder et al., 2010) and reported a high subjective workload in the first session (>90) that was lower, but still high (>60) in the subsequent sessions. To conclude, it can be stated that the task required in our study seems to be still quite difficult but not more complicated than the AMUSE paradigm. It requires users to concentrate on a particular tone in a rapidly presented sequence of tones. This is an unusual task that requires high concentration, which can, however, be learned as shown in the current study.

Compared to the classic visual row/column speller, auditory BCIs based on this paradigm impose higher workload on the user (Käthner et al., 2013). Several other authors proposed auditory spellers in which tones represent the rows and columns of the speller (Sellers and Donchin, 2006; Furdea et al., 2009; Klobassa et al., 2009; Höhne et al., 2011; Käthner et al., 2013). To keep the workload (the number of tones that need to be discriminated) at an acceptable level, a two-step procedure, similar to the one implemented in the present study, was used in several studies. The procedure of first choosing a certain row followed by a particular column to select the desired letter is used by many potential end users in a partner assisted scanning approach. The partner first presents groups of letters to the end user, who then makes a selection and in a second step chooses the letter. Therefore, this system is advantageous, once the attributions of the animal sounds to the individual rows/columns are learned. Klobassa et al. (2009) reported that all healthy participants of their study could correctly recall the assignments of tones to the corresponding rows and columns after only one or two sessions. If this is also possible for motor impaired end users, remains to be shown. In the following paragraphs, alternatives to the row/column based speller with regard to usability are discussed.

To reduce the amount of workload needed to operate an auditory multiclass BCI, Höhne and Tangermann (2014) proposed a BCI, in which voice recordings of 26 letters and four command items serve directly as target stimuli. Thus, just one step is required for making a selection and the mental effort of having to memorize sounds that represent the desired letters is eliminated.

To allow for a competitive spelling speed, the alphabet was split into three groups that were each presented in a stream from a different direction over headphones (left, central (both speakers), right) and the letters of the individual groups were presented in sequential (alphabetical) order. Due to the simple instructions required to operate the system ("listen/attend to the letter you want to spell") learnability/ease of use can be considered high. However, participants did not reach a satisfactory performance level for spelling (on average 34.7% of letters were correctly chosen across all participants). Hence, the authors of the study suggest reducing the stimulation speed, as this might improve classification accuracies.

For patients, who are unable to operate an auditory multiclass BCI or for an initial communication attempt with completely locked-in patients, paradigms that allow for a binary choice were proposed. Halder et al. (2010) tested a three-stimulus paradigm, based on the classic oddball paradigm, but including a second target. In this paradigm, users have to attend to one of two rare target tones among frequent non-target tones. With targets differing in pitch, offline analysis revealed that healthy users achieved an accuracy of 76.5% correct with two sequences (1.7 bits/min). De Vos et al. (2014) evaluated a similar paradigm with a low density, mobile EEG system and reported a maximum ITR of 1.07 bits/min with an average accuracy of 71% using one sequence. The advantage of this approach is that instructions are easy to understand (e.g., "listen/attend to the high pitched tone if you want to select yes, attend to the low pitched tone if you want to select no") and stimuli can be presented via a single speaker, thus allowing control also for participants with deafness of one ear. Hill et al. (2004, 2005) proposed a streaming approach in which participants shift attention to one of two auditory streams presented simultaneously via headphones (left/right). In a subsequent online study, Hill and Schoelkopf (2012) showed that high online accuracies (85%) could be achieved with short stimulation intervals of a few seconds. Lopez-Gordo et al. (2012) also tested a "streaming approach" in which a dichotic listening task was employed with human voice stimuli. Although only one electrode was used (Cz), classification accuracy was high with subjects achieving 69% (1.5 bits/min). In general, these results demonstrate that the binary approaches provide reliable selection accuracies with simple to understand instructions and only low workload requirements. However, usability would decrease substantially, when trying to implement a spelling solution based on binary approaches. Users would have to complete several sub-steps to reach the desired letter which could lead to error accumulation and requires users to be aware of the current step in the spelling tree that has to be completed to reach the desired letter selection.

Binary auditory BCIs do not guarantee high spelling accuracies in situations where the windows of attention are unknown. This can be the case for participants who are in the minimally conscious state (Pokorny et al., 2013).

LIMITATIONS

For online spelling in the second session, classification parameters of the first session were used. This is a shortcoming of the current study since offline classification accuracies using three words from Session 2 to train the classifier, yielded significantly higher accuracies in Session 2 than did the classification parameters of Session 1. On the other hand this is also an important finding, which indicates that individual parameters used for spelling can change even over a short period of time (1 day) and that contradicts (Nijboer et al., 2008b). Particularly for auditory BCIs there might be a larger variance in the individual parameters between sessions than for visual paradigms. Thus, individual classification weights were created at the beginning of both sessions for the participant with ALS. Recently Kindermans et al. (2014) proposed a probabilistic framework for BCI applications that requires no calibration run. Their zero-training approach with dynamic stopping yielded competitive results compared to a state of the art supervised method. While this was only shown in a simulated online experiment for the visual modality, the authors state that they plan to apply their approach to auditory as well as tactile BCIs. This is a promising approach that could be particularly beneficial for end users who have a limited attention span.

In this study we compared performance between the same paradigm using different stimuli across studies to estimate the effect of natural stimuli on spelling performance. While we kept most parameters, including electrode montage and classification parameters constant (same as in Käthner et al., 2013), it is likely that other factors, in particular different study participants influenced the results.

During the experiment, participants were assisted with visual aids to remember the assignment of tones to specific rows and columns. It remains to be shown in a purely auditory experiment how quickly participants can learn the assignments and use the BCI for spelling without visual aids.

CONCLUSIONS

The study combined natural stimuli and directional cues, which have been shown to be beneficial in previous studies, with a row/column speller paradigm as a further step to optimize auditory BCIs such that they can eventually be used as assistive technology in a home environment. The study demonstrated high accuracies in two sessions that were achieved by healthy participants. Compared to a study using the same paradigm but shorter artificial stimuli (Käthner et al., 2013), an improvement of BCI performance could be observed.

Since spelling performance increased from 76 to 90% (offline) correctly selected letters in two sessions, the study also indicated a training effect that should be taken into account when testing multiclass auditory BCIs. It has yet to be shown if this effect is due to a stimulus specific learning effect (ability to discriminate the target tones) or a general adaptation to the task (familiarity with the task and the required actions for BCI control).

The training effect was also apparent during an initial test with a participant with ALS. However, the end user did not achieve accuracies sufficient for satisfactory communication, thus more training might be needed to improve spelling performance with the proposed BCI. Further improvements of the BCI could include modifications of the paradigm as well as individualized timing parameters, improvements of the stimulus material and signal processing. The effect of training in more sessions and the applicability for (completely) locked-in patients using a purely auditory paradigm without visual cues remains to be demonstrated in further studies.

ACKNOWLEDGMENTS

The study was funded by the European ICT Program Project FP7-288566. This publication was funded by the German Research Foundation (DFG) and the University of Würzburg in the funding program Open Access Publishing. This paper only reflects the authors' views and funding agencies are not liable for any use that may be made of the information contained herein.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnhum.2014.01039/abstract

Supplementary Audio File 1 | Exemplary recording of the stimuli presented during one trial (selection of one letter).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 22 September 2014; accepted: 11 December 2014; published online: 09 January 2015.

Citation: Simon N, Käthner I, Ruf CA, Pasqualotto E, Kübler A and Halder S (2015) An auditory multiclass brain-computer interface with natural stimuli: Usability evaluation with healthy participants and a motor impaired end user. Front. Hum. Neurosci. ***8****:1039. doi: 10.3389/fnhum.2014.01039*

This article was submitted to the journal Frontiers in Human Neuroscience.

2.4 Halder, S., Käthner, I., Kübler, A. (in press). Training leads to increased auditory brain-computer interface performance of end-users with motor impairments. *Clinical Neurophysiology*

Abstract

Objective: Auditory brain–computer interfaces are an assistive technology that can restore communication for motor impaired end-users. Such non-visual brain–computer interface paradigms are of particular importance for end-users that may lose or have lost gaze control. We attempted to show that motor impaired end-users can learn to control an auditory speller on the basis of event-related potentials.

Methods: Five end-users with motor impairments, two of whom with additional visual impairments, participated in five sessions. We applied a newly developed auditory brain–computer interface paradigm with natural sounds and directional cues.

Results: Three of five end-users learned to select symbols using this method. Averaged over all five end-users the information transfer rate increased by more than 1800% from the first session (0.17 bits/min) to the last session (3.08 bits/min). The two best end-users achieved information transfer rates of 5.78 bits/min and accuracies of 92%.

Conclusions: Our results show that an auditory BCI with a combination of natural sounds and directional cues, can be controlled by end-users with motor impairment. Training improves the performance of end-users to the level of healthy controls.

Significance: To our knowledge, this is the first time end-users with motor impairments controlled an auditory brain–computer interface speller with such high accuracy and information transfer rates. Further, our results demonstrate that operating a BCI with event-related potentials benefits from training and specifically end-users may require more than one session to develop their full potential.

Originally published in: Clinical Neurophysiology | doi:10.1016/j.clinph.2015.08.007

ARTICLE IN PRESS

Clinical Neurophysiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Training leads to increased auditory brain–computer interface performance of end-users with motor impairments

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ARTICLE INFO

Article history:
Accepted 5 August 2015
Available online xxxx

Keywords:
Assistive technology
Communication
Brain–computer interfaces
End-user evaluation

HIGHLIGHTS

- Motor impaired end-users can communicate with an auditory brain–computer interface.
- End-users' performance increases with training.
- To our knowledge, this is the first time end-users controlled an auditory brain–computer interface speller with such a high accuracies and information transfer rates.

ABSTRACT

Objective: Auditory brain–computer interfaces are an assistive technology that can restore communication for motor impaired end-users. Such non-visual brain–computer interface paradigms are of particular importance for end-users that may lose or have lost gaze control. We attempted to show that motor impaired end-users can learn to control an auditory speller on the basis of event-related potentials.
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Results: Three of five end-users learned to select symbols using this method. Averaged over all five end-users the information transfer rate increased by more than 1800% from the first session (0.17 bits/min) to the last session (3.08 bits/min). The two best end-users achieved information transfer rates of 5.78 bits/min and accuracies of 92%.
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1. Introduction

Brain–computer interfaces (BCIs) can provide a muscle independent communication channel for people with neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), or acquired brain injuries (Vidal, 1973; Kübler et al., 2001). All BCIs require that a control signal is recorded, that can be modulated (either by attention or another mental task), if the system is intended for communication and control purposes. The methods for recording these signals range from electrophysiological (electroencephalogram (EEG) and magnetoencephalography (MEG)), metabolic (functional magnetic resonance imaging (fMRI) and functional near infrared red spectroscopy (fNIRS)) to invasive (electrocorticography (ECoG), microarray) recordings (Birbaumer et al.,

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http://dx.doi.org/10.1016/j.clinph.2015.08.007
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1999; Weiskopf et al., 2004; Hill et al., 2006; Mellinger et al., 2007; Sitaram et al., 2007). In the EEG components that can be directly modulated are e.g., the sensorimotorrhythm (SMR) and slow cortical potentials (SCPs). Common components that are modulated by directing attention toward specific stimuli are steady state evoked potentials (SSEPs) and event-related potentials (ERPs). Of these components the P300 is often used for communication with motor impaired end-users (Nijboer et al., 2008).

The P300 ERP component of the EEG is elicited by a rare stimulus in a series of frequent stimuli. To utilize this potential for BCI control with visual stimuli the user attends to a matrix on a computer screen, often with 6×6 symbols (Farwell and Donchin, 1988). These symbols are then flashed in a random pattern. Visual P300 BCIs were used by end-users also with complex applications such as painting and web browsing (Mugler et al., 2010; Zickler et al., 2013; Halder et al., 2015) and can be used to achieve high communication speeds (Kaufmann and Kübler, 2014; Käthner et al., 2015). In some cases, if gaze or vision are not impaired, eye trackers may be used to accomplish the same task with higher speed and lower workload than visual P300 BCIs (Pasqualotto et al., 2015). It must be considered though, that some neurological diseases or acquired brain injuries can lead to impaired gaze control or vision which prevents focusing visual attention on a particular stimulus or direction. The solution to this problem may be eye-gaze independent P300 BCIs (Riccio et al., 2012). In principle any modality of human perception can be used to deliver stimuli. Somatosensory and auditory domains have proven to be the most practical (Kaufmann et al., 2013). Tactile stimuli have been used for applications such as communication and simulated wheelchair control (Brouwer and van Erp, 2010; Kaufmann et al., 2014). Two distinct branches of auditory P300 based BCIs have evolved. The first focuses on basic communication, mostly binary choice, with low complexity for users with severe brain injuries and short attention span that have no other method of communication (Halder et al., 2010; Hill and Schölkopf, 2012; Pokorny et al., 2013). These paradigms are also robust enough to be used by healthy controls in a mobile setting (De Vos et al., 2014). The second branch that has developed is that of multi-choice auditory P300 BCIs. This type of BCI is desirable for users with longer attention spans who wish to control more complex applications. Initial implementations of auditory multi-choice BCIs assigned words or stimuli based on naturally occurring sounds to rows and columns of the matrix (Furdea et al., 2009; Klobassa et al., 2009). Despite some success the requirements on sustained attention due to long selection times led to little success with end-users (Kübler et al., 2009). Continued development, in particular of the stimuli by including spatial cues, led to substantial increases in performance (Schreuder et al., 2010; Höhne et al., 2012).

In an attempt to combine spatial cues with the portability of stereo headphones we implemented an auditory P300 BCI utilizing interaural time difference (ITD) and interaural level difference (ILD) to create the impression of sounds originating from five different directions (Käthner et al., 2013). This concept was further improved by using animal sounds as stimuli (Simon et al., 2014). These stimuli require only a short duration to be recognized by the user and are easily discriminated. Additionally, we found that there is a strong training effect in healthy participants (Baykara et al., 2015). In this paper we proceed to show that this auditory BCI can also be applied to end-users with motor impairments.

2. Materials and methods

Five end-users were trained with an auditory P300 BCI using animal sounds as stimuli for five sessions on different days.

2.1. Participants

Five end-users agreed to participate in the study. See Table 1 for details. The ALS functional rating scale revised(ALS FRS-R) was administered in the first session (0 locked-in state, 48 no impairment). None of the end-users had previous experience with the auditory BCI paradigm.

2.2. Procedure

To investigate the effects of training with the auditory BCI the end-users participated in five sessions on separate days. On the basis of the findings in (Baykara et al., 2015; Simon et al., 2014) we retrained the classifier with two five-letter words at the beginning of every session. The words consisted of the letters on the diagonal of the 5×5 letter matrix used in this study (AGMSY; see Fig. 1(A)). After calibration the participants wrote five words comprising five letters each (VARIO, GRUEN, RUBIO, TUMBI, PHLEX). The words were chosen such that the stimuli needed to select the target symbols were equally distributed across the five different rows and columns.

The stimuli used in this study were modified to create an impression of directionality using ITD and ILD as described in Käthner et al. (2013). We used the stimuli found to provide the best results in Simon et al. (2014). Duck, bird, frog, gull and pigeon were arranged on positions of a circle from left, middle left, front, middle right to right and presented using Sennheiser HD280 Pro stereo headphones (see Fig. 1(B) for the spatial arrangements and (C) for the spectrograms).

None of the end-users except end-user one were provided with the static visual support matrix in Fig. 1(A). All other end-users received only auditory cues as described in Fig. 1.

End-user two completed four sessions only. In session three the quality of the calibration data was not sufficient to train the classifier for feedback. End-user three requested to discontinue participation in the study after session three.

2.3. Calibration

For calibration each stimulus was presented ten times. Thus, for selection of one letter the participants had to attend to twenty stimuli (ten for the row, ten for the column). On the basis of the calibration data the number of repetitions was reduced to avoid a ceiling effect. We set the number of repetitions such that 70% accuracy was reached (based on offline analysis of the calibration data) plus three additional repetitions. This procedure was repeated in each daily session. Previous calibration data was not used. Timings were identical to the copy spelling task (except number of repetitions). Collecting the calibration data required approximately ten minutes. In all sessions all calibration data was used to calibrate the classifier.

2.4. Copy spelling

In each session the end users wrote five words comprising five letters (see above). The system paused for twelve seconds between letter selections to give the user time to focus on the stimulus that needed to be attended, to select the next letter (see Fig. 1). There was a two seconds pause between the stimuli for the rows and those for the columns (also Fig. 1). The stimuli lasted for 150 ms with an inter stimulus interval (ISI) of 287.5 ms. These parameters (437.5 ms stimulus presentation, ten stimuli, ten repetitions, two seconds between rows and columns, twelve seconds between letters) lead to a maximum time of 57.75 s per letter. These parameters are identical to the ones used in Baykara et al. (2015). Note, that in most cases the time per letter was reduced

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Table 1
Description of end-users participating in the study. None of the end-users received artificial nutrition.

End-user	1	2	3	4	5
Gender	m	m	f	f	m
Age (years)	79	56	45	53	73
Diagnosis	Muscular dystrophy	Anoxic brain injury	Multiple sclerosis	ALS	ALS
Diagnosis (years since)	25	22	21	1	3
ALS-FRSR	39	18	23	25	30
Ventilation	no	no	no	no	At night
Vision	Intact	Strongly affected	Affected	Intact	Intact
Motor function	Weakness in limbs Walking affected	Control only over Eye/tongue movement	Facial muscles Right hand intact	Walks with Assistance	Upper extremities Affected
Speech	Normal	Lost	Strongly affected	Affected	Normal

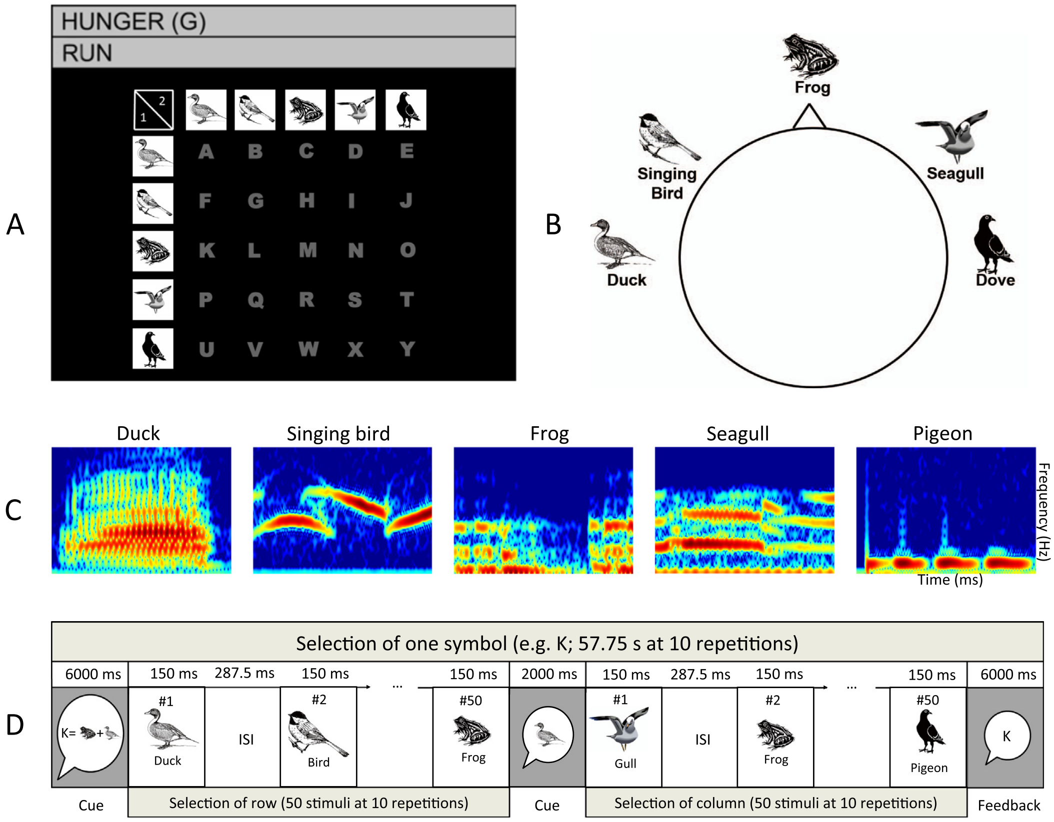

Fig. 1. (A) The matrix coding the 25 symbols that were used in the experiment. (B) The spatial arrangement of the stimuli around the user. (C) Spectrograms of the stimuli used during the experiment with time in ms on the *x*-axis (0–150) and frequency in Hz on the *y*-axis (0–5512.5). (D) During training a pre-recorded voice announced the stimuli that needed to be attended, to select a particular letter. When switching from rows to columns the voice reminded the end-user which stimulus to attend to for the column. After presenting the stimuli for the columns the letter selected by the classifier was announced. End-user one used the system with the visual support matrix (A), all other end-users the auditory only system (D).

from session-to-session due to a decrease of the number of repetitions needed to reach 70% accuracy as described above.

2.5. Data acquisition

A g.tec g.USBamp amplifier (bandpass from 0.1 to 30 Hz, notch filter at 50 Hz, sampling rate 256 Hz) was used for EEG recordings. We used 16 g.gamma electrodes at positions FC3, FCz, FC4, C3, Cz, C4, CP5, CPz, CP6, P3, Pz, P4, PO5, POz, PO6 and Oz. Data were recorded with a Hewlett–Packard ProBook 6460b with a dual-core CPU, 4 GB of RAM and a 64-bit Windows 7. BCI2000 was used to control stimulus presentation, signal processing and data recording (Schalk et al., 2004).

2.6. Signal processing

Stepwise linear discriminant analysis (SWLDA) was used to determine the weights for online classification of the data. An extensive description and comparison to other classification techniques can be found in Krusienski et al. (2006). A review of classification techniques was provided by Lotte et al. (2007). SWLDA was applied to all channels in a time window from 0 to 800 ms post-stimulus. A moving average filter with a width of 20 samples was applied to these segments and the data was subsampled by a factor of 20. After extracting the features the algorithm calculates *p*-values from an *F*-statistic for each feature. If the feature fulfills the significance threshold (p-value < .1; forward step) this feature

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is included in the discriminant function. Each time a new feature is added by the algorithm a reanalysis of all features is performed and those that are no longer significant (p-value > .15, backward step) are removed. A graphical representation of this process can be found in Halder et al. (2010). A maximum number of 60 features was added. Information transfer rates (ITRs) were calculated with the formula proposed by Wolpaw et al. (2002). We used the timings described in Section 2.2 with the individually adjusted stimulus repetitions to calculate bits/min.

In cases when the calibration data described in Section 2.3 did not contain any features that satisfied the inclusion criteria a classifier could not be created and we did not perform the online spelling session. In the current study this occurred once (for end-user two in session three; only the calibration data was collected and then the session was aborted).

Online the classification weights were applied to the EEG segment after each stimulus presentation. Classifier outputs based on segments following the same stimulus type were summed and then the row and column with the maximum value was selected.

2.7. Offline analysis

Offline analysis of ERPs was performed with EEGLAB and other Matlab scripts (Delorme and Makeig, 2004). Amplitude of the P300 was defined to be the maximum between 400 and 800 ms on Cz and latency as the time between stimulus onset and the maximum amplitude. The average amplitude from −100 to 0 ms pre-stimulus was subtracted as a baseline. Amplitudes and latencies were extracted for each session (five sessions) and letter (25 per session) individually and tested for significant differences between sessions with repeated analysis of variance (ANOVA). The classifier could not be trained for end-user two in session three, thus all ANOVAs for this end-user were performed on four sessions. End-user three completed only three sessions, consequently the ANOVAs were performed only for three sessions.

To determine if there was an effect of stimulus type we calculated the confusion matrix and analyzed the number of times per session each stimulus was selected correctly per session (between zero and ten times for 22 sessions) and how many times per session it was selected wrongly (between zero and in theory 50 times for 22 sessions). The values were averaged across sessions for each end-user. In both cases this yielded a 5×5 matrix for a repeated measures ANOVA with stimulus type as factor.

3. Results

3.1. BCI performance

The mean ITR of the participants increased from 0.17 bits/min in session one to 3.08 bits/min in session five. In relation to session one performance increased by more than 1800%. Selection accuracy increased from 11.2% in session one to 52.8% in session five (i.e. to 470% of session one). Fig. 2 shows that the sample consisted of three end-users that improved performance with training (end-users one, four and five) and two end-users (two and three) who did not. The three end-users that improved, increased ITR from 0.15 bits/min to 5.12 bits/min and accuracies from 9.33% to 84.00%. The highest ITRs in the sample were achieved by end-users one and four in session five with 5.78 bits/min. In contrast, in end-user two and three ITR decreased 0.19 bits/min to 0.04 bits/min and accuracy from 14% to 6%. The values of end-user three are close to zero and thus not visible in Fig. 2 (B).

The average number of repetitions per stimulus decreased from 9.6 (56 s per symbol) in session one to 6.75 (43.43 s per symbol) in session five. Based on the heuristic described in Section 2.2 to determine the number of stimulus repetitions, the fastest participants were end-user one in sessions three and four and end-user five in session five with five sequences (34.88 s per symbol).

The confusion matrix is shown in Table 2. The mean correct selections for each stimulus ranged from 55.45% (frog, middle) to 66.82% (duck, left). A repeated measures ANOVA with stimulus type (duck, bird, frog, gull, pigeon) as factor revealed no trend in the percentage of correct selections ($F_{4,16} = 1.62, p = 0.22$). Errors ranged between 37.88% (gull, middle right) and 41.43% (duck, left). Again, a repeated measures ANOVA with stimulus type as factor was conducted and revealed no trend in the number of errors ($F_{4,16} = 1.73, p = 0.19$).

3.2. Physiological data

We analyzed the ERPs elicited by the auditory stimuli during copy spelling using repeated measures ANOVA with session as factor (5 levels) to determine if there was an effect of session on maximum amplitude. The ERPs are displayed in Fig. 3. There was a main effect of session on amplitude of the P300 for end-users one, four and five (end-user one: $F_{4,96} = 15.89, p < 0.05$; end-user

Table 2
Confusion matrix for the five stimuli used for spelling in this experiment. The table shows the number of times each stimulus was selected. Numbers on the diagonal are correct selections and thus printed in bold. Other numbers are errors. The number on the diagonal divided by the sum of the corresponding row yields the % correct selections in the rightmost column. The sum of all non-diagonal values per column divided by the sum of all values in the column yields the % of erroneous selections in the bottom row.

	Duck	Bird	Frog	Gull	Pigeon	% correct
Duck	**147**	17	19	18	19	66.82
Bird	29	**126**	22	20	23	57.27
Frog	36	23	**122**	17	22	55.45
Gull	22	28	17	**123**	30	55.91
Pigeon	17	20	20	20	**143**	65.00
% errors	41.43	41.12	39.00	37.88	39.66	–

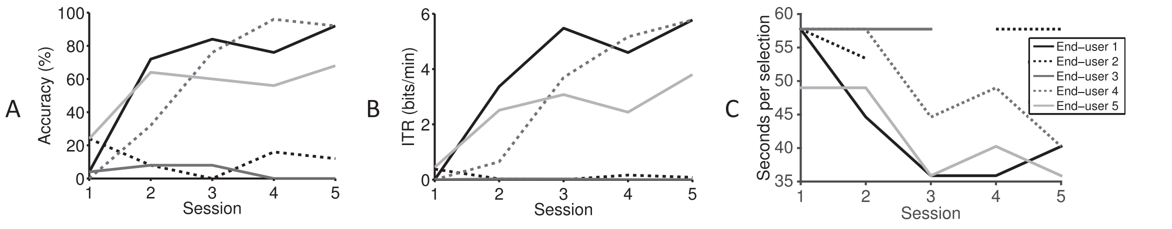

Fig. 2. Information transfer rate (ITR; A) and symbol selection accuracy (B) as a function of session. One line per end-user is shown in the two plots. Note that the study protocol was aimed at avoiding accuracy ceiling effects to determine the extent of the training effect by decreasing the time per selection (C) based on the calibration data collected in each session. Thus, the ITR (A) is more representative of the performance of the participants.

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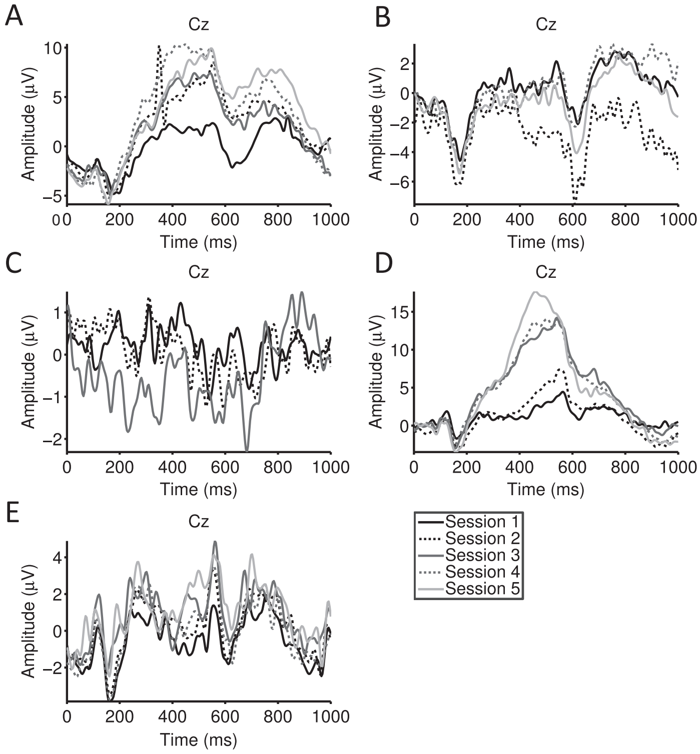

Fig. 3. The responses (in µV as function of time at Cz) to the target stimuli are shown in plots A to E for end-users one to five. One line per session is shown in each plot. Note that the amplitude scale is adapted to the minimum and maximum of each end-user.

four: $F_{4,96} = 59.6, p < 0.05$; end-user five: $F_{4,96} = 6.8, p < 0.05$) whereas no main effect was found for end-users two and three (end-user two (without session three): $F_{3,72} = 0.44, p = 0.73$; end-user three (three sessions): $F_{2,48} = 0.6, p = 0.56$). Fig. 4(A) shows the mean values of peak amplitude per session and end-user.

The same analysis was performed for the latency of maximum amplitude. In that case a main effect was only found for end-user four ($F_{4,96} = 6.58, p < 0.05$). No main effect of session on latency was found for the other four end-users (end-user one: $F_{4,96} = 1.29, p = 0.28$; end-user two (without session three): $F_{3,96} = 0.64, p = 0.6$; end-user three (three sessions): $F_{2,48} = 0.2$, $p = 0.82$; end-user five: $F_{4,96} = 1.96, p = 0.11$). Fig. 4(B) shows the mean values of peak latency per session and end-user.

4. Discussion

We conducted five sessions of auditory P300 BCI training with five end-users with motor impairments. The participants increased their ITR from 0.17 bits/min in session one to 3.08 bits/min in session five.

4.1. Comparison of the auditory speller with previous versions by our group

The BCI presented in this paper belongs to the class of multi-choice auditory P300 BCIs. We had particular interest in comparing the version presented in this paper to other versions developed by our group to illustrate the evolution of the paradigm (see Fig. 5). Since the signal processing was not modified we can determine solely the effect of the paradigm modifications. With the initial version of the auditory speller healthy participants achieved ITRs between 0.8 bits/min (Halder et al., 2013) and 1.54 bits/min (Furdea et al., 2009). Accuracies were around 60% and symbol selections required more than one minute. The long selection times were due to the use of words as stimuli for coding rows and columns of the matrix. These required long presentation times to be recognizable by the participants. Additionally, ERPs were not very pronounced probably due to variations in the onset of stimulus recognition which caused a jitter effect. Our initial attempts to apply this paradigm to a sample of end-users with disease did not result in accuracies above 50%, thus, no information was transferred (Kübler et al., 2009). We retained the design of the paradigm (row/column coding of 25 symbols) and changed the stimuli to artificial tones. Additionally, we added spatial information to the stimuli since no clear association between the tones and the rows and columns of the symbol matrix existed and other studies showed spatial information to be advantageous (Schreuder et al., 2010). These modifications increased ITR to 2.76 bits/min (Käthner et al., 2013). In a subsequent study we found that animal sounds are easier to recognize than artificial tones and that the recognition of these stimuli can be trained (Simon et al., 2014; Baykara et al., 2015). The ITR increased to 3.76 bits/min with the natural stimuli and to 5.13 bits/min with training. These improvements increased the ITR from 1.54 bits/min to 5.13 bits/min. This is an increase of more than 300% which was achieved by optimizing the paradigm while keeping aspects such as signal processing constant. Similar performance increases were possible in visual P300 BCIs as shown by Townsend et al. (2010) and Kaufmann et al. (2013). The ITR achieved by the end-users in our current sample is lower than that of the healthy controls (3.08 bits/min as opposed

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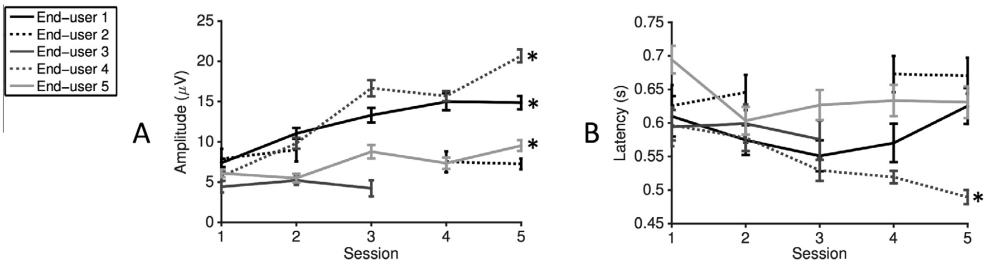

Fig. 4. Maximum peak amplitude (A) and maximum peak latency (B) shown as a function of session. One line per end-user is shown in the two plots. The curves of end-users with a main effect of session (ANOVA, $p < 0.05$) were marked with a "*" in the corresponding plots. End-user two did not complete session three, end-user three did not complete sessions four and five.

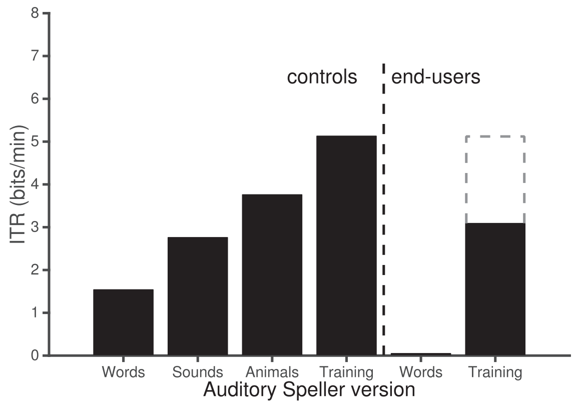

Fig. 5. Information transfer rates (ITRs) of auditory P300 speller paradigms developed by our group in the past years. Studies with healthy controls are showed to the left of the vertical dashed line, studies with end-users to the right. The initial version ("Words"; Furdea et al. (2009)) used words as stimuli and was not successful with end-users (end-users "Words"; Kübler et al. (2009)). A version using artificial tones almost doubled the ITR ("Sounds"; Käthner et al. (2013)) which was further increased by animal sounds ("Animals"; Simon et al. (2014)). The final increase in performance was achieved by conducting several training sessions per user ("Training"; Baykara et al. (2015)). This effect was reproduced with end-users (end-users "Training"; this paper). Performance of the end-users who achieved control is shown by the dashed lines.

to 5.13 bits/min). This effect is commonly observed in many studies comparing controls to end-users (Mugler et al., 2010; Müninger et al., 2010; Ortner et al., 2011). Regarding only the three participants of the current study who learned to control the auditory BCI, the bitrates were very similar to those of healthy participants (5.12 bits/min vs. 5.13 bits/min). Compared to our previous attempt in which symbol selection accuracies were slightly above chance with 12% (0.05 bits/min; Kübler et al. (2009)), the attempt described in the current paper was more successful (three of five users above 70% accuracy and, thus, sufficiently high for meaningful communication, see Kübler et al. (2001)). Care should be taken though when directly comparing the results from Kübler et al. (2009) and this paper due to the differences between and small size of the two samples.

In summary, based on the data presented in this paper we cannot claim having achieved communication with a person in complete locked-in state (CLIS) and this work represents another step in the evaluation of non-visual BCIs with end-users. The minimum ALS FRS-R score was 18, and this participant (end-user two) did not learn to control the BCI. Both end-users diagnosed with ALS (end-users four and five) were able to obtain control. This is of particular importance due to the possibility that these end-users may develop a loss of gaze control (ophthalmoplegia) in later stages of the disease. If the level of control could be maintained until then it would be of great benefit for these end-users. End-user four, together with end-user one (muscular dystrophy), achieved the highest ITR in this study.

4.2. Comparison with other gaze independent BCIs

Research with gaze independent BCIs can be split into three branches: auditory, tactile and gaze independent visual (Schreuder et al., 2010; Hill and Schölkopf, 2012; Brouwer and van Erp, 2010; Treder et al., 2011; Kaufmann et al., 2013). A recent review can be found in Riccio et al. (2012).

We consider certain aspects of the gaze independent visual BCIs to be debatable, because they require gaze to be focused on at least the main direction of the visual stimuli. This requires a minimum of gaze control and ability to fix the gaze which is not always possible even when vision is still present (Kaufmann et al., 2013). Possibly, alternative ways of presenting the stimuli over a broad range of the visual field such as head-mounted displays will help alleviate this issue (Käthner et al., 2015). If the eyes roll uncontrollably, possibly so far upward that the pupils are covered by the eyelids, use of such a BCI is no longer possible (Murguialday et al., 2011). Certainly, there is a continuum of gaze control, in which control over visual P300 BCI implementations such as described in Treder et al. (2011) is maintained the longest. This makes the development of such BCIs important to the field but also, in our opinion, places them in a different category than completely gaze-independent BCIs.

Considering tactile BCIs, in at least one case mechanoreceptive receptors were affected by ALS (Murguialday et al., 2011). This does not appear to be a generalizable result, as in one end-user with whom tactile, auditory and visual (gaze independent) BCIs were applied the best results were obtained with tactile stimulation (Kaufmann et al., 2013). However, this end-user was diagnosed with locked-in syndrome due to brain stem stroke. Thus, the underlying disease may play a crucial role in what type of stimulation may be the most appropriate, which then has to be defined individually following the user-centred approach (Kübler et al., 2014).

Although hearing remains unimpaired by ALS, it is difficult for end-users to control an auditory P300 BCI (Kübler et al., 2009). This was further illustrated by a case described in Schreuder et al. (2013). The authors argue that one of the difficulties in controlling an auditory P300 BCI lies in the high workload and attentional demands such a system poses (see also Nijboer et al. (2008)). This may be in part circumvented by a binary class auditory BCI (Hill et al., 2004; Halder et al., 2010; Hill et al., 2012). Recently, promising results with a binary choice BCI have been shown for two ALS patients (Hill et al., 2014), but not in disorders of consciousness (Pokorny et al., 2013).

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With regard to the overview presented in Riccio et al. (2012) auditory and tactile BCIs have converged on ITRs of 5 bits/min and "gaze-independent" visual BCIs on 10 bits/min. Clearly, the visual modality offers the highest communication speed. Additionally, the auditory design requires that end-users memorize the letter matrix. Since many end-users already utilize letter matrices for partner assisted communication we believe that memorizing letter matrices is possible or the design may even be adapted to the individually used letter presentation. Due to the aforementioned restrictions there is nonetheless the need to further develop BCI with auditory or tactile stimulation. Due to improvement as shown in Fig. 5, we are optimistic that performance with end-users will continue to improve regardless of modality. This is also based on observations that in some cases lack of communication with one kind of BCI may be circumvented by using another modality (Kaufmann et al., 2013; Schreuder et al., 2013).

4.3. Training effects

Training effects were observed in three out of five end-users in this study. The verbal reports indicated that with training it became easier for the end-users to discriminate the stimuli. We would expect this to be reflected in a decrease in latency of the ERPs, but we observed this only in end-user four. Increases in amplitude were observed for end-users one, four and five, i.e., all end-users who learned. An impact of training on ERP amplitudes has been shown previously (Kraus et al., 1995; Tremblay et al., 2001). In a recent study, the ability to discriminate pitch differences has been shown to differ between musicians and non-musicians (Paraskevopoulos et al., 2014). The authors attributed the difference in this ability to the training of the musicians which was also reflected in higher combined MEG and EEG responses (quantified as statistical parametric maps and global field power). Similarly, the training conducted with auditory paradigms may affect the ability to discriminate the stimuli and thus be reflected in the ERP amplitudes.

The reasons why end-users two and three did not learn may be related to their diagnosis. End-user two had diffuse brain damage due to hypoxia. Even though the EEG showed stimulus locked responses there were no differences between attended and non-attended stimuli. This indicates that end-user two was able to hear the tones, but not necessarily to sufficiently discriminate them even though he communicated that he was able to do so. Finally, time periods between sessions varied considerably for this end-user (between one and four weeks). End-user three, who was diagnosed with multiple sclerosis (MS) also did not learn to control the BCI. In this case no stimulus locked responses were visible (see Fig. 3(C)). Since all users reported to be able to discriminate the stimuli, it is unlikely that the lack of control was caused by the physical properties of the stimuli. Previous neurophysiological studies have shown an effect of MS on ERPs latency (increase of latency of N200 and P300; see Piras et al. (2003)). Another study found particular impairment of the verbal as opposed to visual working memory of people diagnosed with MS (Ruchkin et al., 1994). Both factors may have contributed to the lack of stimulus locked responses in our study.

In addition to disease, influences on performance variations are numerous and have been analysed extensively showing influence of physiological, psychological and anatomical factors (Grosse-Wentrup et al., 2011; Halder et al., 2011, 2013,; Hammer et al., 2012; Mak et al., 2012; Kasahara et al., 2015). A conclusive model explaining these variations has not been suggested yet.

4.4. Generalizability of results

Our sample included five different participants with four different diagnoses (ALS, MS, anoxic brain injury, muscular dystrophy) and diverse degrees of motor impairment. The sample size and composition in the current study pose a limitation for the generalization of the results. Additionally, the diagnoses (ALS, MS, anoxic brain injury, muscular dystrophy) and degrees of functional impairment are diverse. This does however contribute to the external validity of our approach. End-user two had visual impairments due to drug intolerance (gaze control was not affected) and end-user three due to a strong loss of visual acuity (color vision was unaffected). MS and ALS are known to potentially affect vision or gaze control (Frohman et al., 2005; Mizutani et al., 1992). Loss of gaze control (ophthalmoplegia) usually only manifests if end-users with ALS are artificially ventilated (and has been described in single cases Murguialday et al. (2011)). Both end-users with ALS who participated in the study were in earlier stages of the disease. Taken together, the small sample size and idiosyncratic approach restricts generalizability of results to other end-users of non-visual BCIs.

With this small sample we could show that control of a BCI is possible. However, the results do not allow us to predict successful communication given a particular diagnosis or functional impairment of the participants. Additionally, the question of functional vision remains unaddressed. Even though visual feedback or cues were not given to any of the end-users except end-user one we cannot claim to have provided control over a BCI for a participant without vision.

Even in samples of healthy participants variability with auditory BCIs tends to be higher than with visual BCIs (Halder et al., 2013). In previous studies one end-user performed best with a tactile BCI (Kaufmann et al., 2013). End-users who have progressed to the CLIS may no longer be able to use a conventional BCI system (Murguialday et al., 2011). In these cases other BCI paradigms may be required (De Massari et al., 2013). When applying this BCI to participants in the minimally conscious state (MCS) entirely different difficulties will be encountered that the current paper does not to address, such as short attention spans or windows of consciousness (Lulé et al., 2013).

Our current evaluation was performed with one set of stimuli. Informal feedback from the end-users suggested that the comfort in using the system depends on the subjective perception of the stimulus material. Animal sounds may not be the optimal stimulus material for all end-users. Future versions of the paradigm should include a method of determining the optimal stimulus set for a particular end-user which may be preferred by a given user even though it does not provide the highest accuracy (Kübler et al., 2014).

Additionally in our evaluation only one application was provided, a simple spelling system. Which applications can be controlled with auditory BCIs, or non-visual BCIs in general, should also be evaluated in future studies. Providing additional applications may be required to increase the value of the system for the end-user and to fulfill individual requirements (Kübler et al., 2014).

Further studies are required with locked-in end-users over longer time periods (Holz et al., 2015). This long-term deployment would also require that the family members or care givers set up the system, which might reveal additional short-comings of the paradigm. The high attentional and workload demands of non-visual BCIs may have effects that only become apparent during long-term usage (for effects of workload see Käthner et al. (2014)).

In the developmental process taken by Furdea et al. (2009) to Baykara et al. (2015) our current work constitutes another step forward. Nonetheless, concerning the full scope of evaluation with end-users it can only be considered a pilot study. Further research is required for additional optimization of stimulus material, applications that can be controlled with non-visual paradigms and generalizability of the paradigm to other end-users with higher degrees of impairment and especially long-term usage in the homes of the end-users.

Please cite this article in press as: Halder S et al. Training leads to increased auditory brain–computer interface performance of end-users with motor impairments. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.08.007

4.5. Conclusions

The attempt was partially successful to increase auditory P300 BCI performance with training of end-users with motor impairments. Three of five end-users managed to use the auditory BCI with ITRs comparable to those of healthy participants. Nonetheless, further evaluation with end-users and especially long-term evaluation is required.

Conflicts of interest

None of the authors have potential conflicts of interest to be disclosed.

Funding

The study was funded by the European Community for research, technological development and demonstration activities under the Seventh Framework Programme (FP7, 2007–13), project grant agreement number 288566 (BackHome). This paper reflects only the authors' views and funding agencies are not liable for any use that may be made of the information contained herein. Author S.H. has received funding as International Research Fellow of the Japan Society for the Promotion of Science – Japan and the Alexander von Humboldt Foundation – Germany.

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Please cite this article in press as: Halder S et al. Training leads to increased auditory brain–computer interface performance of end-users with motor impairments. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.08.007

2.5 Käthner, I., Kübler, A., Halder, S. (2015). Comparison of eye tracking, electrooculography and an auditory brain-computer interface for binary communication: a case study with a participant in the locked-in state. *Journal of NeuroEngineering and Rehabilitation*

Abstract

Background: In this study, we evaluated electrooculography (EOG), an eye tracker and an auditory brain-computer interface (BCI) as access methods to augmentative and alternative communication (AAC). The participant of the study has been in the locked-in state (LIS) for 6 years due to amyotrophic lateral sclerosis. He was able to communicate with slow residual eye movements, but had no means of partner independent communication. We discuss the usability of all tested access methods and the prospects of using BCIs as an assistive technology.

Methods: Within four days, we tested whether EOG, eye tracking and a BCI would allow the participant in LIS to make simple selections. We optimized the parameters in an iterative procedure for all systems.

Results: The participant was able to gain control over all three systems. Nonetheless, due to the level of proficiency previously achieved with his low-tech AAC method, he did not consider using any of the tested systems as an additional communication channel. However, he would consider using the BCI once control over his eye muscles would no longer be possible. He rated the ease of use of the BCI as the highest among the tested systems, because no precise eye movements were required; but also as the most tiring, due to the high level of attention needed to operate the BCI.

Conclusions: In this case study, the partner based communication was possible due to the good care provided and the proficiency achieved by the interlocutors. To ease the transition from a low-tech AAC method to a BCI once control over all muscles is lost, it must be simple to operate. For persons, who rely on AAC and are affected by a progressive neuromuscular disease, we argue that a complementary approach, combining BCIs and standard assistive technology, can prove valuable to achieve partner independent communication and ease the transition to a purely BCI based approach. Finally, we provide further evidence for the importance of a user-centered approach in the design of new assistive devices.

Originally published in: Journal of NeuroEngineering and Rehabilitation, *12*: 76
doi: 10.1186/s12984-015-0071-z

Käthner *et al. Journal of NeuroEngineering and Rehabilitation* (2015) 12:76
DOI 10.1186/s12984-015-0071-z

JOURNAL OF NEUROENGINEERING AND REHABILITATION

RESEARCH Open Access

Comparison of eye tracking, electrooculography and an auditory brain-computer interface for binary communication: a case study with a participant in the locked-in state

Ivo Käthner[1*], Andrea Kübler[1] and Sebastian Halder[1,2]

Abstract

Background: In this study, we evaluated electrooculography (EOG), an eye tracker and an auditory brain-computer interface (BCI) as access methods to augmentative and alternative communication (AAC). The participant of the study has been in the locked-in state (LIS) for 6 years due to amyotrophic lateral sclerosis. He was able to communicate with slow residual eye movements, but had no means of partner independent communication. We discuss the usability of all tested access methods and the prospects of using BCIs as an assistive technology.

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Background

Neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) or lesions in the brainstem caused by stroke, traumatic or anoxic brain injury can lead to a locked-in syndrome (LIS). First coined by Plum and Posner in 1966 [1], the term describes a state in which persons are severely paralyzed (quadriparesis or quadriplegia), unable to speak (aphonia or severe dysphonia), but aware of their environment and show cognitive abilities on examination. Eye opening is sustained and the principle methods of communication are vertical or horizontal eye-movements or blinking (according to the criteria suggested by the American Congress of Rehabilitation Medicine [2]). The term total (or complete) LIS refers to a state of complete motor paralysis with no control over eye movements [3, 4].

Persons in the locked-in state require augmentative and alternative communication (AAC) to replace speech. These AAC systems can range from communication based on eye movements during face-to-face communication with caregivers to technical aids that allow for communication independent of the caregiver. While there are several high-tech communication aids available

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such as dynamic touch screens for persons who have residual muscular control [5], access options to AAC for persons in LIS are sparse. One of the most promising options is an eye-tracking based approach. A recent survey among 30 persons with advanced ALS using an eye-tracking computer system showed a high acceptance and average daily usage of 300 min of the device [6]. However, almost every fourth participant of the study ($n = 7$) reported a low daily utilization. Eyestrain and the inability to move the eyes sufficiently precise were the most frequent reasons reported for non-use. Another access option to AAC repeatedly proposed uses electrodes placed around the eyes of the user to record the electrooculogram (EOG) and thereby identify eye movements and/or blinks [7–9]. Similar to the eye tracker, this method relies on the users' abilities to control their eye-muscles.

Brain-computer interfaces (BCIs) can provide a muscle-independent communication channel (for reviews, [10, 11]). A BCI based on event-related potentials (ERPs) in the electroencephalogram (EEG) was first proposed by Farwell and Donchin (1988 [12]) and ERPs are now the most widely applied control signals to enable communication with a BCI (for reviews see [13, 14]). Usually ERPs are elicited in so-called oddball paradigms. The users have the task of attending rare (odd) target stimuli in a series of frequent stimuli. These rare target stimuli elicit specific ERPs that can be classified and translated into computer commands. The most prominent among the elicited ERPs is the P300. It is a positive deflection in the EEG that occurs approximately 200–500 ms after the onset of a rare attended target stimulus with maximum amplitudes over central and parietal areas of the scalp [15]. For many years research focused on BCIs that apply visual stimulation to elicit ERPs. Most healthy users are able to control visual ERP-BCIs with high accuracies [16] and persons with severe paralysis were able to gain control over it [17–19]. Even control over complex applications such as a web browser, multimedia player and a painting application and long-term independent home use by ALS patients have been demonstrated [20–22]. Pasqualotto et al. [23] revealed a higher performance and usability for an eye-tracking system compared to a visual BCI with a group of persons with severe motor impairment. Nevertheless, there are situations in which a BCI might be advantageous. For instance, the participant with ALS of the long-term case study by Holz et al. [21] reported that it was less straining for her to make selection with the BCI, because unlike with her eye tracker, no eye blinks were required to make a selection. Because neither visual ERP-BCIs nor eye trackers can be controlled by persons with severe visual impairments and/or disability to control eye movements, e.g., persons in LIS, BCIs based on auditory and tactile stimulation were proposed in recent years (for a review see [24]).

Two types of auditory ERP-BCIs emerged. The first allows simple (binary) communication and is either based on attending target tones in a sequence of tones (sequential approach: e.g., [25–28]) or shifting attention to one of two auditory streams (streaming approach: [29–31]). Binary auditory BCIs are particularly suited for re-establishing simple communication with severely paralyzed persons since attentional and working-memory demands are low. The second type, multi-class BCIs, enable persons with long attention spans and good cognitive abilities to control spelling applications. For this, the number of tones to be differentiated in a sequential approach are increased ([32–38]).

The participant of the current study was in the locked-in state due to amyotrophic lateral sclerosis. At the time of the study, he did not use any AAC that would allow him to communicate independent of his caregivers and has not been using such technology previously. His family contacted us, because he had read about the possibility of using EOG and brain-computer interfaces as a method of communication in the study by Kaufmann et al. [8]. Although he could still communicate via eye movements, he wanted to test these methods as an alternative, since he had noticed a decline in his ability to control his eye movements. Hence, the aim of the study was to test a gaze independent BCI system that he could control without muscle activity and an EOG system as an alternative to his current method. We compared these systems to an eye tracking system. The advantages and disadvantages of each system are discussed, the prospects of using BCIs as assistive technology are reviewed and the need is emphasized for user-centered design in AAC in general and BCI development in particular.

Methods

Participant

At the time of the study, the Norwegian participant was 55 years old and has been in the locked-in state for 6 years. He was diagnosed with amyotrophic lateral sclerosis 9 years and 2 months prior to the study with first symptoms occurring 5 months prior to the diagnosis (muscle weakness in his legs). He was able to move slowly his eyes vertically and horizontally. Voluntary blinking was not possible. As the cause of an accident, he had lost hearing of his right ear. He was artificially ventilated (tracheostomy mechanical ventilation) and fed (percutaneous endoscopic gastrostomy). Full-time care was provided in his home, where the study was conducted.

Conventional communication

To communicate with caregivers and family members the study participant relied on a letter board. The same groups of letters were printed on both sides of a cardboard frame. The caregiver or family member held the frame, facing the user. The user could then select letters with a two-step procedure. Via eye gaze he first selected a group of letters. The caregiver read out the letters of the selected group one at a time and the user indicated the letter he wanted to spell by slightly twitching his left eyebrow, when the desired letter was read. If control of eye movements was not possible due to fatigue, the first step was also done with partner assisted scanning (i.e., the caregiver pointed to the groups of letters one after the other and the user selected a group with a short twitch of his eye).

About 7 years prior to the study, the user had tried an eye tracking based system with Rolltalk communication software (Abilia AB, Sweden), but communication had worked better with the letter board described above.

Procedure

On four consecutive days, the participant tested an EOG based system (3 sessions), an eye tracking based approach (1 session) and an auditory BCI (3 sessions) for communication. Since the participant was particularly interested in the EOG as an alternative communication channel, we started testing this system followed by the eye tracking and tested the BCI last. For all systems we optimized the parameters in a stepwise procedure to allow the participant to gain control over them. The procedure for each system is described below. Main parameters for each session are listed in Table 1. During the measurements, the participant sat in his wheelchair in a reclining position. He gave informed consent prior to participation (a signature stamp was used by his caregivers). The study was carried out in accordance with the guidelines of the Declaration of Helsinki.

Data acquisition

Stimulus presentation, data processing and storage were controlled by the BCI2000 software framework [39]. EEG data during BCI and EOG use was amplified with a g.USBamp (g.tec, Austria) with a sampling rate of 256 Hz, a bandpass filter from 1 to 30 Hz and a notch filter around 50 Hz. The EyeX eyetracker was connected to BCI2000 using the software development kit provided with the hardware by Tobii Technology. Recordings were made with a Hewlett-Packard ProBook 6460b with a dual-core CPU, 4GB of RAM and a 64-bit Windows 7.

EOG

The eye movement that the participant used to communicate during the partner scanning approach (twitching his left eyebrow) was not strong enough to be registered with an electrode placed above his left eyebrow. Thus, we asked the participant to perform another eye movement that he could control reliably and that was not too strenuous. The participant chose looking to the left and back to the center as control signal for the EOG. To record this movement we placed one electrode next to the outer canthus of his left eye. Stepwise linear discriminant analysis (SWLDA, [40]) was applied to determine features and feature weights of the EOG data acquired during the training runs that were subsequently used for online classification during the feedback runs. During both the training and the feedback runs we asked the participant to respond with an eye movement to a predefined target letter. Voice recordings of the letters “A” and “B” were played in random order via the built in speakers of the notebook. Presentation of these two letters constituted one sequence. Stimulus duration was set to 1 s and the interstimulus interval (ISI) to 2.5 s, hence stimulus onset asynchrony (SOA) was 3.5 s. During the feedback runs, the selected letter, “A” or “B”, was presented after a short signal tone. The pause between sequences was set to 5 s, thus 12 s were needed for one selection with this two choice paradigm. Later during that session the participant decided to switch to “looking to the right and back to the center” as control signal for the EOG. Therefore, we placed an additional electrode next to the outer canthus of his right eye and used the differential activity of both electrodes to classify his eye movements. Because eye movements of the participant were slow, we changed the time window for classification from originally 1000 to 2000 ms during the process of testing (see Table 1 for an overview of the applied parameters).

To increase the number of possible selections to 5 we presented the letters A, B, C, D and E. To increase the discriminability of the letter recordings (the letters D and E sounded similar), we later asked the daughter of the participant to record the letters F, G, H, I and J in Norwegian. These letters were played in random order and the participant was instructed to respond with eye movements to the target letter. On day 2, we facilitated the task by playing the letters in alphabetical order. On both days, the feedback consisted of the chosen letter that was played after a short signal tone. Selection of one letter took 22.5 s with one sequence. On day three we asked the participant to spell few words with a two-step procedure. First, we asked the participant to select a group of letters (A-E, F-J, K-O, P-T or U-Y) and in the second step the target letter within the chosen group. The groups of letters and letters within the chosen group were each coded by the spoken numbers 1 to 5. Therefore, he had to respond to the number 1 and after a short break of 7.5 s to the number 3 to select the letter “C”. To facilitate the task for the participant, the assignment of groups of letters and numbers (e.g., during the first step A, B, C, D, E = 1; during the second step A = 1) were presented to the participant on a sheet of paper.

Table 1 Parameters used and selections made during the measurements

	Session	Sequences	Possible choices	Selections
EOG				
Day 1				
- control signal: looking to the left and back to the center				
- one electrode placed next to the outer canthus of the left eye				
- 1000 ms classification window				
	Training	*10*	*2*	*2 runs*
	1.1	1	2	6
- classification window changed to 2000 ms				
	1.2	1	2	14
	Training	*- data from 1.2 used to train new classifer*		
	1.3	1	2	5
	1.4	1	5 (A, B, C, D, E)	5
-voice recording by daughter				
	1.5	1	5 (F, G, H, I, J)	15
- added second electrode (next to canthus of right eye)				
- new control signal: looking to the right and back to the center				
	1.6	1	5 (F, G, H, I, J)	10
Day 2				
- stimulus presentation in alphabetical order				
- 1500 ms classification window				
	Training	*3*	*5 (F, G, H, I, J)*	*1 run*
	2	1	5 (F, G, H, I, J)	19
Day 3				
	Training	*3*	*5 (F, G, H, I, J)*	*15*
- two step procedure to select letter group and target letter				
	3.1	1	5(25)letters A to Y	12
	3.2	2	5(25)letters A to Y	12
	3.3	2	5(25)letters A to Y	4
Eye Tracker				
Day 2				
	2	1	2	38
BCI				
Day 2				
	Training	*20*	*2*	*8 runs*
	2.1	10	2	3
	2.2	7	2	3
Day 3				
	Training	*20*	*2*	*6 runs*
	3.1	20	2	2
	3.2	7	2	3
	3.3	10	2	6
Day 4				
- classifier from day 3 applied				
	4.1	20	2	4
- data from 4.1 added to data from day 3 to train new classifier				
	4.2	10	2	4

Feedback about the chosen group and letter was provided acoustically after every step. Selection for one step took 25 s, hence the time needed to spell one letter was 50 s with this paradigm.

Eye tracking

Eye movements were recorded with a Tobii EyeX Dev Kit (Tobii Technology, Sweden) that is based on the principle of corneal reflection tracking. The eye tracker was attached to a metal post using a flexible holder and positioned in front of the user such that the eyes could be recognized by the system (see Fig. 1). The area above the eye tracker (corresponding to a screen size of 1680×1050 pixels) constituted the area in which the gaze point could be determined. We ensured that this area was within the participant's field of view. To calibrate the system, we asked the participant to follow the predefined movements of a pen that we held in his field of view. To allow for a comparison with the EOG, we chose looking to the left or right as control signal. Similar to the procedure for the EOG, the letters "A" and "B" were played over speakers (one sequence). Before each run, the user was asked to respond to one of the two. If "A" was the designated target, the user was asked to look to the left and for "B" to the right. The gaze point was determined at the end of each sequence. During free runs we asked the user to respond to either of the two stimuli and asked him afterwards which selections he had aimed for. Stimulus duration was set to 1 s and the inter-stimulus interval to 1.5 s. Between sequences of letters there was a pause of 3 s in which the user was instructed to look straight ahead and during which he received acoustic feedback. A voice recording saying "left" or "right" was played depending on the determined position of the gaze point (in the left or right half of the field of view). Including the time for feedback, 8 s were needed for one selection.

Auditory BCI

During BCI use, the EEG was recorded with 16 active Ag/AgCl electrodes mounted in an elastic fabric cap and positioned at FC3, FCz, FC4, C3, Cz, C4, CP5, CPz, CP6, P3, Pz, P4, PO5, Poz, PO6 and Oz according to the modified 10–20 system of the American Electroencephalographic Society [41]. A ground electrode was positioned at AFz

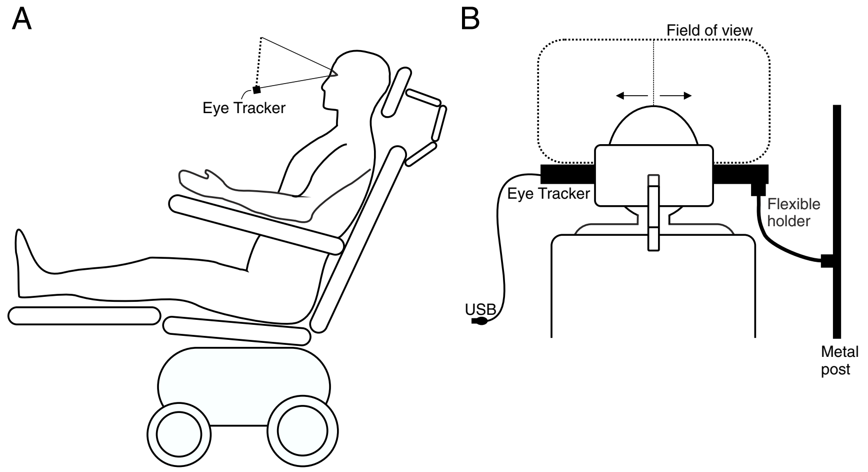

Fig. 1 Schematic figure depicting the position of the eye tracker in front of the user. Lateral view (**a**) and rear view (**b**). The user's fixation point could be determined in the area above the eye tracker. The fixation point was determined as being either in the left or right half of this area and thus, the user could make a binary choice

and the data was referenced to an electrode clipped to the right earlobe. The EEG was amplified with a g.USBamp (g.tec, Austria) and sampled at 256 Hz. A notch filter around 50 Hz and a bandpass filter between 0.1 and 30 Hz were applied. Auditory stimuli were presented over circumaural headphones (Sennheiser HD 280 pro, Germany).

The task consisted of a three stimulus oddball paradigm as suggested for binary BCI communication by Halder et al. [26]. Three different tones were presented in random order: A high pitched target tone with a frequency of 1000 Hz, a low pitched target tone of 100 Hz and a standard tone which consisted of pink noise. One sequence consisted of three standard stimuli and the two target tones. All stimuli had a duration of 80 ms and the stimulus onset asynchrony was 1000 ms. The participant was instructed which target tone to attend to before each run. He was asked to focus on the appearance of that tone and silently count whenever it sounded and ignore all other tones. To acquire data to train the classifier, 20 sequences were played per training run. Stepwise linear discriminant analysis [40] was applied to determine features and feature weights for online selections with the BCI. During these online runs, the number of sequences was reduced and the user received feedback according to the classifier results. Hence, the time needed for one selection depended on the number of sequences (e.g., with 10 sequences: 50 s plus 2 s for feedback).

Questionnaire

At the end of testing, after the fourth session, we presented a summary of the achieved performance and the general advantages and disadvantages for each of the tested systems to the participant (similar to the ones summarized in Table 2). To gather his feedback, we then asked him the same set of questions for all three systems. The questions are listed below. We started with the questions about the EOG and ended with

Table 2 Characteristics of the tested systems

	EOG	Eye Tracker	BCI
Allows communication independent of the caregiver	yes	yes	yes
Enables muscle-independent communication	no	no	yes
Speed of communication	medium	fastest	slowest
Commercially available			
• Hardware	yes	yes	yes
• AT software and support	no	yes	no
Costs	medium	lowest	highest
Burden on the caregiver	medium	lowest	highest
Applications	communication	communication	communication (binary)

the set of questions for the BCI. The participant answered all questions with his conventional communication method (partner scanning approach with eye movements).

- How difficult/easy was it for you to control the EOG/eye tracking/EEG(BCI) based system, on a scale from 0 to 10 (if 0 = very difficult and 10 = very easy)?
- How tiring was using the EOG/eye tracker/BCI for you, on a scale of 0 to 10 (if 0 = not tiring at all and 10 = extremely tiring)
- How long (hours/minutes) do you think you would be able to use it before you would need a longer break?
- Given that your current method of communication still works, would you consider using EOG/eye tracking/BCI as an additional communication method?
  If no, which are the obstacles of use?
  If yes, what would be the most important improvement?
- Would you consider using the EOG/eye tracking/EEG(BCI) based system if your current AT system was no longer working?
  If no, which are the obstacles of use?
  If yes, what would be the most important improvement?

Results

Performance

The participant was able to control the EOG, eye tracking and BCI based system. Figure 2 shows the performance comparison for all tested systems across all sessions.

With the EOG based system the user reached above 70 % accuracy with the two choice paradigm on the first day, but had difficulties with five selections on the same day. When we presented the 5 letters in alphabetical order on day two, he reached an accuracy of 79 %. On day 3, we introduced the two step procedure that theoretically allowed him to choose any letter of the latin alphabet except the Z. He reached 100 % accuracy in session 3.2 in which we asked him to spell two 3 letter words (12 selections in total), but two sequences (stimulus repetitions) were needed. In session 3.3 the user tried to spell a word of his choice, but stopped after the third attempt (fourth selection), because he could not concentrate on the target sounds necessary to select the desired letters (unable to recall the position in the spelling tree).

With the eye tracking based system all selections were classified correctly. However, placing the eye tracker in front of the user in a way that the system could recognize the reflections of the light source on his cornea and in his pupil was difficult. Set-up and calibration took about 20 min. The user had difficulties looking in a particular direction; therefore we facilitated the task for the first 12 selections, by holding a pen above the eye tracker within the designated target half to help him fixate. For the remaining selections, in which the user could choose the side he wanted to look to, we asked him to only make small eye movements to either of the sides. The system still identified all intended selections correctly.

With the auditory BCI, the study participant reached accuracies above 70 % on all three days of testing. To reach this threshold, 10 or 20 sequences were needed during online selections. Exemplary EOG and EEG traces are provided as Additional files 1 and 2.

User feedback

Figure 3 depicts a comparison of the user ratings regarding the ease of use and the operator fatigue for all systems. The user indicated that he would not consider any of the tested systems as an additional method of communication, although he estimated that he could use the EOG for about 2 h, the eye tracker for 4 h and the BCI for about 1 h before he would need a longer break. The obstacles of use for the EOG system were the strong eye movements required for the system to work and he stated that it was unlikely that the system would be able to detect movements that could not also be detected by the caregiver. Although the eye tracking system would allow him to communicate independent of the caregiver, he expressed a clear preference for the partner scanning based approach. The only system that he would consider using if he was no longer able to control his current method, was the BCI. He did not think that the other systems could help him in that case. He considered the ease of use of the BCI as the highest among the tested systems, but also rated it as the most tiring.

Discussion

The study demonstrated that a person in the locked-in state can gain control over an EOG based system, an eye tracker and an auditory BCI for binary communication with satisfactory accuracies (>70 % correct). Nevertheless, the participant expressed a preference for his low-tech method of communication over the tested systems and did not consider using them as an additional method. The only system that he would consider as a communication aid is the BCI, in case the partner assisted scanning approach (with a letter board based on eye movements) was no longer working.

The focus of this case study was on testing possible input signals that could be implemented to control AAC devices, rather than providing ready-to-use communication applications. Due to the study design with only one

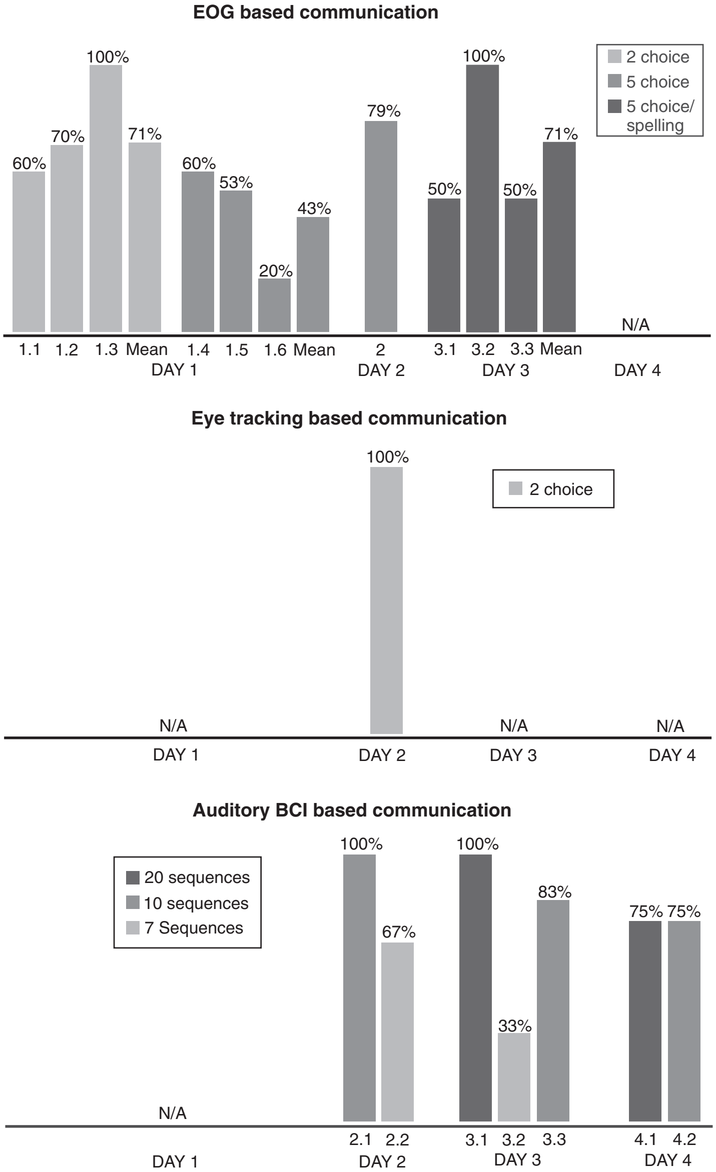

Fig. 2 Online selection accuracies for all tested systems and sessions. The mean accuracies for the EOG based system were calculated by weighting the depicted accuracies by the number of selections made. Starting from day 2, stimuli were presented in alphabetical order for the EOG based system and in session 3.2 and 3.3 two sequences were used instead of one. Please refer to Table 1 for a detailed listing of the applied parameters and selections made in each session

participant, it is important to stress that generalization to the general population of persons in LIS is not possible. The iterative process of tailoring the different technologies to the participant's needs prevented us from comparing them in terms of assistive efficacy. Therefore, we will discuss in detail the results obtained for the participant and only briefly address the potential of each system as AAC device with references to other studies.

An overview of the main features of the tested systems is provided in Table 2. In the following, we will discuss the results obtained with each system and considerations for future work.

Electrooculogram

The participant rated the ease of use of the EOG lowest. The main reason was the relatively strong horizontal eye

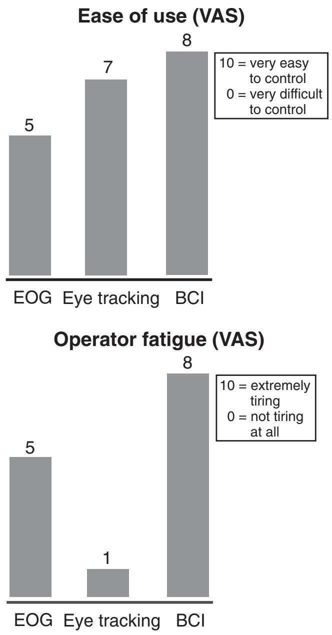

Fig. 3 User ratings (VAS) of fatigue and ease of use for the tested systems

movements required that were strenuous for the participant. While it was therefore not an option for the participant as an input signal for AAC, it could be a good option for some users. For instance, Kaufmann et al. [8] showed that lifts of the eyelid of their study participant with LIS could reliably be classified and used for spelling of words after a short calibration phase.

Eye tracking

The participant of the current study rated the eye tracker as the least tiring of the tested systems. A similar result was obtained by Pasqualotto et al. [23], who could show that the workload of an eye tracker was lower than that of a P300 BCI. Although an eye tracking based system would allow for communication independent of the caregivers or even control of technical devices (e.g., a TV or radio), the participant of our study did not consider it as an additional communication method. The participant had full-time care and with most caregivers and family members, who we met during the study, he had achieved a high speed of communication. This was mostly due to the familiarity of the caregivers and the participant. Hence, the communication partners could suggest letters or words based on their personal knowledge about the participant and based on the context or topic of the conversation. They could also react flexibly to his ability to move the eyes and adapt the partner scanning approach accordingly. This level of flexibility and efficiency would be difficult to reach with an eye-tracking based system. Another reason for his preference of the low-tech method may have been that during the partner assisted communication method there is a direct interaction between the user and the interlocutor.

Despite the demands on the communication partners, the spontaneous face-to-face conversation mode was reported by caregivers to be the most frequent with persons with ALS in a study by Fried-Oken et al. [42]. Similarly, in a study by Spataro et al. [6] half of the study participants, who had an eye tracking system available, communicated regularly with a letter board. Further, there is evidence that these low-tech methods are predominant for persons with most severe levels of disability (e.g., persons in the locked-in state) [5, 6, 43]. Nevertheless, for those persons with no residual motor control except eye movements, it is often the only (commercial) method to gain access to AAC. Studies including persons with late-stage ALS could show an improvement in the quality of life for persons using an eye tracking system, a high satisfaction with the system for most participants and a reduced burden on caregivers [6, 44–46]. Shortcomings frequently reported are difficulties operating under a range of changing light and postural conditions, determining the optimal dwell time and technical support required [5, 43, 47, 48].

Brain-computer interfaces

In this study we tested an auditory ERP-BCI with simple to understand instructions ("please listen to the high/low pitched tone") that would allow for binary communication [26]. The participant achieved a satisfactory level of control. He rated the ease of use as the highest of the tested systems, but also described it as the most tiring. These ratings suggest that the ease of use was rated as high since no muscle movements were required, but that the attentional demands were substantially higher for the BCI compared to the other systems. Due to the deafness of his right ear, we could not test a streaming approach as suggested by Hill & Schölkopf [29, 30] that requires dichotic listening. For a person with intact hearing, a streaming approach could substantially speed up the selection rate. Another improvement could be to replace the beep sounds by more natural sounds, such as recordings of yes or no [28, 31].

For persons with long attention spans and sufficient cognitive abilities, auditory multi-class BCIs could provide spelling solutions (e.g., [33–38]). With training, a satisfactory level of control could be achieved [49, 50]. Tactile ERP-BCIs could be an option for persons who are unable to control auditory BCIs [8, 24].

In case all voluntary muscular activity is lost, i.e., in the complete locked-in state, communication based on recordings of brain-activity might still be possible. Brain-computer interfaces enabled severely paralyzed persons, even users in the locked-in state, to communicate [17, 18, 51, 52]. However, only few reports on communication attempts with persons in the complete locked-in state exist [53, 54]; see [17] for an overview) and only one reported significantly above chancel level performance [55].

Considerations for future work

Brain-computer interfaces could prove valuable for participants in situations when the preferred method is not operable due to muscular fatigue among others. For these situations, a robust and simple to operate BCI is needed, particularly for those users, who usually rely on low-tech partner assisted communication such as the participant of this study. For persons, who use more advanced AT such as an eye tracker, a complementary or hybrid approach could ease the transition to a purely BCI based AT if control over all muscles is lost (i.e., in CLIS caused by a neurodegenerative disease). Recently hybrid BCIs (hBCIs) were proposed that consist of a combination of one or more conventional AT input devices or biosignals and at least one BCI channel (for a review of the state-of-the-art see [56]). Although case studies demonstrated the feasibility of long-term independent home use of BCIs, [21, 22, 57], usability has to be improved before BCIs be considered as assistive technology for a larger group of persons. To achieve this goal, it is important to engage the potential end-users during all steps of the development process from the definition of user requirements to the implementation and the iterative testing of prototypes [58]. Measures to operationalize usability for the evaluation of BCIs were proposed by [21, 59, 60] among others.

Conclusions

We demonstrated that a person in the locked-in state was able to gain control over an EOG, an eye tracker and an auditory brain-computer interface. Due to the end user's and his caregivers' proficiency in using a low-tech communication method based on residual eye movements, he did not consider using the tested systems as an access method to AAC. He would consider using a BCI once control over his eye muscles will be no longer possible.

BCIs can extend the range of available access methods and the combination with existing assistive technology should be considered. A user-centered design approach in the development of these systems will increase the likelihood that they will be used as assistive technology in daily life. For persons with severe paralysis, who could benefit from a BCI (immediately or in the future), solutions tailored to the users' individual needs are required and thus, the engagement of targeted end-users in all steps of the development process is needed as requested by the user-centered design [58].

Additional files

Additional file 1: Figure S1. Average EOG traces for the training run on day 3. The task of the participant consisted of looking to the right and back to the center in response to the target letter. (PDF 18 kb)

Additional file 2: Figure S2. Averaged ERP waveforms at Cz; and scalp plot of differential ERP activity (targets minus non-targets) at the peak latency of the P300 for session 2.1. (PDF 88 kb)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IK and SH conducted the experiments. SH modified the software for stimulus presentation and control with the eye tracker. IK analyzed the data and drafted the manuscript. SH and AK helped to draft the manuscript. IK, SH and AK conceived of the study, IK and SH participated in its design and coordination. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank the participant and his family for their support and patience during the evaluation of the systems and Tobias Kaufmann for his help during the planning of this study. The study was funded by the European ICT Program Project FP7-288566. This publication was funded by the German Research Foundation (DFG) and the University of Würzburg in the funding program Open Access Publishing. This paper only reflects the authors' views and funding agencies are not liable for any use that may be made of the information contained herein. SH received funding as International Research Fellow of the Japan Society for the Promotion of Science and the Alexander von Humboldt Foundation.

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Received: 20 May 2015 Accepted: 27 August 2015
Published online: 04 September 2015

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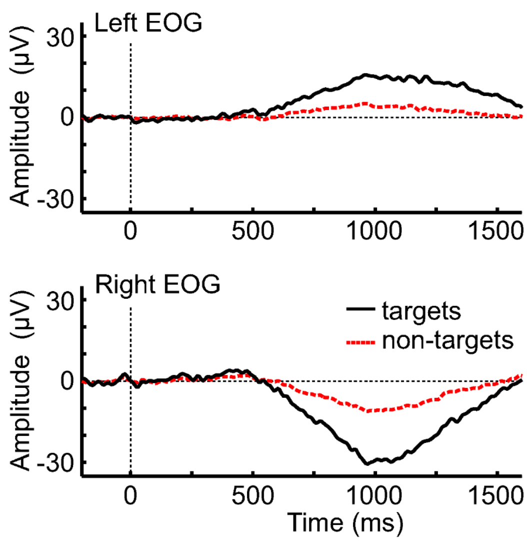
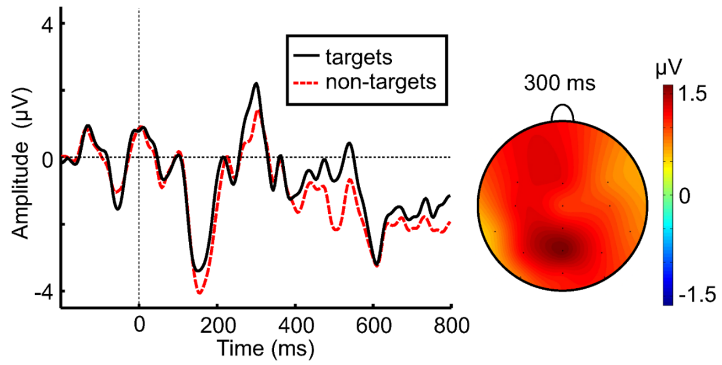
Supplementary Material



Additional file 1: Figure S1. Average EOG traces for the training run on day 3. The task of the participant consisted of looking to the right and back to the center in response to the target letter.



Additional file 2: Figure S2. Averaged ERP waveforms at Cz; and scalp plot of differential ERP activity (targets minus non-targets) at the peak latency of the P300 for session 2.1.

3 Discussion

The primary aim of this dissertation was to advance brain-computer interfaces based on event-related potentials such that they can eventually be used as assistive technology for communication by persons with severe paralysis. The five conducted studies of this thesis focused on BCIs utilizing visual or auditory stimuli. Thereby addressing the necessity for BCIs based on non-visual modalities, while also demonstrating and exploiting the advantages of the widely investigated visual paradigm.

The first study demonstrated the robustness of the visual ERP-BCI and its users maintained a satisfactory level of control despite constant distraction. Furthermore, neurophysiological markers of high mental workload and fatigue were identified, which could be used for future applications (chapter 2.1). The second study demonstrated that high information transfer rates can be achieved with a visual speller using a head-mounted display and it could therefore be a suitable display option for persons in the locked-in state for situations in which mounting a conventional monitor is difficult (chapter 2.2). The two studies which aimed at improving auditory multiclass BCIs were successful. All but one healthy study participant was able to control the implemented BCI within the first session and, for the first time, potential end users gained control over an auditory BCI for spelling with training (chapters 2.3 and 2.4). The fifth study furthered understanding of the needs of persons in the locked-in state by evaluating an auditory BCI for binary communication and eye-gaze dependent input methods with a person in LIS (chapter 2.5).

In this section, the main findings and their implications are discussed. In particular, the prospects of using ERP-based visual and auditory BCIs as assistive technology in daily life are addressed and suggestions on how to further improve the systems are presented.

3.1 Robustness of a visual ERP-BCI and detection of mental states

With a conventional visual ERP-BCI for spelling, a satisfactory performance could be achieved despite constant distraction in the form of background noise and long operation (Käthner et al., 2014b). This result demonstrated the robustness of the ERP-BCI and is promising for home use, where distraction is inevitable. During long-term use, a BCI that automatically adapts to the mental state of the user (e.g. pauses if high mental workload is detected) is desirable. This would be of particular interest for persons who mainly rely on brain-activity to control assistive technology and who cannot easily convey their mental state. For these users, it would be advantageous if the mental state could be inferred from EEG signals that are recorded during BCI use. As a first step in this direction, we were able to identify neurophysiological markers of mental workload and fatigue by experimentally manipulating these mental states in a controlled study (see chapter 2.1). A range of behavioral measures confirmed that the manipulation was successful.

The study revealed indicators of mental workload and fatigue in the time and frequency domain of the EEG on the group level. In order to serve as reliable indicators of mental workload or fatigue during operation of an ERP-BCI, indicators need to be consistent across individuals. Furthermore, it remains to be investigated if these markers are reliable enough to be implemented in a practical application for persons, who would most benefit from the technology. Gathering clean EEG data in a home environment can be challenging and it is likely that the signals differ for persons with disease compared to healthy controls.

Within this thesis, the detection of mental states was proposed to improve the usability of an ERP-BCI. Beyond the use in "traditional" BCIs, there are many other potential applications for systems that infer the mental state of the user from neurophysiological data. For instance, monitoring the user's mental state in environments where low alertness/attention can have severe consequences (e.g. air traffic control, driving a car, surveillance services) might lead to safety improvements (Brookings et al., 1996; Kohlmorgen et al., 2007). As another example, determining the cognitive load could help during learning tasks by adapting levels of difficulty according to the user's state (Gerjets et al., 2014). Many other usage scenarios were proposed and a variety of cognitive and affective states have been shown to be reflected in neurophysiological signals (see Frontiers Research Topic "Using neurophysiological signals that reflect cognitive or affective state" edited by van Erp, Brouwer & Zander, 2015). The term 'passive BCI' was coined to describe a system in which the user is not actively performing a mental task in order to achieve voluntary control over a device, but the ongoing brain activity is recorded in order to enhance an application (Zander et al., 2008; Zander & Kothe, 2011). Current commercially available applications do not yet meet high scientific standards and if and how they benefit the user is unclear (Brouwer et al., 2015). Regarding the detection of mental workload, using features of the EEG seems to be the most promising approach. The EEG performed best compared to other physiological variables (skin conductance, respiration, ECG, pupil size, eyeblinks) during offline classification in a recent study by Hogervorst et al., (2014). The same conclusion has previously been drawn for indicators of alertness (for a review see Lal & Craig, 2001).

Alternative methods have been previously proposed to prevent false positive selections with an ERP-BCI. The classic ERP speller operates in a synchronous mode, i.e. a selection is exectuted following a specified number of stimulus repetitions, which can lead to false positive selections. Asynchronous approaches aim to detect the attentional state and either refrain from a selection if the user is not paying attention to the stimuli or to adapt the number of stimulus repetitions according to the detected state (Aloise et al., 2011). For instance, Pinegger et al. (2015) proposed a method that could differentiate between a control and non-control state with an accuracy of 95% in their offline study. They utilized information from the frequency domain to determine if the users were fixating their gaze on the stimuli and combined it with a statistical analysis of the classifier output. For a practical application, they suggested that the detection of a predefined number of non-control states would pause the system and the user would have to select a specific element in the matrix twice in a row to restart the system.

A variety of methods have been suggested that do not depend on eye gaze in order to dynamically adjust the number of stimulus repetitions and to reduce the time needed for selections and the number of false positive selections. With these methods a selection is executed as soon as the likelihood for a correct decision reaches a predefined threshold. Schreuder et al. (2013b) systematically compared the performance of several methods and concluded that they are generally beneficial and the best performance was achieved by the algorithms proposed by Zhang, Guan and Wang (2008), Höhne et al. (2010), and Lenhardt, Kaper and Ritter (2008).

To conclude, the detection of mental states through the identification of markers in the EEG is a promising approach that should be further explored. It could have many applications in the field of traditional and passive BCIs and is, therefore, of interest for a wide target population. In the case of BCIs for communication, it could help to adapt to the mental state of users who are unable to convey their mental states overtly. Currently, there are other options for asynchronous BCIs available which might serve as a practical alternative until the detection of mental states with EEG has been further developed.

3.2 Usability of a visual BCI with a head-mounted display

The attempt to use a virtual-reality headset as an alternative display option for healthy users and a person in the locked-in state for spelling with an ERP-BCI was successful. The head-mounted display (HMD) allowed healthy users to achieve the same performance (94%) as with a conventional monitor, while using only three stimulus repetitions. The low resolution of the tested virtual reality headset did not allow face stimuli to be dispayed, as initially proposed by Kaufmann et al. (2011, 2013); therefore, rows and columns were overlaid with smileys during the stimulation. These have previously been shown to elicit the face-specific N170 component (Sagiv & Bentin, 2001) - a finding that we could confirm within our study (Käthner, Kübler & Halder, 2015a; chapter 2.2). Due to the salient stimulus material that improved the signal-to-noise ratio of the data, high ITRs could also be achieved during online spelling with one flash sequence using the HMD (single trial analysis of the EEG). In this condition, healthy participants achieved an average bit rate of 32 bits/min (64%) and approximately half of the participants spelled with ≥70% accuracy. This is equivalent to a rate of 9.91 letters spelled correctly per minute. This in turn is a value that the majority of potential users (59%) would find satisfying according to the survey among persons with ALS by Huggins, Wren & Gruis (2011). The maximum bit rate achieved by an individual participant in our study was 72 bits/min (100% accuracy) and was in the range previously reported with invasive recording methods, such as ECoG (Brunner et al., 2011; Speier, Fried & Pouratian, 2013).

Following the proof-of-principle step with healthy users, the headset was tested with an 80-year-old woman, who was in the locked-in state due to ALS. She could only communicate with horizontal eye-movements. After two unsuccessful attempts to gain control over an ERP-BCI with a conventional monitor, she achieved 100% spelling accuracy with the HMD, albeit with ten sequences. While the HMD has the advantage of always displaying the stimuli in the field of view of the user, communication via eye movements is no longer possible when wearing the headset. In the current state, the HMD has some additional disadvantages that might decrease usability, such as wearing comfort or low resolution. Hence, we concluded that the HMD is particularly suited to establish a first communication when applying an ERP-BCI to a person in the LIS and a conventional display could still be advantageous for long term use (Käthner, Kübler & Halder, 2015a).

Within the study, we also exploited an additional feature of the virtual reality headset (gyroscope) with healthy participants. It allowed them to focus on individual letters via head movements, such that they filled their field of view, thereby increasing the salience of target stimuli. However, in this condition classification accuracies were not increased compared to the other display conditions, probably due to a ceiling effect. In the future, features of virtual reality headsets, such as accelerometers and gyroscopes, could improve the usability of BCIs for persons with motor impairments by exploiting residual movements of the user. For instance, different control elements could be displayed depending on the head position. Furthermore, creating virtual environments and enabling control over these environments via a BCI is already highly motivating for users and it might become an important tool for persons with disabilities (Bayliss, 2003; Leeb et al., 2006).

3.3 Auditory BCIs for communication

BCIs based on non-visual modalities were proposed to include those users who do not have sufficient vision or control over eye movements to operate a visual ERP-BCI (for a review see Riccio et al., 2012). Within this doctoral dissertation, important advances towards the applicability of auditory BCIs as communication aids for persons with severe paralysis were made (chapters 2.3 and 2.4). It was demonstrated that healthy users could achieve high information transfer rates within the first session with the implemented multiclass BCI (3.29 bits/min; 77% accuracy) and that these rates increased further in the second session, in which all users achieved above a 70% spelling accuracy (mean: 90%, 4.23 bits/min). This is an improvement compared to the study by Käthner et al. (2013) and this indicates that the increases in bit rate could mainly be attributed to changes in the stimulus material (Simon et al., 2015). Rows and columns of the auditory speller were coded with animal sounds instead of brisk artificial tones. By applying the paradigm to persons with motor impairments, we could show, for the first time, that potential end users could gain control over auditory multiclass BCIs (Halder, Käthner & Kübler, in press). The study highlighted the importance of training with this type of BCI, in particular for end users. Three of the five users enrolled in the study learned to spell with the BCI. For those users, bit rates increased from 0.15 bits/min (9%) in the first session to 5.12 bits/min (84%) in the fifth and the maximum bit rates achieved by two participants were 5.78 bits/min, which equals a letter selection every 35 seconds. Taking into account all users, mean ITRs in the fifth session were 3.08 bits/min. Although this is an increased rate compared to other auditory multiclass BCI studies with potential end users (Kleih et al., 2015: 1.33 bits/min; Kübler et al., 2009 and Schreuder et al., 2013a: no bit rate reported, accuracy below 50%), it is below the average ITR achieved after training in the fifth session by healthy participants (5.6 bits/min; Baykara et al., in press). However, it must be considered that the comparability across studies is limited due to the different degrees of functional impairments of the study participants and the small sample sizes. Nevertheless, the results presented in chapter 2.4 are promising since the average bit rates of all end users are in the range of those previously reported for healthy users with other auditory spelling paradigms (Höhne et al., 2011: 3.4 bits/min; Schreuder et al., 2011: 2.84 bits/min).

The animal sounds employed in this dissertation are particularly suited as stimulus material because they have natural characteristics and are highly distinguishable despite a short presentation time. Stimuli were played in rapid succession in order to allow for a high bit rate. Participants reported that it was initially difficult to discriminate the individual tones, but that it became easier to differentiate between and focus on the target tones with training. The improved performance with training was represented in an increased amplitude of the P300 for those users who gained control. Apart from this stimulus-specific training effect, adaptation to the task could also have contributed to the improved performance (Simon et al., 2015).

The proposed auditory multiclass BCI has the disadvantage that it requires a substantial amount of attention and imposes a high workload on the user. Subjectively experienced workload in Simon et al. (2015) was similar to the values reported in Käthner et al. (2013) for the auditory speller and almost twice as high compared to the visual speller tested in that study. A proposed solution to further improve the speller and to reduce the workload of the end user is to adapt the speller to the needs of the individual user. This could include individualized timing parameters and creating a set of adequate stimuli that users could choose from according to their preferences (Halder, Käthner & Kübler, in press; Simon et al., 2015). In order to facilitate the memorization of the assignments of stimuli to rows and columns of the matrix, the content of the matrix could be adapted to match the letter/communication boards that are possibly already in use for a partner based scanning approach. This has not been tested and it remains to be shown that the proposed auditory speller can be operated without any visual aids or auditory cues.

Binary auditory BCI approaches generally have lower workload requirements and can be reliably operated with easy to understand instructions (Hill & Schölkopf, 2012; Riccio et al., 2012). However, the advantages are likely to diminish if one would implement a spelling solution based on a binary approach. If, for instance, it was based on a spelling tree, for which several steps have to be completed in order to select the desired letter, the user would have to remember the current step and error accumulation would be a further impediment. Hence, binary auditory BCIs are better suited for an initial communication attempt in the acute phase of LIS for persons with a limited attention span (Hill & Schölkopf, 2012).

Other multiclass BCI studies that proposed intuitive spelling solutions yielded low accuracies (Höhne & Tangermann, 2014) or bit rates (Kleih et al., 2015) compared to the paradigm evaluated in the present thesis.

Auditory BCIs promise to allow for muscle-independent communication in a state of complete paralysis. Unfortunately, none of the published studies, including the work presented in this thesis, could demonstrate that communication is reliably possible with a BCI for a person in the complete locked-in state and few attempts have been reported (Gallegos-Ayala et al., 2014; Hinterberger, Birbaumer & Flor, 2005; De Massari et al., 2013; Murguialday et al., 2011; Naito et al., 2007; Wilhelm, Jordan & Birbaumer, 2006). For persons with neurodegenerative diseases, Kübler and Birbaumer (2008) suggested that it might be possible to retain BCI control in CLIS if it has been learned before entering this state. A problem that has not yet been accounted for by BCIs is the fact that LIS is often accompanied by a some sort of disorder of consciousness (DOC) in the acute phase following a pontine stroke or in the late stage of ALS (Kübler & Kotchoubey, 2007). Previous attempts to apply auditory BCIs as communication aids to persons with DOC have not been successful (Halder, Käthner & Kübler, 2014; Pokorny et al., 2013).

Also, further improvements are necessary in order to allow the most severely paralyzed persons to gain control over an auditory BCI, such as reducing the workload, dealing with DOC and increasing the ease of use. The studies of this dissertation are an encouraging step towards the goal of auditory BCIs being used as assistive technology (AT) by persons in need for muscle-independent communication. They highlight the importance of training with end users and, again, demonstrate that the choice of the stimulus material is a crucial factor in the design of practical BCIs (Höhne et al., 2012; Höhne & Tangermann, 2014; Kaufmann et al., 2011, 2013; Lopez-Gordo et al., 2012).

In a subsequent study, Herweg et al. (2015) performed an evaluation of a tactile ERP-BCI with a group of elderly participants within five sessions. In the fifth session, participants achieved an information transfer rate of 20.73 bits/min (96%), thereby far exceeding the mean values previously reported in online studies. This suggests that training might not only play an important role for BCIs based on auditory, but also for BCIs based on tactile stimuli.

3.4 Usability of communication aids in the locked-in state

To answer the question as to how an auditory BCI compares to gaze dependent input methods to AAC, a study with a participant in the locked-in state was conducted. At the time of the study, the 55-year old man had been in the locked-in state for 6 years due to amyotrophic lateral sclerosis. His only means of communication was a partner assisted scanning approach with a letter board. He indicated the desired letters with residual eye movements and a twitch of his eyebrow. He, his family members and most of his caregivers had achieved a level of proficiency that allowed them to communicate effectively. Due to a deterioration in his ability to move his eyes, he and his family were searching for an alternative method of communication. In our study we were able to adjust the parameters of an EOG, an eye tracker and an auditory BCI system to allow for communication in an iterative process that conformed to the user's needs. Despite his ability to gain control over all three systems (≥70% accuracy) within a relatively short time he expressed a preference for his low-tech communication method. The main reason for this preference compared to the other gaze-dependent input methods (EOG, eye tracking) was that his interlocutors could detect more subtle eye movements and react flexibly to his ability to move the eyes. Thus, only the auditory BCI, as a muscle-independent communication system, was an option for him in case the partner assisted scanning approach would no longer be feasible. The evaluated auditory BCI required a substantial amount of attention for a single, binary choice. For that reason he rated the auditory BCI as the most tiring, although he judged the ease of use as the highest among the tested systems. We had tested a binary auditory BCI, as suggested by Halder et al. (2010) and which could be operated with simple to understand instructions, nevertheless, it was not suited for his use in daily life because the low-tech method was more convenient, faster and could be operated without the need for technical skills or additional equipment other than a cardboard letter frame. As revealed by a survey by Fried-Oken et al. (2006), the face-to-face conversation mode with AAC was the most frequent for caregivers and persons with ALS and in the study of Lugo et al. (2015) all respondents (members of ALIS) used a yes/no communication system based mainly upon eye-movements. It is therefore likely that the direct social interaction with the interlocutors is valued, despite the time required for the message generation and the burden on the caregivers. Our study participant did not have a strong desire for AAC devices, such as an eye tracking system or an EOG, that he could operate independently from his caregivers, probably due to the good service provided. For him and persons in similar situations, it is crucial that they receive access to BCIs once the partner-dependent method is no longer feasible. These BCI systems cannot rely on the visual system and must be easy to operate. Depending on the user's capabilities, these could rely on auditory or tactile stimulation as discussed above. In the case study with a participant in the LIS by Kaufmann, Holz & Kübler (2013), a tactile BCI yielded better results as compared to an auditory BCI (data analysed offline) and the participant could reliably make selections with lifts of her eyelid detected via EOG. These findings highlight the importance of tailoring AAC solutions to the users' capabilities and needs. For many users who would like to access AAC and have sufficient control over eye movements, eye tracking can provide a fast method that reduces the burden on the caregivers and allows access to all kinds of computer programs, such as word processing and internet browsers (Beukelman et al., 2007; Spataro et al., 2014). The investigation by Pasqualotto et al. (2015) with 12 severely motor impaired persons revealed that an eye tracker outperformed the visual ERP-BCI tested in the study: The eye tracker obtained a higher ITR and usability score and the subjectively experienced workload was lower. Therefore, in most cases the use of an eye tracker will probably be more advantageous than the use of a visual BCI. Nevertheless, in some situations, the use of a hybrid BCI solution could be valuable. These hybrid BCIs consist of a combination of different BCI control signals (e.g. SMR, SSVEP) or at least one BCI channel and assistive technology based on other input methods, e.g electromyography (EMG), a joystick or eye tracking (for reviews see Amiri, Fazel-Rezai & Asadpour, 2013; Millán et al., 2010; Pfurtscheller et al., 2010). For instance, users who have residual muscular control could exploit this as a control channel and switch to a BCI if no control via the preferred method is possible, for instance due to muscular fatigue. Millán et al. (2010) speculated that once control over all motor activity is lost for persons with progressive neurodegenerative diseases, the use of a hybrid BCI that combines standard AT with a BCI could ease the transition to a BCI as a sole input. To increase the likelihood that BCIs conform to user requirements, target users should be included in all steps of their design and implementation (Zickler et al., 2009) and user feedback should be collected during the evaluation of prototypes (Holz et al., 2015; Riccio et al., 2011, Zickler et al., 2011, 2013). For this user-centered design process of BCIs several measures were proposed to operationalize usability (for a review see Kübler et al., 2014).

In this thesis the focus was exclusively on BCIs intended as communication aids for persons with most severe paralysis. To meet user requirements, BCIs should allow control over other applications, such as web browsers, wheelchairs, prostheses or orthoses, and over the environment, as requested by persons with a wide range of motor impairments (Huggins, Wren & Gruis, 2001; Zickler et al., 2009).

3.5 Conclusions and Outlook

Over the last two decades, the research field of brain-computer interfaces has made substantial progress toward the practical applicability of BCIs as communication aids. Nevertheless, BCIs are currently rarely used as assistive technology by persons in need for muscle-independent communication. This dissertation contributed substantially to advance the practical applicability of both visual and auditory BCIs based on ERPs for persons with severe paralysis. The successful transfer of an auditory BCI that allows for spelling from the laboratory to potential end users is one key achievement in the context of this thesis. For the first time persons with motor impairments gained control over an auditory multiclass BCI. This was possible by changing the stimulus material and by conducting training with end users (see chapters 2.3 and 2.4). Performance improvements through changes in the stimulus material have recently been shown for visual BCIs by Kaufmann et al. (2011; 2013) and the importance of the choice of the stimuli for auditory BCIs was also stressed in previous studies (Höhne et al., 2012; Höhne & Tangermann, 2014; Lopez-Gordo et al., 2012). Within the studies of this dissertation, stimuli that were highly distinguishable despite a short presentation time allowed for information transfer rates in the range of the highest that have been previously reported for multiclass BCIs in online studies. However, the conducted studies are only one step further for the development of practical non-visual BCIs as their successful control by persons in the complete locked-in state has not yet been demonstrated. This remains the most urgent and complicated challenge.

For persons with neurodegenerative diseases who still have residual control over eye muscles and sufficient vision, ERP-BCIs based on visual stimuli could prove invaluable. They allow to achieve higher accuracies and information transfer rates compared to BCIs based on non-visual modalities. In the present thesis, the robustness of a visual speller could be demonstrated and satisfactory accuracies could be achieved despite constant distraction in the form of background noise (chapter 2.1). To improve the applicability for persons in the locked-in state, a commercial virtual reality headset was tested as an alternative display option (chapter 2.2). The evaluation revealed that it might be particularly suited to re-establish communication with persons in the LIS in situations where mounting a conventional monitor is difficult or not feasible. Moreover, virtual reality-headsets offer possibilities that should be further explored as severely paralyzed users could benefit from them. For healthy users speed of character selection using the headset was in the range deemed acceptable by the majority of persons with ALS interviewed in a telephone survey (Huggins, Wren & Gruis, 2011). However, this selection speed could not be achieved by the person in the LIS. Therefore, further improvements are necessary.

The field of BCI research will likely benefit greatly from hard- and software developments in the future, such as the development of portable and wireless EEG amplifiers and comfortable, small and inconspicuous electrodes (Bleichner et al., 2015; Debener et al., 2012; De Vos et al., 2014; Looney et al., 2012), or through the implementation of novel algorithms for performance optimization, such as dynamic stopping methods, methods for continuous unsupervised adaptation, auto complete functions for text input, and the creation of intuitive user interfaces that can be operated after little training by non-experts (Höhne et al., 2011; Kindermans et al., 2014a, b; Schreuder et al., 2013b). In this thesis, a BCI was proposed that adapts to the mental state of the user by detecting neurophysiological markers of high mental workload or fatigue in the EEG. As a first step, markers were identified on the group level (chapter 2.1). Inferring the mental state of the user from neurophysiological data could be advantageous for various tasks and situations as discussed above and by Zander & Kothe (2011).

It is important to stress that performance with a BCI does not only depend on technical aspects of the system, but also on the user and his psychological and physiological state. Instructions prior to training, feedback and the application can influence these states (Kübler et al., 2011). Therefore, apart from technical developments, psychological aspects must not be neglected during the implementation and testing of BCIs. This includes providing adequate instructions and designing effective paradigms and training protocols. As an example, the provided feedback plays an important role during BCIs based upon operant conditioning, such as SMR-BCIs, for which the modulation of sensorimotor rhythms has to be learned (Sollfrank et al., 2015, in press). It was demonstrated that a rich visual representation of the EEG signal in a virtual environment can be highly motivating (Leeb et al., 2006) and motivation was also enhanced during multimodal feedback (Sollfrank et al., in press). Motivation in turn can positively influence BCI performance for SMR- and ERP-BCIs (Kleih et al., 2010; Nijboer, Birbaumer & Kübler, 2010). Moreover, it was repeatedly shown that the type of stimuli, timing parameters and modality of the presentation influence performance and that optimal settings differ between users (Höhne & Tangermann, 2012; Käthner et al., 2013, 2015b; Kaufmann et al., 2011, 2013; Sellers et al., 2006).

A prerequisite for user satisfaction is that BCI technology conforms to user requirements. Hence, the development and design of BCIs should follow a user-centered approach (Kübler et al., 2014). In this context, studies with persons in the locked-in state, such as the one presented in chapter 2.5, that compare BCI technology and conventional input methods to AAC are of importance to clarify users' needs and to identify the best available communication aids for persons with severe paralysis. The combination of BCIs and standard assistive technology was proposed to offer users a wide range of input methods that can be used according to situational user preferences and ease the transition to solely BCI controlled applications for persons with neurodegenerative muscular disorders (Millán et al., 2010).

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Affidavit

I hereby confirm that my thesis entitled *Auditory and visual brain-computer interfaces as communication aids for persons with severe paralysis* is the result of my own work. I did not receive any help or support from commercial consultants. All sources and / or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation *Akustische und visuelle Gehirn-Computer Schnittstellen als Kommunikationshilfen für Menschen mit schweren Muskellähmungen* eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Ort, Datum

Unterschrift

APPENDIX B: FULL REFERENCE TO PUBLICATIONS THAT WERE A RESULT OF THIS THESIS

2015

- Halder, S., **Käthner, I.**, Kübler, A. (in press). Training leads to increased auditory brain-computer interface performance of end-users with motor impairments. *Clinical Neurophysiology*. doi: 10.1016/j.clinph.2015.08.007

- **Käthner I.**, Kübler, A., Halder, S. (2015). Comparison of eye tracking, electrooculography and an auditory brain-computer interface for binary communication: a case study with a participant in the locked-in state. *Journal of NeuroEngineering and Rehabilitation*, *12*: 76. doi: 10.1186/s12984-015-0071-z

- **Käthner, I.**, Kübler, A., Halder, S. (2015). Rapid P300 brain-computer interface communication with a head-mounted display. *Frontiers in Neuroscience*, *9*: 207. doi: 10.3389/fnins.2015.00207

- Simon, N., **Käthner, I.**, Ruf, C. A., Pasqualotto, E., Kübler, A., Halder, S. (2015). An auditory multiclass brain-computer interface with natural stimuli: Usability evaluation with healthy participants and a motor impaired end user. *Frontiers in Human Neuroscience*, *8*: 1039. doi: 10.3389/fnhum.2014.01039

2014

- **Käthner, I.**, Wriessnegger, S.C., Müller-Putz, G.R., Kübler, A., Halder, S. (2014). Effects of mental workload and fatigue on the P300, alpha and theta band power during operation of an ERP (P300) brain-computer interface system. *Biological Psychology*, *102*, 118-129. doi: 10.1016/j.biopsycho.2014.07.014

APPENDIX C: APPROVAL OF A "DISSERTATION BASED ON SEVERAL PUBLISHED MANUSCRIPTS"

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Graduate School
Life Sciences

Approval of a "Dissertation Based on Several Published Manuscripts"

for the doctoral researcher

Ivo Käthner

(Name)

who has accomplished a publication record significantly above average as documented in the attachment.

The **Section Speakers and the Thesis Committee** therefore approve a "Dissertation Based on Several Published Manuscripts".

The **Thesis Committee** additionally confirms that the doctoral researcher has fulfilled all requirements of the GSLS program "life science".

Thesis Committee

Supervisor	Name	Date	Signature
1	Prof. Dr. Andrea Kübler	24.8.15	
2	Prof. Dr. Stefan Debener	11.9.15	
3	Prof. Dr. Erhard Wischmeyer	25.8.15	
4 (if applicable)			

Section Speakers

Speaker	Name	Date	Signature
1	Prof. Dr. Michael Sendtner	7.10.2015	
2	Prof. Dr. Paul Pauli	9.10.15	
3 (if applicable)	Prof. Dr. Esther Asan	8.10.2015	

APPENDIX D: STATEMENT ON INDIVIDUAL AUTHOR CONTRIBUTIONS

"Dissertation Based on Several Published Manuscripts"

Statement of individual author contributions and of legal second publication rights

(if required use more than one sheet)

Publication (complete reference): Käthner, I., Wriessnegger, S.C., Müller-Putz, G.R., Kübler, A., Halder, S. (2014). Effects of mental workload and fatigue on the P300, alpha and theta band power during operation of an ERP (P300) brain-computer interface system. *Biological Psychology*, *102*, 118-129.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design	IK	SH	AK		
Data Collection	IK				
Data Analysis and Interpretation	IK	SH	AK		
Manuscript Writing	IK	AK	SH	SCW	GRMP

Explanations (if applicable):

Publication (complete reference): Käthner, I., Kübler, A., & Halder, S. (2015). Rapid P300 brain-computer interface communication with a head-mounted display. *Frontiers in Neuroprosthetics*, *9*, 207.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design	IK	SH			
Data Collection	IK	JR	SH		
Data Analysis and Interpretation	IK	AK	SH		
Manuscript Writing	IK	SH	AK		

Explanations (if applicable): Johanna Räderscheidt (JR) helped during data acquisition

Publication (complete reference): Simon, N., Käthner, I., Ruf, C. A., Pasqualotto, E., Kübler, A., & Halder, S. (2015). An auditory multiclass brain-computer interface with natural stimuli: Usability evaluation with healthy participants and a motor impaired end user. *Frontiers in Human Neuroscience*, *8*, 1039.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design	NS	IK	CAR	SH	
Data Collection	NS				
Data Analysis and Interpretation	IK	NS	SH	CAR	AK
Manuscript Writing	IK	NS	SH	AK	CAR & EP

Explanations (if applicable):

Publication (complete reference): Käthner, I., Kübler, A., & Halder, S (2015). Comparison of eye tracking, electrooculography and an auditory brain-computer interface for binary communication: A case study with a participant in the locked-in state. *Journal of NeuroEngineering and Rehabilitation*, *12*: 76.

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design	IK	SH			
Data Collection	IK	SH			
Data Analysis and Interpretation	IK	SH	AK		
Manuscript Writing	IK	SH	AK		

Explanations (if applicable):

APPENDIX D: STATEMENT ON INDIVIDUAL AUTHOR CONTRIBUTIONS

Publication (complete reference): Halder, S., Käthner, I. & Kübler, A. (in press). Training leads to increased auditory brain-computer interface performance of end-users with motor impairments. *Clinical Neurophysiology*.					
Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design	SH	IK			
Data Collection	IK	SH			
Data Analysis and Interpretation	SH	IK	AK		
Manuscript Writing	SH	IK	AK		

I confirm that I have obtained permission from both the publishers and the co-authors for legal second publication.

I also confirm my primary supervisor's acceptance.

Ivo Käthner

___

Doctoral Researcher's Name Date Place Signature

APPENDIX E: CURRICULUM VITAE

For reasons of data protection, the curriculum vitae is not published in the electronic version.

APPENDIX E: CURRICULUM VITAE

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