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Abstract

A brain-computer interface (BCI) is a system that directly translates brain activity into control signals for external devices. Within this thesis, novel electroencephalogram (EEG)-based BCI solutions are explored with the aim to provide a means of communication for non-responsive patients. The term "non-responsive patients" refers to patients suffering from disorders of consciousness (DOCs) like minimally conscious state (MCS) or vegetative state/unresponsive wakefulness syndrome (VS/UWS), who show no or only minimal behavioral signs of awareness but have preserved some level of covert consciousness and communication abilities.

In the tactile domain, BCI approaches based on steady-state somatosensory evoked potential (SSSEP) and tactile P300 were developed. As a basic requirement to realize a tactile BCI in non-responsive patients, a stimulation device for EEG measurements in clinical environments was developed. When applying an SSSEP-based paradigm to MCS patients, results were found to be largely inconclusive for various reasons. Therefore, in order to not rely on SSSEPs alone, a hybrid BCI was designed which integrates P300 potentials into a typical SSSEP-based BCI setup, making such a BCI potentially applicable to a broader range of subjects or patients. In this way, interaction effects between different types of combined stimulation signals could be demonstrated, revealing new insights which may be important for the future development of hybrid BCIs.

In the auditory domain, the paradigm transition from healthy subjects to minimally conscious patients using an auditory P300 paradigm based on tone stream segregation was demonstrated. In healthy subjects promising results could be reached while in MCS patients none of the results were sufficient for communication purposes. Nevertheless, signs of consciousness were detected in many patients after averaging all available data segments, making this paradigm an important complementary tool to support bedside clinical assessment of non-responsive patients.

The BCIs developed within this thesis therefore contribute to the range of novel methods described in literature and extend the range of potential tools for bedside assessment and communication with DOC patients.

Kurzfassung

Eine Gehirn-Computer-Schnittstelle (brain-computer interface; BCI) ist ein System, das die Gehirnaktivität direkt in Kontrollsignale für externe Geräte umwandelt. Im Rahmen dieser Dissertation wurden neuartige, Elektroenzephalogramm (EEG)-basierte BCI-Lösungen mit dem Ziel erforscht, eine Kommunikationsmöglichkeit für nicht-responsive Patienten herzustellen. Der Begriff "nicht-responsive Patienten" bezeichnet Personen, die an einer Bewusstseinsstörung leiden und sich im Wachkoma – im minimal-bewussten Zustand (minimally conscious state; MCS) oder vegetativen Zustand (vegetative state; VS) – befinden, und die keine oder nur minimale Anzeichen von Bewusstsein zeigen, jedoch über gewisse verborgene Kommunikationsfähigkeiten verfügen.

Im taktilen Bereich wurden BCI-Lösungen basierend auf stationären somatosensorisch evozierten Potentialen (steady-state somatosensory evoked potentials; SSSEPs) sowie taktilem P300 entwickelt. Als Grundvoraussetzung zur Realisierung eines taktilen BCI für nicht-responsive Patienten wurde ein Stimulationsgerät für EEG-Messungen im klinischen Umfeld entwickelt. Ein SSSEP-basiertes Paradigma wurde anschließend mit MCS-Patienten getestet, die Ergebnisse waren jedoch aus vielfältigen Gründen nicht eindeutig. Um sich daher nicht allein auf SSSEPs zu verlassen, wurde ein hybrides BCI entwickelt, welches P300-Potentiale in ein typisches SSSEP-basiertes BCI-Setup integriert, um ein solches BCI für eine breitere potenielle Zielgruppe an Personen anwendbar zu machen. Auf diese Weise konnten Wechselwirkungen zwischen verschiedenen Arten von kombinierten Stimulationssignalen nachgewiesen werden, wodurch neue Einblicke, welche wichtig für die zukünftige Entwicklung von hybriden BCIs sind, gewonnen werden konnten.

Im auditorischen Bereich wurde die Überleitung eines auditorischen P300-Paradigmas basierend auf Tonserien von gesunden Probanden zu MCS-Patienten demonstriert. Während bei gesunden Probanden vielversprechende Ergebnisse erzielt werden konnten, war bei MCS-Patienten keines der Ergebnisse für Kommunikationszwecke ausreichend. Allerdings konnten in vielen Patienten nach der Mittelung aller verfügbaren Datensegmente Anzeichen von Bewusstsein gefunden werden, wodurch dieses Paradigma ein wichtiges, ergänzendes Hilfsmittel zur klinischen Untersuchung von nicht-responsiven Patienten am Krankenbett darstellt.

Die im Rahmen dieser Dissertation entwickelten BCIs stellen somit einen wichtigen Beitrag zu den neu in der Literatur beschriebenen Methoden dar und erweitern die Menge der potentiellen Hilfsmittel zur Untersuchung von sowie Kommunikation mit nicht-responsiven Patienten.

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Acronyms

ALS	amyotrophic lateral sclerosis
BCI	brain-computer interface
c-VEP	code-modulated visual evoked potential
CRS-R	JFK Coma Recovery Scale-Revised
CSP	common spatial pattern
DOC	disorder of consciousness
DTI	diffusion tensor imaging
ECG	electrocardiogram
ECoG	electrocorticogram
EEG	electroencephalogram
EMG	electromyogram
EOG	electrooculogram
ERD	event-related desynchronization
ERP	event-related potential
ERS	event-related synchronization
FES	functional electrical stimulation
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
FOUR	Full Outline of UnResponsiveness
GCS	Glasgow Coma Scale
HMM	hidden Markov model
HPC	harmonic phase coupling
HSD	harmonic sum decision
ICA	independent component analysis
LDA	linear discriminant analysis
LIS	locked-in syndrome
MCS	minimally conscious state
MEG	magnetoencephalogram
MMN	mismatch negativity
NN	neural network
PET	positron emission tomography
SCP	slow cortical potential
SEP	somatosensory evoked potential
SMR	sensorimotor rhythm
SNR	signal-to-noise ratio
SSAEP	steady-state auditory evoked potential
SSEP	steady-state evoked potential
SSSEP	steady-state somatosensory evoked potential
SSVEP	steady-state visual evoked potential

SVM support vector machine
TMS transcranial magnetic stimulation
UCD user-centered design
UWS unresponsive wakefulness syndrome
VEP visual evoked potential
VS vegetative state

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1. Introduction

1.1. Disorders of Consciousness

In recent years, the number of patients who survive severe brain injuries has considerably increased due to significant improvements in intensive care and resuscitation techniques [90, 203]. While some patients recover through different stages and eventually regain consciousness, many of them remain in one of different states known as "disorders of consciousness" (DOCs) [84, 86, 90, 203], such as coma, vegetative state (VS)[1], and minimally conscious state (MCS).

DOCs pose severe challenges regarding diagnosis, prognosis, potential treatments, daily care, and ethical considerations. Clinical assessment of such patients is difficult and typically relies on subjective interpretation of observed behavior, which is reflected in a high rate of misdiagnoses between states, and even a confusions in terminology [14, 48]. However, advances in the research on DOCs continuously contribute to a better understanding of the underlying mechanisms in order to improve diagnosis and therapeutic choices, and may even provide key insights about the nature of human consciousness itself [84, 203].

The normal human consciousness is typically characterized by two main components, arousal and awareness [86, 90]. Arousal (also referred to as vigilance, alertness, or wakefulness) defines the global level of responsiveness to environmental stimuli, ranging from different stages of sleep to wakeful states of high arousal. During sleep for example, only strong stimuli will elicit a response whereas during high arousal states, even weak stimuli are sufficient to elicit a response. Different subcortical structures, such as the thalamus, brainstem, and basal forebrain play an important role in maintaining and controlling sleep-wake cycles and the overall level of arousal [155, 246].

Awareness [86, 90] can be seen as the ability of conscious, intentional perception of specific internal or external stimuli, and the motivation to act on such stimuli that have entered conscious awareness. Awareness can be subdivided into awareness of the environment and awareness of oneself. Awareness of the environment is characterized by the conscious perception of one's environment through different sensory modalities. Awareness of oneself refers to internal processes that are not dependent on external stimuli, such as mind-wandering,

[1] In 2010, the neutral descriptive term "unresponsive wakefulness syndrome" (UWS) was suggested as new name for VS [145]. Within this thesis, the term VS/UWS is used to keep consistency with most literature.

mental imagery, but also knowledge of one's social and cultural background. While the level of arousal is related to the overall activity in the brain, conscious awareness is a more dynamic process which is assumed to depend on complex interactions between the cortex and thalamic nuclei [156, 266].

The different aspects of consciousness cannot be regarded on their own but they depend on each other [86, 90]. For example, a person needs to be awake to be aware, but not the other way round. But also awareness can have an influence on arousal, when for example an alarm goes off, the level of arousal will be increased. Moreover, in high arousal states, awareness can be directed to one sensory modality at the expense of others. In general, normal states of consciousness require some overall level of arousal, sensory processing, and intention. DOCs can results from injuries at any of these levels, resulting in a continuum of different states of consciousness. Figure 1.1 illustrates the continuum of the various states of consciousness, including anesthesia, deep and light sleep, conscious wakefulness, and DOCs like coma, VS/UWS, and MCS.

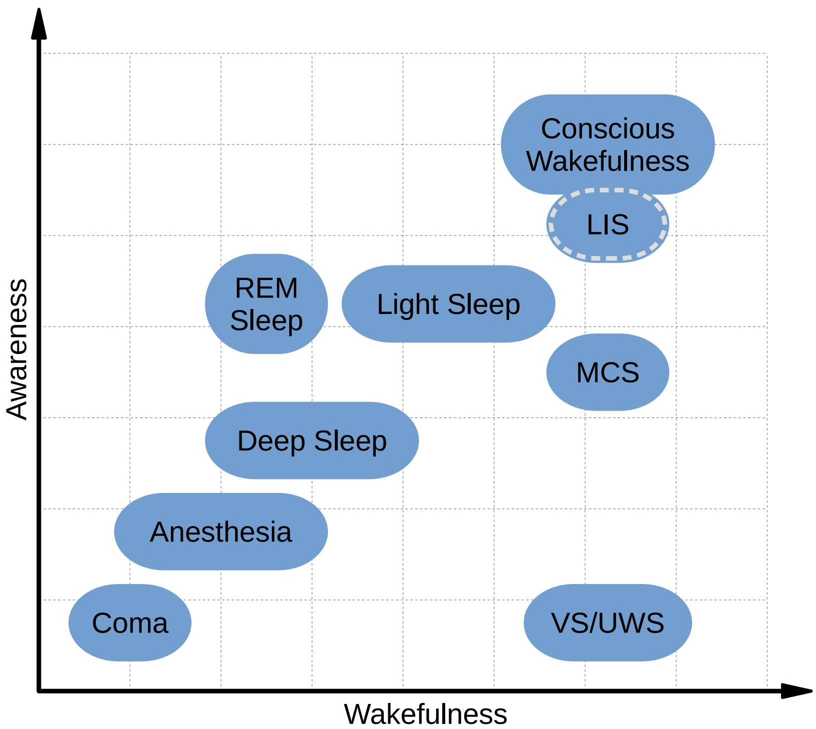

Figure 1.1.: Continuum of the various states of consciousness, including anesthesia, deep and light sleep, conscious wakefulness, and DOCs like coma, VS/UWS, and MCS (adapted from [90]).

In general, DOCs result from acute traumatic or non-traumatic (e.g., stroke, anoxia) brain injuries after which patients fall into coma first [90]. Some of these patients may open their eyes but remain unresponsive, meaning that they have entered VS/UWS. Typically, VS/UWS patients gradually recover awareness, evolving into MCS and eventually fully regain consciousness. However, some patients may also remain in VS/UWS or MCS for several months or even years. One special condition which is not a DOC is the so-called locked-in syndrome (LIS) in which patients awake from coma with intact consciousness, but are unable to move or communicate. LIS patients typically have only minimal residual communication abilities through eye movements. In the following subsections, the definitions and typical characteristics of the different states of consciousness and DOCs can be found.

1.1.1. Coma

Coma [84, 86, 90, 203] is a DOC which most commonly follows severe brain injuries, such as diffuse, bihemispheric lesions of the cortex or underlying white matter, bilateral thalamic damage, or focal brainstem lesions. Coma is characterized by the complete loss of arousal. Comatose patients lie with eyes closed and fail to respond to even vigorous stimulation [230]. No sleep-wake cycles are present and patients are assumed to have no awareness of themselves or their environment. Only reflexive, stereotyped movements may be present in response to noxious stimulation. The cortical metabolism is typically reduced to 50-70 % of the normal range [141]. Most survivors recover within 2-4 weeks, but many of them will remain in VS/UWS or MCS [203].

1.1.2. Vegetative State/Unresponsive Wakefulness Syndrome

The VS/UWS (in German: "Apallisches Syndrom") was first characterized by the Austrian neurologist Franz Gerstenbrand in 1967 [78]. The English term "persistent VS" was then described in 1972 by Jennett and Plum [110] and later refined by the Multi-Society Task Force on PVS [188]. More recently, "unresponsive wakefulness syndrome" (UWS) was presented as new name for the pejorative term "vegetative state" [145] and is a condition of wakeful unconsciousness [84, 86, 90, 203]. Unlike coma, the VS/UWS is characterized by cycles of eyes-opened and eyes-closed periods. Patients may show a wide range of reflexive, non-purposeful movements, but they show no evidence whatsoever of language comprehension or expression, or of voluntary purposeful responses to visual, auditory, tactile, and noxious stimuli [188]. Patients suffering from VS/UWS are awake, but they do not show any signs of awareness of themselves or their environment. No eye tracking of moving objects or their image in a mirror is present. Basic brainstem functions typically are intact and are involved in eye opening and in maintaining an overall level of arousal. In general, the VS/UWS may results from different types of structural injuries [86]: (i) Diffuse cell loss in cortex and thalamus, caused for example by global hypoxia [3], (ii) diffuse axonal injury, which is a widespread damage to axons in the subcortical white matter, resulting from traumatic brain injuries [2], and (iii) extensive damage to the upper brainstem and thalamus, caused for example by basilar artery stroke. All these cases are characterized by a loss of corticothalamic function, caused either from cell death, disconnection, or loss of brainstem drive.

In the VS/UWS, the cerebral metabolic rate for glucose is typically reduced by 50 % or more compared to age-matched healthy controls [152, 265]. Comparable reductions in global metabolism have been observed in healthy controls during general anesthesia [7] and slow-wave sleep [164]. In some patients, activation of brainstem and primary sensory areas, without activation of higher sensory or association areas, were reported in response to auditory [138] and noxious [140] stimuli. Moreover, residual processing in cortical and subcortical islands of preserved metabolism, together with isolated fragments of behavior may be present [247].

The VS/UWS may be a transitional state when recovering consciousness, or a chronic condition. After three month following a non-traumatic brain injury, or after twelve month following a traumatic brain injury, the VS/UWS should be regarded as permanent, as the chances for recovery are very small [189]. Nevertheless, even after much longer time periods, patients may show signs of recovery in exceptional cases.

1.1.3. Minimally Conscious State

The MCS [84, 86, 90, 203] is a relatively new diagnostic category and is a transitional state across the continuum of the different states of consciousness. The MCS usually follows coma and VS/UWS when gradually recovering consciousness or may reflect progressive decline in neurodegenerative diseases, while some patients may also permanently remain in an MCS. The MCS is defined as condition of severely altered consciousness which is characterized by minimal but clear evidence of awareness of oneself or the environment [82]. As in VS/UWS, the appearance of sleep-wake cycles by cycles of eyes-opened and eyes-closed periods is present. While patients in VS/UWS only show reflexive movements, patients in an MCS may demonstrate a wide range of behaviors, such as simple command-following, intelligible speech, verbal or gestural yes-no responses, or other non-reflexive, purposeful movements. Moreover, emotional behaviors, such as smiling or crying, and tracking a mirror, persons, or objects may be observed. Since responses are inconsistent, meaning that clear signs of volitional behavior can be observed in one examination, but not in another, it may be difficult to distinguish MCS from VS/UWS. However, such a distinction is important since the prognosis for recovery is significantly better in MCS than in VS/UWS. Patients have emerged from MCS once they consistently and reliably demonstrate functional interactive communication and/or functional use of at least two different objects [82].

In MCS, the overall cerebral metabolism is reduced by more than 50 % of normal values, which is in the same range as in VS/UWS [142]. MCS is typically caused by similar injuries as VS/UWS, such as diffuse cortical damage, thalamic damage, or diffuse axonal injury, but with sufficient residual cortical activity and connectivity between cortex, thalamus, and brainstem to support some level of responsiveness [111, 139]. In many patients, an activation of higher-order association areas similar as in healthy controls can be observed in response to sensory stimuli, indicating that widely distributed cortical systems and higher-order integrative processes may remain intact [30, 248]. However, fluctuations in responsiveness may indicate an underlying inability to consistently maintain integrative functions [86].

1.1.4. Locked-In Syndrome

The LIS [84, 90, 203], also known as pseudocoma, is not a DOC but a rare condition in which patients are fully aware of themselves and their environment but completely paralyzed and unable to move or speak [12, 143, 230]. While oral or gestural communication is impossible, limited eye movements and blinking are typically spared, so that eye-based communication and environmental control may be possible.

Most common cause is a lesion in the brainstem disrupting the efferent pathways, leaving sensation, consciousness and cognition intact. In most cases, the etiology is vascular, but in rare cases it can also be traumatic. Since the loss of almost any motor behavior may be erroneously attributed to disturbances in consciousness, LIS may often be mistaken for VS/UWS. Making a diagnosis even more difficult, LIS may be mutually associated with VS/UWS or MCS, meaning that patients who initially were in VS/UWS or MCS in the acute stage may subsequently evolve into LIS when recovering consciousness [73].

1.2. Brain-Computer Interfaces

A brain-computer interface (BCI) [9, 26, 132, 172, 281] is a system that directly translates brain activity into control signals for external devices. Bypassing the normal muscular output pathways, a BCI can provide a means of communication and control for persons who have lost their motor functions due to a severe neurological disease or injury. Especially for individuals in a complete LIS, a BCI may be their only way to communicate with the external world.

As depicted in Figure 1.2, a typical BCI system [26, 42, 132, 281] is composed of the following components. As input to the BCI, brain signals from the user are acquired in real-time. Brain signals can be recorded non-invasively or invasively [102]. One common way to non-invasively record brain activity is to use electroencephalogram (EEG) signals [22] recorded from the scalp. Other non-invasive methods that may be used for BCI purposes include magnetoencephalogram (MEG) [118, 169], functional magnetic resonance imaging (fMRI) [259, 277], and functional near-infrared spectroscopy (fNIRS) [53, 260]. Invasive methods are typically based on electrocorticogram (ECoG) [151, 241]

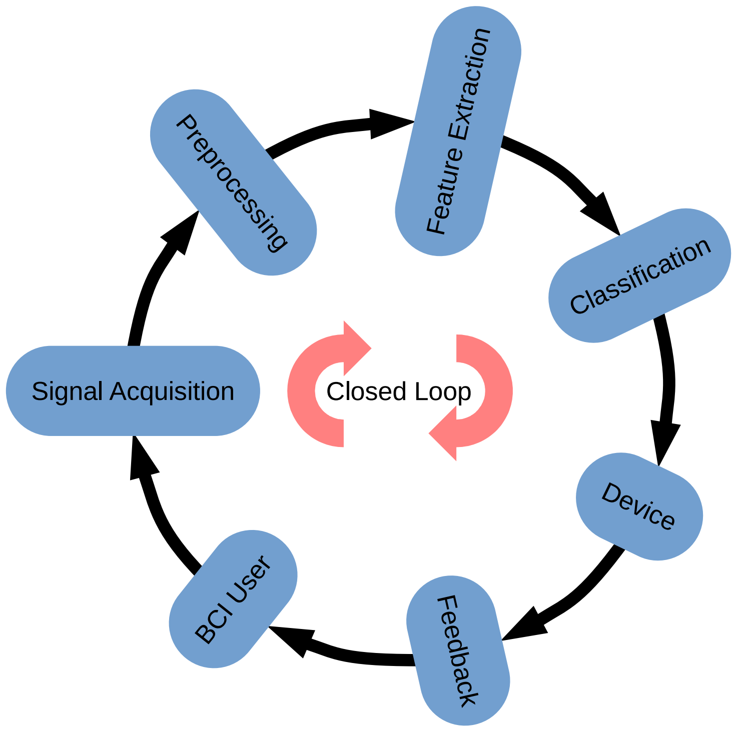

Figure 1.2.: Schematic representation of a typical brain-computer interface. Brain signals from the BCI user are acquired in real-time and preprocessed. Predictive features are extracted and by means of a classifier translated into output signals to control some external device. The BCI output is then fed back to the user.

or intracortical microelectrodes [50, 103, 104, 122, 199]. ECoG electrodes are implanted on the surface of the brain either outside (epidural) or under (subdural) the dura mater, while intracortical microelectrodes are implanted under the surface of the brain. After signal acquisition, the recorded signals are preprocessed (e.g., filtered), and predictive features which represent the user's intent are extracted from the preprocessed signals. Different types of time-domain and/or frequency-domain features may be extracted, depending on the user's mental task which is used to operate the BCI. The next stage of the BCI is to translate these extracted features into output signals to control an external device or software program. Usually, this is done by means of a classifier which is trained to classify the signal features into one of two or more response classes. Since the brain signals are non-stationary and subject to trial-to-trial and subject-to-subject variability, machine learning methods are usually required for feature selection and classification in a robust way [177]. In order to concentrate the discriminative information relevant for classification, different transformation based on neurophysiological knowledge (e.g., frequency or spatial filtering), supervised learning (e.g., common spatial pattern; CSP), or unsupervised learning (e.g, independent component analysis; ICA) can be applied [176]. Commonly used classifiers for BCI applications involve linear discriminant analysis (LDA), support vector machines (SVMs), neural networks (NNs), hidden Markov models (HMMs), and Bayesian classifiers [17, 159]. Importantly, the output from the BCI is fed back to the user who should learn in this way to develop or maintain a good correlation between signal features and his or her intent. Usually, there is a training phase at the beginning where no feedback is provided to the user. The data from this training phase are required to select useful signal features and to train a first classifier, which can be adapted later on, in a supervised way. So the BCI is a closed-loop system where the successful operation depends on the interaction between two adaptive controllers, the BCI and the user's brain.

The first BCI was developed in the 1970s by Jacques Vidal [272] using visual evoked potentials (VEPs) to control the movement of a symbol on a screen [273]. Nowadays, a variety of brain signals that can voluntarily be controlled by the user have successfully been used to realize a BCI. In general, three fundamental classes of BCIs can be distinguished [132]: (i) BCIs that make use of operant learning of certain brain responses, (ii) BCIs that rely on specific mental operations, and (iii) BCIs that are based on responses to specific sensory stimuli.

In the first class of BCIs, users are trained to self-regulate certain target EEG signals, such as the slow cortical potential (SCP) amplitude [25] or the μ rhythm (8-12 Hz frequency band) amplitude [279]. Even self-control of the action potential firing rate of single neurons, invasively recorded with electrodes within the cortex, can be learned and used to operate a BCI [122]. In all these cases, successful learning of self-regulation of EEG activity or other physiological parameters that usually cannot be perceived consciously depends on three elements [132]: (i) real-time feedback of the EEG activity, (ii) positive reinforcement of correct behavior, and (iii) an individual training schedule with progressively more demanding tasks.

The second class of BCIs is based on the assumption that mental tasks, such as motor imagery [213, 167], evoke reproducible EEG patterns that can be detected by the BCI. In the third class of BCIs, EEG patterns in response to specific external stimuli the user focuses attention on, such as P300 potentials [63, 70] or steady-state evoked potentials (SSEPs) [234], are detected and used for the selection of communication symbols. No sophisticated learning procedures are usually required in these classes of BCIs.

In the next subsections, the types of BCIs and brain signals that are most commonly used to realize a BCI are described in more detail.

1.2.1. Slow Cortical Potential

SCPs [27, 25, 101, 281] are slow voltage changes generated in the cortex which occur over 0.5-10 s. Healthy subjects [100] as well as severely paralyzed patients [28] can learn to self-regulate their SCPs, i.e. to voluntarily produce positive or negative potential shifts when provided with proper feedback of their SCPs. Typically, negative SCPs are associated with increased neuronal activity, whereas positive SCPs reflect decreased cortical activation [237]. Based on the self-regulation of SCPs, a BCI referred to as "thought translation device" [29, 131] was developed which allowed locked-in patients diagnosed with amyotrophic lateral sclerosis (ALS) to communicate by selecting letters on a screen. A language supporting program with dichotomic spelling structure, meaning that one letter was selected based on a series of two-choice selections (half/quarter/etc. of the alphabet), was used for this purpose. The thought translation device could even provide access to the Internet, allowing patients to communicate worldwide [29]. In order to increase the autonomy of the patients, a stand-by mode was developed so that they could switch the BCI on and off without external assistance [113]. Due to the slow nature of SCPs, communication rates are usually very limited (0.15-3.0 letters per minute with two-choice accuracies of 65-90 % [281]), and weeks or months of feedback training are required until a stable and sufficiently high accuracy is reached. Despite this low communication rates, SCPs have proven to be useful for patients who cannot use conventional assistive technologies for communication.

1.2.2. Sensorimotor Rhythm

The sensorimotor rhythm (SMR) is the rhythmic brain activity recorded over the sensorimotor cortex [287]. More specifically, the μ rhythm refers to the EEG activity in the 8-12 Hz frequency band recorded over primary sensory or motor cortical areas in awake people when not engaged in sensory processing or motor output [212, 281]. The μ rhythm is thought to be an idling activity produced by thalamocortical circuits. Depending on location, frequency, and relationship to sensory input or motor output, different μ rhythms exist. Usually, they are associated with β rhythms (18-26 Hz frequency band) which are either harmonics of the μ rhythms or may represent independent EEG features [212, 215, 167].

During movement or movement preparation, a decrease in μ and β rhythms contralateral to the movement can be observed. Such a power decrease in the μ and β frequency bands is referred to as event-related desynchronization (ERD) [211, 212, 281]. In contrast, a power increase in these frequency bands after movement or with relaxation is referred to as event-related synchronization (ERS) [210, 212, 281]. Such ERD/ERS phenomena do not require actual movements but also occur with motor imagery [213], and are therefore suitable to realize a BCI. Such a BCI relies on the assumption that specific EEG frequency patterns associated with different imagery tasks (e.g., left/right hand or foot movement) can be distinguished and encode different commands [214]. For example, such a BCI allows a user to control a cursor on a screen [217, 280], or an orthotic [216] or functional electrical stimulation (FES) [218] device for movement restoration. Also severely disabled patients suffering from cerebral palsy [198] or ALS [134] can operate such a BCI with accuracies of 70 % and higher.

Typically, in an initial training session, a motor imagery paradigm is selected for the user. The EEG is recorded over the sensorimotor cortex, and subject-specific frequency features are extracted and used for classification. The classifier is trained to predict from the EEG which action the user is imaging, and translates motor imagery into continuous or discrete output presented as feedback to the user. The classifier is then adjusted between daily sessions. After 6-7 sessions, classification accuracies over 90 % are possible, and around 90 % of people can successfully use such a system [281].

Not only movement-related imagery tasks, but also other mental tasks, such as mental arithmetics, geometric figure rotation, mental letter composing, word association, visual counting, spatial navigation, or auditory imagery may results in distinct EEG frequency patterns [58, 69, 74, 119]. Communication can be established by detecting which of the tasks a user is performing. However, the information throughput in such a BCI is rather low, since switching between mental tasks and identifying mental tasks via EEG are both slow processes [9].

1.2.3. P300 Potential

The P300 potential is a positive component of the event-related potential (ERP) with a peak latency of about 300 ms which usually occurs in response to uncertain or rare stimulus events [63, 66, 263]. The P300 is an endogenous ERP, so it largely depends on behavioral and psychological processes related to the event rather than on the physical quality of the stimulus itself [132]. It can be elicited using the "oddball paradigm" [229] in which (i) a target stimulus is presented infrequently in time with no other stimuli (single-stimulus task), (ii) infrequent targets occur in a background of frequent standard stimuli (traditional two-stimulus task), or (iii) targets are presented infrequently in a background of frequent standard stimuli and infrequent distractor stimuli (three-stimulus task). In any case, the subject is asked to mentally or physically respond to the target stimuli only, and to ignore any other stimuli. The less probable the eliciting target stimulus is, the larger the P300 potential is [64]. The P300 potential is thought to be linked to specific steps in the flow of information processing. Two different subcomponents of the P300 potential can be distinguished [132, 229, 228]: (i) the earlier P3a, associated with frontal attention mechanisms to evaluate incoming stimuli, and (ii) the late parietal P3b, related to context update and memory storage.

The first BCI based on the P300 potential was described in 1988 by Farwell and Donchin [70] and was realized using an oddball paradigm in which letters, numbers and symbols were arranged in a 6x6 matrix on a screen. The rows and columns of this matrix were flashing rapidly in random order one at a time. To make a selection, the users were instructed to focus attention on the desired target symbol and to silently count the number of target flashes, while ignoring all other flashes. So, the two row/column flashes containing the target symbol were rare stimulus events compared to all twelve possible flashes and typically elicited a P300 response. These P300 responses were detected by the BCI to determine the user's choice. Reliable detection usually requires averaging of many trials in order to extract the P300 from the ongoing (noisy) EEG activity.

Increasing the number of averages typically increases the selection accuracy, but reduces the speed of communication. As a tradeoff, communication rates up to 7.8 characters/s at 80 % accuracy level were reported [64].

The P300 is a cognitive component which is independent of the sensory-specific (e.g., visual) components of the ERP [132]. Therefore, for persons with visual impairments, auditory [75, 99, 106] or tactile [36, 37, 269] stimuli, or a visual speller independent of gaze control based on covert spatial attention or non-spatial feature attention [267] can be used as alternatives. In ALS patients, the P300 component could successfully be used to realize a BCI based on an audio-visual four-choice paradigm [254], or by presenting rows and columns of a matrix visually [201] or purely auditorily [135]. With the auditory system, the patients performed above chance level, but with spelling accuracies significantly lower than with the visual system [135]. In an LIS patient, the tactile modality was found to be clearly superior to other modalities, and the patient achieved high accuracies in a classic two-class oddball paradigm and medium accuracies in a four-choice tactile BCI paradigm [116].

As the P300 component is a naïve response, P300-based BCIs do not rely on operant conditioning and require no or only minimal user training [9, 281]. However, the P300 may change over time due to habituation effects [232], so readjustments of the BCI (as in other types of BCIs) may be required to prevent performance deterioration [281]. In general, P300-based BCIs are assumed to yield higher performance than BCIs based on SCPs or SMRs [9]. In a group study with 81 healthy subjects it was shown that 89 % of them were able to control a visual P300-based BCI with accuracies of 80-100 % [91].

1.2.4. Steady-State Evoked Potential

Another type of stimulus-induced brain signals are SSEPs which can be recorded in the EEG in response to repetitive (oscillatory) stimuli [234]. SSEPs typically have the same frequency as the driving stimulation and possibly include higher harmonics or subharmonics [96] as well. Depending on the sensory modality, they can be divided into steady-state visual (SSVEP) [271], auditory (SSAEP) [221], and somatosensory (SSSEP) [261] evoked potentials respectively.

Typically, a BCI based on SSVEPs can be realized by presenting virtual buttons on a screen which flicker at different frequencies [170, 276]. The user simply looks at the desired button he or she wants to select, thereby increasing the SSVEP amplitude at occipital areas at the corresponding button's flicker frequency. The BCI monitors such amplitude increases to determine if one of the buttons was selected. Possible applications of SSVEP-based BCIs include two-dimensional cursor control [44], phone number input [45], and environmental control [77].

SSVEP-based BCIs usually provide high information transfer rates, require very little user training, and are less susceptible to electrooculogram (EOG) and electromyogram (EMG) artifacts [271]. By incorporating higher harmonics of the stimulation frequency, the classification accuracy of the BCI may significantly be increased [184]. Simultaneous attention to two or more targets within or across sensory modalities may even further increase the information transfer rate [9]. Typically, such BCIs depend on gaze control and are therefore considered as dependent BCIs [281]. However, SSVEPs can also be modulated by selective spatial attention [179] or divided attention [178] to specific regions of the visual field (with shifting the gaze). Therefore, covert spatial attention [120, 121], or selective attention to spatially overlapping stimuli [10] or superimposed illusory surfaces [289] are possible ways to realize independent BCIs based on SSVEPs.

Also in the auditory and somatosensory modalities attention modulation effects of SSAEPs [163, 239] and SSSEPs [80, 81] could be found. Therefore, BCIs based on SSAEPs [97, 123, 157] and SSSEPs [32, 180] can be realized and may be alternatives for users with visual impairments. In the auditory modality, modulated tones are usually presented to both ears while in the somatosensory modality, repetitive tactile stimuli are simultaneously applied to different body locations (e.g., left and right index finger). The users of such BCIs have to focus attention on one of the concurrent streams of repetitive stimuli to select their target. However, in such BCIs, the number of target stimuli is typically limited to two, and information transfer rates are much lower than in SSVEP-based BCIs.

1.2.5. Hybrid Brain-Computer Interface

A hybrid BCI [13, 186, 182, 219] does not rely on a single brain signal but combines different approaches within one BCI system. Hybrid BCIs can be distinguished based on the types of input signals that are combined [219]: (i) Different types of brain signals (e.g., EEG and fNIRS [71]) can be combined. (ii) One single type of brain signal, such as EEG, associated with different mental tasks (e.g., motor imagery and SSVEPs [11]) can be used. In some BCIs of this category, sensory stimuli can be designed in such a way that different brain responses may be evoked simultaneously (e.g., auditory ERPs and SSAEPs [98], somatosensory ERPs and SSSEPs [256], motor imagery and error potentials [130]), or brain responses associated with different sensory modalities are combined (e.g., SSVEPs and SSSEPs [166]). (iii) A brain signal may be combined with some external (e.g., eye tracker [288], manual joystick [148], shoulder position sensor [238], context awareness [233, 270]) or physiological (e.g., electrocardiogram (ECG) [242], EMG [147], EOG [112]) input signal. A hybrid BCI can either process more than one input signals simultaneously, or operate two systems sequentially, in which case the output of one system is used as input to the other, acting as a selector or brain switch [220].

According to a more general definition, a hybrid BCI combines a BCI with any existing input devices, such that the BCI can be used to extend the types of inputs available to an assistive technology system, but the user can also choose not to use the BCI at all [186, 182]. Typically, a hybrid BCI is designed with regard to certain goals that can be achieved better with a hybrid approach than with a conventional BCI [219]. For example, a hybrid BCI may be more reliable, may offer a higher performance, or make the BCI more applicable to a broader range of subjects or patients. For healthy users, hybrid BCIs may be interesting tools in special working environments or in the field of gaming. For patients, such BCIs could provide maximum control at all times, depending on the current physical and/or mental condition of the patient [129].

1.3. Brain-Computer Interfaces in Disorders of Consciousness

The assessment of consciousness in patients with DOCs is typically done by behavioral testing [86, 90, 203]. Behavioral testing aims to detect signs of awareness of oneself and the environment by observing behavioral responses, as no direct way to measure consciousness is available. In this way, identification of its presence is possible while it is virtually impossible to prove its absence [90]. Recognition of awareness is essential for prognosis, treatment decisions, and to provide the best possible quality of life for patients [14, 90].

Behavioral testing is difficult since motor capabilities of the patient may be very limited, quickly exhaustible, and not reproducible. Moreover, voluntary movements may be misinterpreted as being reflexive, and the level of arousal may fluctuate, such that the patient may for example fall asleep during the examination [90]. For these reasons, around 40 % of patients with DOCs are misdiagnosed as suffering from VS/UWS [14, 48, 251]. Therefore, repeated examinations by trained medical staff using standardized behavioral scales, such as the Glasgow Coma Scale (GCS) [264], the Full Outline of UnResponsiveness (FOUR) score [278], or the JFK Coma Recovery Scale-Revised (CRS-R) [83], are strongly required [251].

Since behavioral testing requires motor capabilities of the patient, a disruption of the motor system may prevent patients to respond to commands despite full comprehension and intention [86, 203]. Therefore, it may be particularly difficult to distinguish LIS from VS/UWS. While the average time between brain injury and a diagnosis of LIS was reported to be 2.5 months, some patients may even remain in LIS for several years before any signs of consciousness are recognized [143]. First contact is usually made through eye blinks or vertical eye movements. In this way, simple communication can be established by defining eye codes for yes and no responses. With sufficient practice, LIS patients can learn more complex codes (e.g., Morse code [72]) to reach a higher level of communication. Most frequently, alphabetical communication systems can be used in which an interlocutor reads the letters of the alphabet, ordered by letter frequency, until the patient blinks when hearing the desired letter. Such method was used by Jean-Dominique Bauby, who suffered from LIS after a brain stem stroke, when writing his well-known book “The diving bell and the butterfly” [18]. Similar methods based on groups or grids of letters, divided into vowels and consonants, are also possible, allowing for remarkably rapid communication [143].

While such communication systems always require assistance from others, computer-aided solutions may provide patients a possibility to initiate conversations and to prepare messages for caregivers without the need for long guessing rounds. Usually, eye movement sensors connected to virtual on-screen keyboards allow patients to control their environment, to use a word processor with speech synthesis, to operate a telephone, and to access the Internet [143].

In recent years, novel solutions based on functional neuroimaging and electrophysiology techniques have been developed to differentiate DOCs and disorders of movement [128] and to assess residual brain functions in DOCs without the need for any overt response [144, 149, 204]. The idea is to use such techniques as complementary examinations to existing clinical and behavioral assessment in order to objectively investigate residual brain functions, to better understand behavioral observations, to reduce diagnostic errors, and for prognostic and therapeutic purposes.

In 2006, Owen and colleagues made the striking observation that a patient who was diagnosed with VS/UWS by a multidisciplinary team clearly demonstrated command following and conscious awareness using fMRI [205]. When the patient was asked to imagine playing tennis or navigating through her home, robust activation patterns in specific brain regions, indistinguishable from those observed in healthy controls performing the same tasks were found [31, 205]. The fact that the patient voluntarily cooperated with the experimenters by intentionally performing imagery tasks when ask to do so confirmed beyond any doubt that the patient was consciously aware of herself and her environment. By mapping these imagery tasks to yes-no responses, a basic communication system based on fMRI was later on developed [174]. Remarkably, in that study, one (other) patient diagnosed with VS/UWS was able to correctly answer a series of autobiographical questions.

These findings demonstrate that patients who are behaviorally diagnosed with VS/UWS or MCS may have preserved some level of awareness and cognition. Moreover, it may even be possible to establish a basic communication with these patients by means of a BCI, without relying on any muscular output. Following this idea, various BCI approaches have been investigated in patients with DOCs [42, 171, 191]. Spectral changes in the EEG during imagined motor and spatial navigation tasks were used to detect awareness in severely brain-injured patients [87]. In that study, EEG from five healthy controls and three patients with severe brain injuries was recorded. Evidence of command following was found in one MCS and one LIS patient, but with spectral patterns different from those observed in healthy controls. In a similar study, command following was assessed in 16 patients diagnosed with VS/UWS and 12 healthy controls using a novel EEG task involving motor imagery [54]. This EEG task consisted of pseudo-randomized blocks comprising right-hand imagery and toe imagery.

Three of the patients were found to repeatedly and reliably generate appropriate EEG responses to these imagery tasks, with classification accuracies between 61 % and 78 %, despite being behaviorally entirely unresponsive. The methods and results of this study were debated a lot in the following years, showing the difficulties to accurately identify covert awareness and the importance of using valid and transparent methods [55, 57, 88, 89, 240]. The same EEG task based on right-hand and toe imagery was also applied to 23 patients diagnosed with MCS [56]. In 5 of the patients, robust and consistent responses to command could be found. Interestingly, the etiology had a significant impact on the ability to successfully follow commands. While all 5 (of 15) patients showing positive results had traumatic brain injuries, none (of 8) of the patients with non-traumatic etiology was able to do so. In an fNIRS study, a means of communication was provided by mapping mental imagery tasks like calculation or singing to yes responses, and low-load tasks (e.g., number counting) to no responses [195]. This paradigm was applicable to 7 of 17 total LIS patients suffering from ALS with accuracies over 75 %, and may therefore be an option for DOC patients. Moreover, a novel hierarchical fMRI assessment approach based on imagined physical activities, such as swimming and playing tennis, was investigated to probe command following and communication capacity in severely brain-injured patients [16]. While in 3 of 6 patients command following could be detected, only one of them responded to one of the communication paradigms. However, the information communicated was incorrect, possibly because response delays longer than expected may have prevented correct detection of the responses.

Except for mental imagery tasks, active auditory event-related paradigms may permit detection of consciousness in patients with DOCs [249, 250]. In these studies, sequences of names including the patient's own name were presented, and the patients were instructed to actively count either the own or an unfamiliar target name. Larger P300 responses were observed in the EEG in 9 of 14 MCS patients [249] and in one complete LIS patient [250] when actively counting the own name compared to a passive listening condition, suggesting voluntary command-following like controls. Similarly, in an fMRI study, brain activation patterns associated with target detection and working memory similar as in healthy controls were detected in one MCS patient when actively counting a given target word in a series of neutral words [173].

1.4. Limitations of Previous Work

In recent years, the great potential of fMRI as a complementary tool to probe command following in DOC patients who do not show any behavioral signs of consciousness, and to provide them with a basic means of communication was demonstrated [174, 205]. fMRI offers a high spatial resolution and covers the whole brain including deep subcortical regions, which is very beneficial for detecting activity patterns in response to certain mental imagery tasks. However, there are some major drawbacks of fMRI, such as scanner availability, high costs, and inapplicability in patients with metal implants. Beyond that, it is not possible to use fMRI at patients' bedsides or homes. Therefore, attempts were made to translate these fMRI paradigms to EEG [54, 56, 87], making them potentially applicable for bedside detection of consciousness in DOC patients. These EEG-based approaches showed promising results and are important proofs of concept. However, it was not yet possible to turn these paradigms into real-time bedside communication systems, as pointed out by [86]. Moreover, interpretation of results is difficult since a high variability in responses [87], differences in responses between patients and healthy controls [87], and negative results even in some healthy controls [54] were reported.

Also other EEG-based paradigms were developed which make use of active ERPs for potentially detecting command following and consciousness in DOC patients [249, 250]. While these approaches seem promising for probing consciousness in DOC patients, communication paradigms based on active ERPs are still missing. Moreover, the use of the patient's own name as in [249, 250] is somehow problematic, since semantic processing of highly salient stimuli like the subject's own name may be preserved in VS/UWS, MCS, and LIS patients [209], and even in unconscious states like sleep [208] or anesthesia [61], and does not necessarily reflect conscious perception.

Moreover, DOC patients are known to have fluctuations in consciousness, which requires very robust and sensitive methods [191]. Also the delay range of responses is usually not known [16], which may explain why some patients show responses to command following, but not in real communication tasks [191]. Especially in ERP-based paradigms, exact and consistent timing of subject performance is usually required, which may lead to false negative results in patients with delayed or variable response times [87].

1.5. Aims of this Thesis

To overcome these limitations, the aim of this thesis is to explore novel BCI solutions with the ultimate goal to provide a non-muscular means of communication for non-responsive patients. For ethical reasons, developing such BCIs is of utmost importance since so far, no or only very few options are available to provide communication for such patients. The term "non-responsive patients" refers to DOC patients who are non-communicative and who show no or only minimal behavioral signs of awareness. These are mostly patients diagnosed with MCS or VS/UWS, but who have preserved some level of covert consciousness and communication abilities. While many BCI studies involve healthy subjects in laboratory settings, the aim of this work is to develop BCIs that may be used as a communication tool for patients at their bedsides and homes. For this reason, potential ways of how to transfer BCI paradigms from laboratory settings to clinical or home environments will be explored. Only EEG-based approaches will be considered since unlike fMRI, they are easily available, less expensive, and likely to be applicable to the widest range of patients as bedside communication tools.

Taking the characteristics and capabilities of non-responsive patients into account, such BCIs need to be very simple, robust, and straightforward to use [191]. Therefore, the idea is to develop so-called single-switch BCIs which are based on one brain signal that can reliably be detected to activate a switch. Such a single-switch BCI can then be combined with existing assistive technology software or devices for communication and control purposes. Using a BCI as input channel for a commercially available assistive technology software was already demonstrated with a visual P300 matrix speller [290]. In general, using appropriate selection methods, a single switch is sufficient to control various kinds of assistive technology software or devices. The most common selection method is row-column scanning used for text composition [60, 258]. Also faster and more flexible methods exist that allow to select arbitrary points on a screen, which is beneficial for drawing applications and web browsers [35].

Since it is not known beforehand which approach will be suitable for a patient, different kinds of single-switch BCIs based on various paradigms, brain signals, and modalities, will be developed. In this way, the best BCI approach can then be individually selected for each patient. As a complement to previous SMR-based approaches [54, 56, 87], the focus of this thesis is on evoked potentials. In particular, the use of BCIs based on P300 and steady-state evoked potentials which both usually require very little user training and showed promising results in healthy subjects will be explored in non-responsive patients. Since most VS/UWS patients are blind or severely visually impaired [14, 85], vision-based BCI are usually not applicable in this group of patients. More promising approaches involve the auditory and tactile modalities. Although it is possible to transfer complex visual BCI paradigms, such as a P300 matrix speller, to the auditory modality [75, 106, 126], such complex paradigms may be too demanding for non-responsive patients. So an alternative auditory P300 approach, namely a two-choice BCI paradigm based on tone stream segregation [114] will be used. SSAEP-based BCIs [123] will not be considered as they may cause sensory stress and irritation [42]. In the tactile modality, both SSSEP [180] and tactile P300 [36] were already shown to be suitable brain signals to realize a BCI in healthy subjects and are therefore also promising candidates for non-visual BCIs explored in this thesis.

1.6. Organization of this Thesis

In Chapter 1: Introduction, an overview about the main topics covered by this thesis is given. DOCs and BCIs are introduced, and the state of the art in brain-computer interfacing in DOC patients is summarized. Limitations of previous work and aims of this thesis are explained.

In Chapter 2: Methods, short summaries of all main publications and how they relate to the aims of the thesis are given.

In Chapter 3: Discussion, an overall discussion and conclusion of this thesis are given. The main findings are compared to the state-of-the-art results from literature. Potential improvements and an outlook to future research directions are provided.

In Appendix A, copies of all publications included in this thesis can be found.

In Appendix B, the current curriculum vitae is attached.

2. Methods

2.1. A Stimulation Device for Tactile BCIs

C. Pokorny, C. Breitwieser, and G. R. Müller-Putz. A tactile stimulation device for EEG measurements in clinical use. *IEEE Trans. Biomed. Circuits Syst.*, 8(3): 305–312, 2014. doi: 10.1109/TBCAS.2013.2270176 [225]

As a basic requirement to realize a tactile BCI in non-responsive patients, a stimulation device for EEG measurements in clinical environments was developed (see Figure 2.1). The device was designed with regard to two main requirements, (i) the ability to generate various stimulation patterns in a frequency range covered by different types of mechanoreceptors in the glabrous skin, and (ii) the compliance with safety regulations such that leakage currents would not exceed the maximum allowable currents defined in the safety standard EN 60601–1:2006 for medical electrical equipment.

Figure 2.1.: Tactile stimulation device. The tactile stimulation device is shown with two C-2 tactors connected. The tactors can be attached to the left and right wrist using elastic wrist bands.

To fulfill these requirements, the device was designed for flexible generation of complex stimulation patterns, including both repetitive and transient stimuli suitable to evoke SSSEPs and P300 potentials as needed. To meet electrical safety requirements, the device was designed to be fully galvanically isolated (see Figure 2.2). Leakage currents of the entire EEG measurement system including the tactile stimulation device were measured by the European Testing and Certifying Body for Medical Products Graz (Notified Body 0636). All measured currents were far below the maximum allowable currents defined in the safety standard for medical electrical equipment.

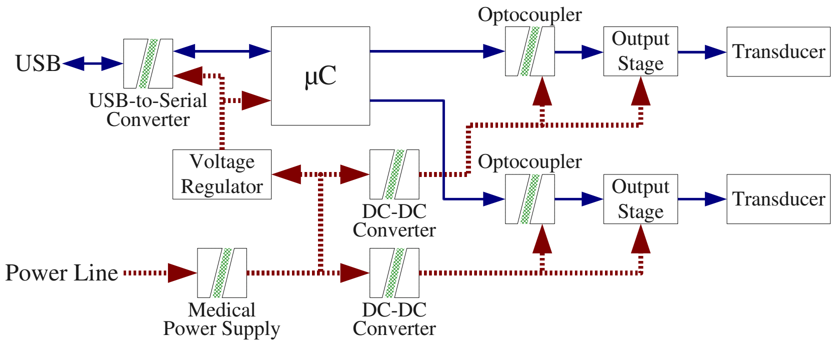

Figure 2.2.: Schematic diagram of the tactile stimulation device. The stimulation device is fully galvanically isolated. The power supply (red thick dashed lines) and signal paths (blue thin solid lines) are shown with all isolation barriers (green hatched areas).

The successful operation of the tactile stimulation device was tested in a real-world EEG experiment. In a screening procedure, the left and right wrist of a healthy subject were randomly stimulated with seven different frequencies. SSSEPs could successfully be evoked and significant tuning curves at EEG channels contralateral to the stimulated wrist could be found, which demonstrated the correct operation of the device. Therefore, the development of this tactile stimulation device was the first step towards the realization of tactile BCIs for non-responsive patients in clinical environments.

2.2. Towards a Single-Switch BCI Based on SSSEPs

C. Pokorny, C. Breitwieser, C. Neuper, and G. R. Müller-Putz. Towards a single-switch BCI based on steady-state somatosensory evoked potentials. In *Proc. Int. BCI Conf.*, pages 200–203, 2011 [222]

In order to provide a potential means of communication for non-responsive patients, a single-switch BCI based on SSSEPs was designed. SSSEPs are promising brain signal since they do not rely on the visual modality, and also the auditory modality is kept free as a feedback and instruction channel. A two-class BCI based on SSSEPs has already been successfully realized in healthy subjects using the index fingers of both hands as target body locations [180]. However, for patients with DOCs, operating a two-class BCI might still be too demanding. With a single-switch BCI, a single brain response that can reliably be detected is sufficient to activate a switch. Eventually, such a single-switch BCI can be connected to assistive technology devices that can be controlled by a conventional switch in order to provide patients with means of communication and control.

The focus of this study was to evaluate the feasibility of realizing a single-switch BCI based on SSSEP in healthy subjects. Starting point of this investigation was a two-class BCI similar as proposed in [180], but using only one of the hands. The thumb and middle finger from the right hand were simultaneously stimulated with frequencies individually selected by means of a screening procedure [175]. The subjects were instructed to randomly focus attention on one of these fingers. To make focusing attention easier, short amplitude attenuations, also known as "twitches" [180], were embedded in the stimulation signals at random time points. In an offline analysis, focused attention periods on the thumb or middle finger were classified against the reference period. The idea was to determine the more responsive class which could then be used as target class to activate a brain switch. Thirteen of fourteen subjects performed above chance level [181] for at least one class (see Figure 2.3), demonstrating that a single-switch BCI based on SSSEP can in principle be realized in healthy subjects. This study was an important step towards a tactile single-switch BCI that eventually may provide non-responsive patients with an alternative means of communication and control.

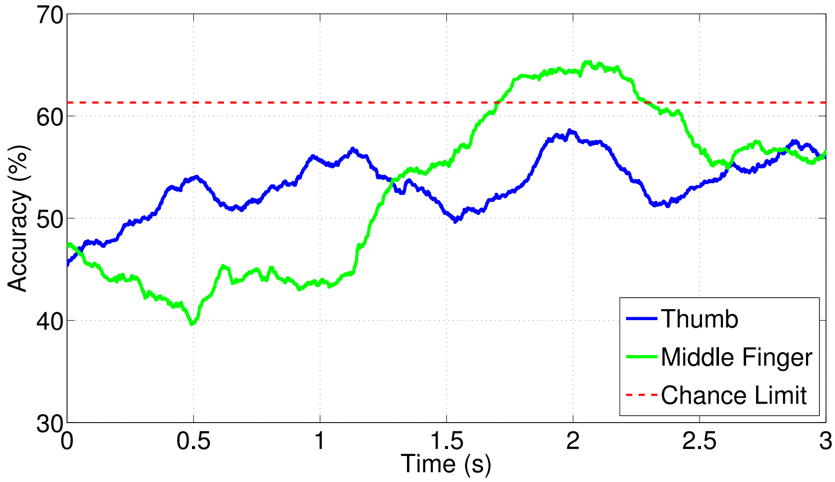

Figure 2.3.: Classification accuracies of the SSSEP-based single-switch BCI. The offline results of one subject are shown for focused attention on the thumb (blue) and on the middle finger (green) against reference. The dashed horizontal line at 61 % indicates the confidence limit ($\alpha = 5\,\%$) of the chance level.

2.3. SSSEPs in Minimally Conscious Patients

C. Pokorny, G. Pichler, D. Lesenfants, Q. Noirhomme, S. Laureys, and G. R. Müller-Putz. Steady-state somatosensory evoked potentials in minimally conscious patients – Challenges and perspectives. In *Proc. Int. BCI Conf.*, number 055, 2014. doi: 10.3217/978-3-85125-378-8-55 [226]

In order to realize a BCI based on SSSEPs, stimulation frequencies with the highest SSSEP responses, also known as "resonance-like" frequencies of the somatosensory system [175], are typically used as target frequencies for operating the BCI [32, 180]. Within this study, a well-established screening paradigm [33] was adapted for this purpose to be applied to patients in an MCS, taking their specific needs and capabilities into account. In this pilot study, only patients diagnosed with MCS were included since they were more likely to be able to follow instructions and operate a BCI than VS/UWS patients.

EEG measurements were conducted in seven patients at the Albert Schweitzer Clinic (Graz, Austria) and the Liège University Hospital (Liège, Belgium) respectively. Tactile stimuli with seven different frequencies were randomly applied to the patients' left and right volar wrist. The wrists were selected as target location since some of the patients suffered from hand spasticities, making it not easily possible to use more sensitive locations like finger tips. The tactile transducers were attached using elastic wrist bands. To avoid attention modulation effects of the SSSEPs, relaxing music was presented via headphones to distract the participants.

As shown in Figure 2.4, a significant tuning curve could be found only in one of the patients (PA_{05}). In all other patients, stable SSSEPs were not present. In

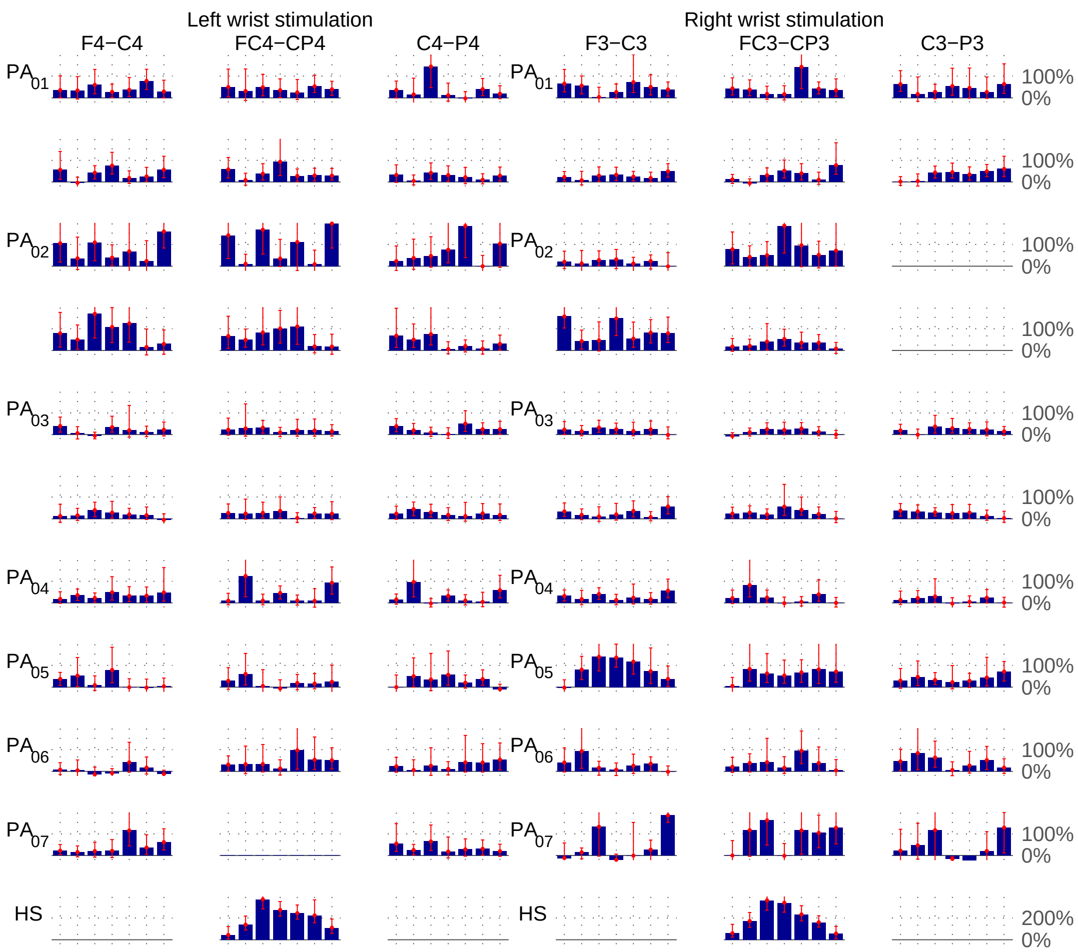

Figure 2.4.: SSSEP screening results in MCS patients. The results of all patients and sessions (rows) from three representative (bipolar) EEG channels contralateral to the stimulated wrist (columns) are shown. The bars correspond to the relative bandpower increase (in %) with 95 % confidence intervals of all seven stimulation frequencies. The last row shows the results of a healthy subject (HS), using a different y axis scaling.

some patients, an increase in band power of only certain single frequencies could be found. However, it is not yet known if perhaps such frequencies could intentionally be modulated and thus be sufficient to realize a BCI. While technical problems were ruled out by a control experiment, various other reasons such as impairments of the somatosensory system and a huge amount of EEG artifacts could explain the inconclusive outcome of most patient measurements. Further investigations and improvements are therefore required before a tactile BCI may be realized in non-responsive patients.

2.4. P300 Potentials in a Hybrid SSSEP-Based BCI Setup

C. Pokorny, C. Breitwieser, and G. Müller-Putz. The role of transient target stimuli in a steady-state somatosensory evoked potential-based brain–computer interface setup. *Front. Neurosci.*, 10(152), 2016. doi: 10.3389/fnins.2016.00152 [227]

Since previous SSSEP screening results of patients in an MCS were mostly inconclusive, the idea of this study was to realize a tactile BCI in non-responsive patients without relying on SSSEPs alone, making such a BCI potentially applicable to a broader range of patients [182, 186, 219]. For this purpose, a hybrid BCI was designed which integrates P300 potentials into a typical SSSEP-based BCI setup. Tactile P300 potentials are another class of promising brain signals for realizing non-visual BCIs [36]. The hybrid BCI was designed in such a way that P300 potentials were evoked by transient target stimuli, so-called "twitches" [180], which were embedded at random position in the streams of repetitive tactile stimuli. In earlier literature [4, 32, 80, 81, 180, 207, 256], similar twitches were typically used to support a user to focus attention on the desired target locations.

This hybrid BCI was evaluated in fourteen healthy subjects, stimulating the left and right index fingers with frequencies individually determined by a screening procedure [33]. A third class, representing an idle state, was included in this investigation. Even though SSSEPs and P300 potentials could be evoked in most subjects, the overall BCI performance was found to be rather moderate and hardly sufficient for communication purposes. It could be shown that twitches have an attenuation effect on the SSSEP, referred to as "SSSEP blocking" (see Figure 2.5), suggesting that the attempt to combine different types of stimulation signals like repetitive signals and twitches has a mutual influence on each other. This influence is originated at the level of stimulus generation but becomes apparent as physiological effect in the SSSEP. Therefore, when designing a hybrid BCI based on SSSEPs and P300 potentials, one has to find an optimal tradeoff depending on the overall design goals or individual subjects' performance. The results found in this study give therefore important new insights that may be beneficial for the future design of hybrid BCIs to be used not only in healthy subjects but also in non-responsive patients.

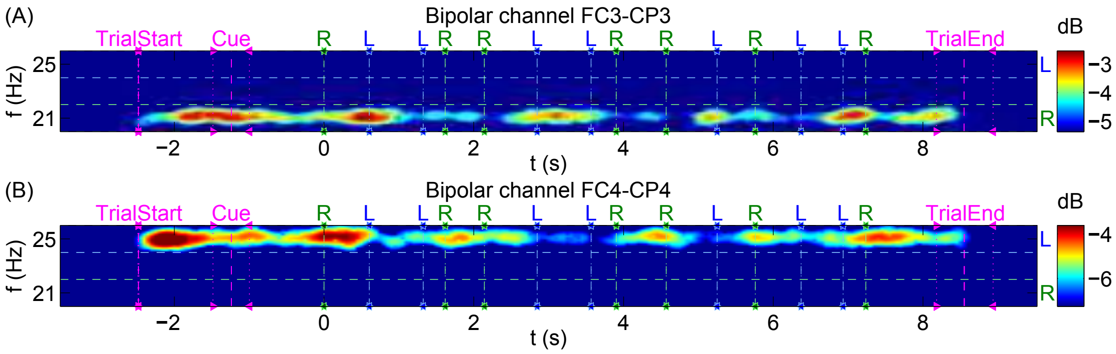

Figure 2.5.: Transient effects in the SSSEP. Spectrograms of one subject are shown for the bipolar channels (A) FC3-CP3 and (B) FC4-CP4. The color axes were scaled to highlight power spectral density variations at each stimulation frequencies. Twitch onsets at left (L) and right (R) index fingers are drawn as vertical dashed lines.

2.5. A Single-Switch BCI Based on Auditory P300

C. Pokorny, D. Klobassa, G. Pichler, H. Erlbeck, R. Real, A. Kübler, D. Lesenfants, D. Habbal, Q. Noirhomme, M. Risetti, D. Mattia, and G. Müller-Putz. The auditory P300-based single-switch brain-computer interface: Paradigm transition from healthy subjects to minimally conscious patients. *Artif. Intell. Med.*, 59(2):81–90, 2013. doi: 10.1016/j.artmed.2013.07.003 [224]

Shifting the focus from the tactile to the auditory modality, a single-switch BCI based on auditory P300 potentials was developed. A two-choice BCI paradigm similar as described in [114] based on tone stream segregation [23] was adapted for this purpose. Since humans are generally very good at selective listening to different concurrent streams of auditory stimuli (referred to as “cocktail party problem” [47]), this paradigm was assumed to be very simple and intuitive, and therefore suitable for non-responsive patients. Two tone streams consisting of short beep tones with infrequently appearing deviant tones at random positions were used as stimuli (see Figure 2.6). The subjects were instructed to focus their attention on one of the streams and to intentionally recognize any occurrence of a deviant tone in this target stream.

Within this study, this single-switch BCI was evaluated in ten healthy subjects and then applied to twelve patients in an MCS at clinics in Graz (Austria), Würzburg (Germany), Rome (Italy), and Liège (Belgium). The results for healthy subjects were promising and most classification results were clearly better than random. In MCS patients, only a small number of classification results were above chance level, and none of the results were sufficient for communication purposes. Nevertheless, signs of consciousness were detected in nine of the twelve patients after averaging all corresponding data segments and computing significant differences (see Figure 2.7). This study shows the paradigm transition from healthy subjects to MCS patients, taking their specific needs and capabilities into account. Promising results in healthy subjects are, however, no guarantee of good results in patients. Therefore, more investigations are required before any definite conclusions about the usability of this paradigm

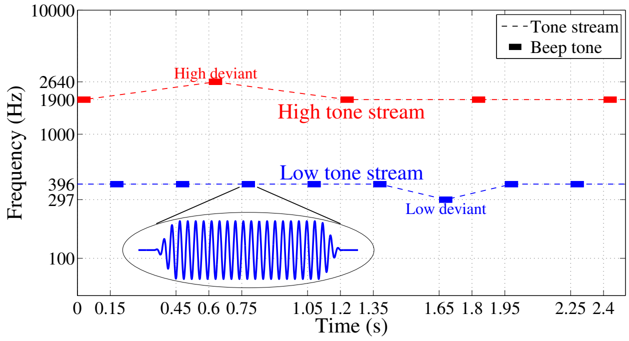

Figure 2.6.: Tone streams in the auditory P300-based single-switch BCI. Two intermixed tone streams are used as stimuli. Both the high and the low tone stream (dashed lines) consisted of short beep tones (short bars) with randomly placed deviants. In the high tone stream, every other tone is omitted corresponding to silent gaps in the tone stream pattern. The waveform of one standard low tone is shown in magnified view.

for MCS patients can be drawn. Nevertheless, this paradigm might offer an opportunity to support bedside clinical assessment of non-responsive patients and eventually, to provide them with a means of communication.

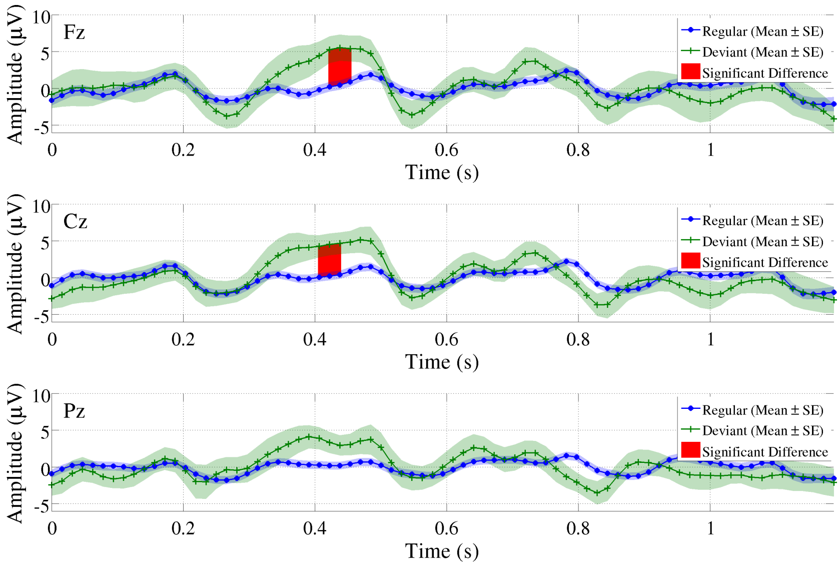

Figure 2.7.: Presence of an auditory P300 in one MCS patient. The averaged data segments at the channels Fz, Cz and Pz of the low standard tones (blue curve; marker type: •) versus the low deviant tones (green curve; marker type: +) can be seen with the low tone stream as target stream. Significant differences were computed using bootstrapping($\alpha = 5\,\%$; red shaded areas). The standard error (SE) is plotted along with the curves (lightly shaded areas).

3. Discussion

The main aim of this work was to explore new ways to provide a means of communication for non-responsive patients. Bypassing the muscular output functions, a direct BCI seemed to be a promising approach for this purpose. In many previous studies it could be shown that BCIs have the potential to realize an alternative communication channel for healthy subject as well as for severely impaired patients [9, 28, 68, 132, 198, 244, 253]. As a complement to previous SMR-based approaches [54, 56, 87], novel BCI solutions based on evoked potentials in the tactile and auditory modalities were developed for non-responsive patients, which are discussed in the following sections.

3.1. BCI Based on Tactile Stimuli

Since vision-based BCIs are assumed to be not applicable in non-responsive patients due to severe visual impairments [14, 85], the tactile modality seemed to be a promising alternative. As a first step to realize a tactile BCI, a stimulation device capable of generating complex, modulated stimulation patterns and suitable to be used at the patient's bedside in home and clinical environments was required. Since none of the commercially available stimulation devices fulfilled these requirements, the prototype of a flexible and low-cost tactile stimulation device was developed within this thesis. To enhance the viability of tactile BCIs, the necessity for standardized vibrotactile stimulators that conform to a variety of requirements has also been recognized in a recent review article about potential future directions of SSSEPs for BCIs [6]. The device developed within this thesis was tested to be electrically safe by the European Testing and Certifying Body for Medical Products Graz (Notified Body 0636), and medically approved to be used in clinical environments by the Ethics Committee of the Medical University of Graz. In a control experiment it was possible to reliably evoke SSSEPs, and the emergence of significant tuning curves on the contralateral side of the stimulated wrist could be observed. These results were fully in accordance with various others studies in literature [32, 33, 175], and were regarded as validation of the correct operation of the stimulation device. Such a device can be used in a variety of applications mentioned in literature, such as BCI applications based on SSSEPs [32, 180], P300 [36], and multimodal BCIs [166], somatosensory evoked potential (SEP) recordings [65], and as a tactile feedback channel for BCIs [43, 49].

As a next step, a single-switch BCI based on SSSEPs was developed. The idea of a single-switch BCI was to reliably detect one certain brain pattern of a patients to activate a brain switch. Such a single-switch BCI can then be connected to various kinds of assistive technology software and devices. For example, it was shown that BCI control using a visual P300 matrix speller could be successfully integrated into a commercially available assistive technology software [290]. The feasibility of realizing a single-switch BCI based on SSSEPs was evaluated in healthy subjects. A two-class BCI similar as proposed in [180] was adapted for this purpose, using only two fingers of one hand and selecting the more responsive class to activate a switch. Individual stimulation frequencies were determined by means of a screening procedure to identify the subject-specific "resonance-like" frequencies of the somatosensory system [175]. The use of subject-specific stimulation frequencies with strongest SSSEP responses is assumed to yield higher BCI performance than using the same standard frequencies for all subjects [180, 256]. Thirteen of fourteen subjects performed above chance level for at least one class. Offline classification accuracies were found in a range between 60 % and 80 % which is similar as reported in earlier literature [180]. These results demonstrated that a single-switch BCI based on SSSEP can in principle be realized in healthy subjects. A more detailed analysis of this study revealed that even though focused attention on one of the stimulated fingers (i.e., single-switch BCI) could be detected quite well, distinguishing between the fingers (i.e., two-class BCI) was hardly possible, with only two subjects reaching classification accuracies above chance level [32].

In order to evaluate the singe-switch BCI based on SSSEPs in non-responsive patients, a screening paradigm similar as described in [33] was developed, taking their specific needs and capabilities into account. Unlike in earlier studies [32, 175, 180, 222], the wrists were selected as target locations, since some of the patients suffered from hand spasticities, which prevented the use of more sensitive locations like finger tips. Separate tuning curves of both wrists were determined, since no assumptions about the similarity of the left and right tuning curves could be made. Taking the short attention spans of non-responsive patients into account, the number of trials and therefore the whole measurement duration was reduced by using a more coarse-grained frequency range. Instead of using a distracting mental arithmetic task [32, 222], patients were distracted by relaxing music to prevent them from focusing attention on the stimuli during screening. Despite these modifications, most of the SSSEP screening results in MCS patients were inconclusive. Only in one of the seven patients, a significant tuning curve could be found. Various reasons may explain the inconclusive outcome of most screening measurements: (i) Due to uncontrolled body movements of the patients, the EEG was contaminated with a huge amount of biological (EOG, EMG) and technical (cable movements, electrodes touching the pillow) artifacts. (ii) It was not clear if the contact pressure of the tactile transducers and the stimulation strength were strong enough to allow patients to properly perceive the tactile stimuli as intended. (iii) The impact of the body location used for tactile stimulation was not investigated in detail. Since the tendons of the finger flexors are located at the volar side of the hand, spasticities may have had a severe influence on the SSSEPs when using the volar wrists as target locations. A full body screening may be required in future to individually identify optimal stimulation locations. (iv) SSSEPs may not have been present due to severe impairments to the somatosensory system, or could not be recorded with EEG due to alterations in the brain topology. Studies investigating ALS patients showed for example an abnormal delay of SEPs, suggesting a slowing of conduction along the central sensory pathways [51, 79]. Moreover, altered or absent SEPs could also be observed in MCS and VS/UWS patients [231]. Therefore, a thorough neurophysiological examination prior to SSSEP recordings is strongly required in future measurements. Nevertheless, this was the first study to investigate SSSEPs in non-responsive patients. Further investigations based on a larger number of patients may be required before any conclusion about the feasibility of a purely SSSEP-based BCI in non-responsive patients can be drawn.

In order to not rely on SSSEPs alone, a hybrid BCI was designed which integrates P300 potentials into a typical SSSEP-based BCI setup, making such a BCI potentially applicable to a broader range of subjects or patients [182, 219]. A third class representing a non-control or idle state similar as in asynchronous BCIs [165] was included in this hybrid BCI setup, which offers users the possibility to consciously control if they desire to operate the BCI during the cue-based control periods or not. It was demonstrated in healthy subjects that both SSSEPs and P300 potentials could successfully be evoked by embedding twiches at random positions into the repetitive tactile stimulation signals. Classification accuracies significantly better than random [181] could be reached by all but one subjects using P300 or SSSEP features. However, the overall BCI performance was rather moderate and hardly sufficient for communication purposes. Typically, a minimum performance level of 70 % is required for communication [133], which could not be reached by any of the subjects. However, this performance level was defined for two-class BCIs and may not be directly applied to this three-class BCI setup.

The main finding in this study was that twitches which were implemented as short interruptions in the repetitive stimulation signals have an attenuation (or blocking) effect on the SSSEP, time-locked to twitch positions. This indicated that both types of brain signals, SSSEP and P300, are not independent features, similar as shown in [283] in the visual domain, and cannot be evoked at the same time, since one is detrimental to the other. Also in another similar study in literature [256], no boost in performance could be found when combining SSSEP and ERP features. Unlike reported in [282] in the context of SSVEP, such SSSEP blocking effects did not contain additional features useful for classification and could not successfully be used to increase classification accuracy. The use of twitches in an SSSEP-based BCI setup should therefore be carefully considered, to find an optimal tradeoff depending on the overall design goals or individual subjects' performance. Especially for non-responsive patients, a setup may be beneficial where the number of twitches is individually chosen to maximize the user's performance based on SSSEP and P300 features. Even a dynamic adaptation based on constantly monitored quality measures of the respective features, similar as proposed in a hybrid BCI in [129], may be investigated in future studies.

Even though a tactile BCI for communication purposes based on SSSEPs could not yet be realized in non-responsive patients, such a tactile BCI could be beneficial as bedside assessment tool to investigate if P300 potentials and SSSEPs are present. Especially SEPs are very good predictors for the outcome after severe brain injuries [39, 236, 284] and are frequently used to evaluate the sensory and cognitive functions of DOC patients [144]. In a similar, purely P300-based tactile BCI paradigm for consciousness detection and communication, classification accuracies up to 100 % could be reached in six chronic LIS patients [161]. In that study, participants were instructed to count the vibrotactile stimuli on either the left or right wrist to answer a series of yes-no questions. This study demonstrated the feasibility of a BCI based on tactile P300 in a group of brain-injured patients. In another study, the performance of a tactile and visual gaze-independent ERP-based BCI was compared in healthy subjects and ALS patients with mild to moderate disabilities [257]. In this study, it could be shown that both tactile and visual gaze-independent spelling systems can be used in ALS patients. However, the visual speller was found to outperform the tactile speller in both healthy subjects and ALS patients.

Further improvements of the hybrid paradigm developed within this thesis may be possible by separately trained classifiers for idle state detection and target finger discrimination using the best respective features for each task. A more detailed analysis of the recorded data set indeed revealed that the idle state could be more accurately detected using an SSSEP classifier, and left versus right target finger using a P300 classifier [34]. These findings are in line with the results already shown in [32] where SSSEPs were suitable for detecting the state of focused attention (versus reference), but not for target discrimination. Also other strategies, such as using combined SSSEP and P300 feature sets for classification instead of a threshold-based fusion of individual classifiers, together with balanced numbers of SSSEP and P300 features, were found to significantly increase the performance [34]. Moreover, SSSEP performance may also be increased by including higher harmonics of the stimulation frequencies by means of harmonic sum decision (HSD) [184, 185, 183] or harmonic phase coupling (HPC) [38] methods, as it was shown in the visual modality in SSVEP-based BCIs. Further improvements may be possible by including spatial information, for example by individual channel selection [185, 223] or CSP [5, 196, 197].

Also user training may play an important role for BCI performance. Subjects in the hybrid study described within this thesis only participated in a single recording session without any prior training. It needs to be investigated if the use of more than one training sessions on different days (as in [180, 256]) has a positive influence on the BCI performance. Since a BCI is a closed-loop system, feedback is very important during the training phase or while controlling some application [8]. Discrete feedback was provided in the hybrid BCI described within this thesis. Unfortunately, such standard training approaches usually do not take into account human learning and instructional design principles to ensure an efficient learning of a skill [160, 158]. For example, standard BCI training approaches typically involve identically repeated and somewhat boring training tasks provided in a synchronous way. In contrast, explanatory and goal-oriented feedback involving multiple sensory modalities in an engaging and challenging environment with adaptive levels of difficulty may be preferable [160, 158]. Also the user's motivational and cognitive state should be considered to ensure efficient learning. For example, the effects of psychological state and motivation on BCI performance were investigated in patients with ALS [202]. In that study, it was concluded that motivational factors may indeed be related to BCI performance in individual subjects and that motivational factors and well-being should be assessed in standard BCI protocols. In this context, alternative BCI training protocols with richer feedback have been explored. In particular, it was shown that game-like environments with virtual reality [21, 67, 146, 243], biased feedback [15], or progressive BCI training tasks [168, 274] can improve BCI performance. Many of these ideas and learning principles may also be applied to the hybrid BCI described within this thesis in order to increase performance.

To avoid unintended interaction effects between repetitive and transient stimulation signals in the hybrid paradigm, one could think of special types of twitches which would not interfere with the SSSEP, e.g. complex twitch patterns or modulation of other signal parameters (instead of amplitude) to draw the subjects' attention to. Alternatively, it could be investigated if the concept of code-modulated visual evoked potentials (c-VEPs) [24, 262] could be transfered to the tactile domain. Instead of embedding twitches into a repetitive stimulation signal, the idea would be to use pseudo-random binary codes based on m-sequences as stimulation signals. Another solution could be to decouple the generation of frequency-domain and time-domain signals, e.g. by using separate transducers for purely repetitive and transient stimulation signals applied to nearby body locations within the same receptive fields (e.g., by means of Braille stimulators). In this way it could be tested if the interference of steady-state and transient signals is only caused by inherent limitations in the stimulation signals (Gabor limit [76]), or is a physiological effect of the somatosensory system as well. Similar interaction effects based on lateral inhibition were already reported separately in the ERP and the SSSEP response [255], while cross-interactions between ERPs and SSSEPs were not yet explicitly investigated. Another idea would be to realize a purely SSSEP-based BCI without any twitches and instruct the subjects to focus attention on the target hand in the following way. Following the idea from [32, 222], two fingers from each hand could be simultaneously stimulated with the same frequency each (but different frequencies for different hands). The stimulation amplitude of one of the stimulated fingers from each hand could be randomly (slightly) attenuated for the duration of a whole trial, and the subjects would be instructed to identify which of the fingers on the target hand has a higher/lower stimulation amplitude. In this way, subjects would be required to continuously focus attention on the target hand without the need for any transient stimuli.

3.2. BCI Based on Auditory Stimuli

In the auditory domain, a two-class P300-based BCI paradigm based on tone stream segregation [23] similar as described in [114] was developed. In healthy subjects, promising results with classification accuracies up to 90 % could be reached. The average performance over all subjects was around 70 % for either of the tone streams, which is in the same range as the cross-validated performance reported in [114], and regarded as performance level sufficient for communication purposes [133].

One of the advantages of this paradigm based on simultaneously presented tone streams is that it does not rely on binaural hearing which may be impaired in non-responsive patients due to the loss of functional connectivity in the brain [30, 138]. Compared to the well-known visual P300 matrix speller [70], it is a much simpler P300 paradigm with only two classes and which does not rely on intact vision. On the one hand, this paradigm is suitable to realize a single-switch BCI by selecting on of the tone streams as target class to activate a brain switch. On the other hand, the number of classes could in principle also be increased by intermixing more than two tone streams, since the number of streams is not limited to the number of ears. This paradigm was assumed to be intuitive, since humans are generally very good at tone stream segregation [47]. In practice, this paradigm turned out to be still rather complicated, even for healthy participants, as many of them reported difficulties in identifying the target tone stream and keeping their attention focused. However, in a follow-up study, both the classification accuracies and the pleasantness of the paradigm could significantly be improved by introducing different modifications to the original paradigm [19]. A disadvantage may still be the long trial duration (33 s), resulting in a relatively low communication speed. The trial duration was chosen in such a way that ten deviant tones could be placed within one trial. Instead of using majority vote as in [114], the time segments after the deviant tones were averaged before classification, since this approach was assumed to be more robust against artifacts by increasing the signal-to-noise ratio (SNR).

Moreover, the paradigm transition from healthy subjects to patients in an MCS was shown, taking their specific characteristics and capabilities into account: (i) Auditory cues were added allowing this paradigm to be operated purely auditorily without relying on intact vision. (ii) Block-based trial sequences instead of random cues were used for patients, since random switching between target streams on a trial-by-trial basis was assumed to be too demanding for them. (iii) Asynchronous stream onsets, meaning that the target stream asynchronously started a few seconds earlier than the non-target stream at the beginning of each trial, were implemented to make it easier for the patients to identify the target stream. (iv) A simpler version of the paradigm with only one of the tone streams was applied prior to the complex BCI paradigm with two intermixed tone streams. This was done to familiarize the patients with the experimental conditions and to find out if the presence of a P300 in the simple and complex paradigms is somehow related. Despite these adaptations, classification accuracies were not sufficient for communication purposes in any of the patients. The main reason for this may be that the patients were not able to understand or correctly follow the instructions since the paradigm was too demanding for them. Moreover, only a low number of trials could be recorded due to the short attention span of the patients, and many of the trials were contaminated by strong artifacts due to uncontrolled body, head, and eye movements. After rejection of contaminated data segments, this resulted in relatively few clean data segments after deviant tones. Therefore, unlike in healthy subjects, no averaging could be applied before classification, which may be another reason explaining the low classification accuracies.

Nevertheless, significant differences between standard and deviant tones could be found not on a single-trial level, but after averaging all available data segments. These differences occurred between around 200 ms and 900 ms with either positive or negative polarity, and may represent P300 potentials or mismatch negativities (MMNs) respectively, as also reported in earlier literature [114]. Apparently, these potentials have been delayed, indicating a slower processing speed than in healthy subjects [127, 209, 249]. Also significantly higher values of P300 latency jitter as compared to healthy controls have been reported, which may limit the P300 classification performance [245]. However, in three of the patients, significant attention modulation effects could be found, indicating that these patients actually understood and followed the instructions, even though not on a single-trial level. Therefore, this paradigm may offer an important complementary tool to support bedside clinical assessment of non-responsive patients. The value of ERP monitoring to investigate residual cognitive functions in DOC patients has already been demonstrated in various recent studies by presenting the subject's own name under passive and active conditions [94, 235, 252]. The advantage of the single-switch paradigm developed within this thesis is that in case consciousness is detected in a patient, this paradigm would allow to provide an immediate means of communication. However, due to the inhomogeneous etiologies and rather low number of patients included in this study, more investigations are still required.

This study was the first attempt to realize an auditory P300-based single-switch BCI in non-responsive patients. A similar attempt to establish communication with MCS, VS/UWS, and LIS patients was made using an auditory 4-choice BCI paradigm, but the results were also mostly inconclusive [162]. Promisingly, in an fMRI study it was confirmed that some patients in VS/UWS and MCS are indeed able to selectively attend to auditory stimuli, thereby demonstrating their ability to follow commands and to communicate [190]. Moreover, new insights were gained by investigating the subcomponents of the P300, the "novelty P3a" which is thought to index exogenous attention, and the later "target P3b" which is seen as a marker of volitional engagement of endogenous attention to task-relevant targets. In one VS/UWS patient, the early, bottom-up P3a and the late, top-down P3b could in fact be dissociated suggesting the presence of a relatively high level of attentional abilities despite the absence of any behavioral indications [46].

In future, the acquisition of more clean trials in patients would be essential, so that averaging of P300 data segments can be applied to increase the SNR and presumably the classification accuracies. For this purpose, better artifact avoidance and removal strategies would be strongly required, since so far, only manual artifact selection was applied. Moreover, following the recommendation regarding human learning and instructional design principles [160, 158], less monotonous and more intuitive or interesting stimuli, such as melodies, syllables, or words instead of artificial beep tones, may improve the performance. On the one hand, such stimuli may be easier to distinguish and elicit a stronger ERP response, similar as for example faces in the visual domain [115, 117]. In the auditory domain, it could be shown that the use of natural syllables improves both the user ergonomics and performance, despite the additional variance introduced by natural compared to artificial stimuli [107]. More recently, a novel, user-friendly, auditory spelling paradigm, the so-called "CharStreamer" paradigm, was introduced where spoken sounds of letters are presented as stimuli [105]. Similarly, an intuitive, word-based, auditory spelling paradigm, the so-called "WIN-speller", was introduced allowing classification accuracies of 80 % and higher in both healthy subjects and end-users with motor impairments [125]. On the other hand, more intuitive or interesting stimuli may also increase the motivation of the users, which was found to correlate with higher P300 amplitude and improved BCI performance [124]. Moreover, also training over several sessions may significantly increase BCI performance [20, 93]. In contrast, the auditory single-switch BCI paradigm developed within this thesis was evaluated in one or two sessions only, so the performance may be improved by increasing the number of training sessions in future studies.

3.3. Alternative Approaches

Besides auditory and tactile BCIs, various alternative BCI approaches for patients with DOCs have been developed in recent years. Most of them aimed at transferring successful mental imagery paradigms from fMRI to EEG, in order to make them applicable at the patient's bedside. Following the EEG studies in [54, 56, 87], a BCI paradigm with visual and auditory feedback based on imagined hand movement or toe wiggling was successfully applied to four patients in an MCS [52]. Similarly, the detection of mental imagery and attempted feet movements with rapid delivery of biased feedback was evaluated in six patients in an MCS [108]. Moreover, the usability of passive and imagined movements in a single-switch BCI for communication based on auditory scanning was demonstrated in healthy subjects answering a series of yes-no questions [187]. Similarly, a listener-assisted scanning system to select sequentially spoken letters by performing a motor or mental imagery task was evaluated in healthy subjects [109]. Such scanning approaches appear to be excellent ways to provide more complex communication capabilities for non-responsive patients not only based on mental imagery, but also when using any other single-switch BCI approach described in this thesis.

Also the idea of combining different brain signals in hybrid BCIs, similar as explored in the tactile modality within this thesis, was investigated in other recent studies. In healthy subjects, motor imagery and selective sensation of vibrotactile stimulation [285] were combined in a novel hybrid BCI modality [286]. In the visual domain, hybrid BCIs combining SSVEPs and visual P300 potentials for detecting awareness in DOC patients were developed. In one study, SSVEPs could be evoked by selectively attending photos with the patient's own or an unfamiliar face flickering at different frequencies on a screen, with the photo frames flashing in random order to evoke P300 potentials [206]. In another study, patients were instructed to selectively attend to one of two flickering number buttons with randomly flashing frames [153]. In a multimodal BCI, temporally, spatially, and semantically congruent audiovisual stimuli involving numbers were used for awareness detection in patients with DOCs, outperforming auditory-only and visual-only systems [275]. Using SSVEP alone, a gaze-independent BCI based on covert attention using an "interlaced squares" stimulation pattern could successfully be applied to healthy subjects and LIS patients [150]. Other promising approaches for detecting consciousness in DOC patients involve volitional EMG responses [92], voluntary control of breathing [41], detection of emotional states [95], number processing and mental calculation [153], detection of activity changes within the attention network [192, 190], and detection of conscious experiences during naturalistic stimulation, such as watching a movie or listening to an audio-story [193, 194].

3.4. Limitations and Outlook

Since behavioral testing in DOC patients is typically unreliable and prone to misdiagnoses, the importance of technology-based, objective tools, such as fMRI, positron emission tomography (PET), diffusion tensor imaging (DTI), or EEG combined with transcranial magnetic stimulation (TMS) for better clinical characterization has been highlighted in recent years [62]. For example, an objective measure of consciousness was developed which involves perturbing the cortex with TMS and measuring the algorithmic complexity of the spatio-temporal pattern of the electrocortical responses [40]. Also hierarchical approaches beginning with the simplest forms of sensory processing and then progressing to more complex cognitive functions have been proposed [203]. However, as pointed out by Owen [203], normal neural responses to external stimuli do not necessarily indicate conscious awareness, since it is usually not possible to verify that patients have even perceived the stimuli as intended. The only reliable way to prove conscious awareness is to directly ask him or her. Since VS/UWS patients are, by definition, unable to show any behavioral response, they cannot convey this information to the outside world. Instead, the activation of certain brain regions can be used as neural marker confirming that he or she can understand instructions and exhibit voluntary behavior. Therefore, BCI paradigms for communication and control, as described within this thesis, can be used as such tools for assessment of consciousness in DOC patients. Most importantly, negative findings in such patients cannot be used as an evidence for the lack of awareness, since false negative findings in functional neuroimaging studies are common, even in healthy controls [203].

As demonstrated in this thesis, it is in general very difficult to transfer BCI paradigms from laboratory settings to end-users in clinical or home environments. For various reasons, promising paradigms in healthy subjects may not yield conclusive results when applied to non-responsive patients. To overcome this problem, the potential target users should be more included in the design process of BCI solutions [200]. A user-centered design (UCD) approach has been proposed for this purpose in order to bridge the translational gap when bringing BCIs from laboratory settings to end-users in clinical or home environments [136, 137]. The UCD describes an iterative evaluation process between developers and end-users with regard to the usability of the system in terms of effectiveness, efficiency, and user satisfaction.

When bringing a BCI system to end-users out of the laboratory, many technical and practical limitations of the EEG recording system, including device safety considerations, need to be taken into account. Most importantly, EEG artifacts due to uncontrolled body movements of the patients dramatically limit the recording signal quality. In future, more sophisticated artifact avoidance and removal strategies, such as ICA, a novel combination of wavelet decomposition, ICA, and thresholding (FORCe) [59], or a combination of different algorithms to correct the signal at multiple processing stages, as suggested in [268], are highly required. Such multi-stage approaches may be particularly useful in hybrid BCIs, such as the hybrid SSSEP-based BCI described within this thesis, considering that different types of features are susceptible to different types of artifacts. Also paradigms that allow averaging of many data segments, such as the auditory tone stream paradigm or the hybrid SSSEP-based paradigm described within this thesis, may be beneficial to increase the SNR and reduce the negative impact of artifacts. Nevertheless, unlike other functional neuroimaging methods like fMRI, PET, or DTI, EEG has the great advantage that it can be easily applied at the patient's bedside. As highlighted recently, also fNIRS may be a feasible future alternative to fMRI for bedside assessment and communication [1].

Moreover, the number of patients included in a study is typically very limited, and only a low number of trials can usually be recorded due to the short attention spans of non-responsive patients. Also the design of BCI paradigms is a crucial factor for the applicability in non-responsive patients. Many communication paradigms used in this thesis and in literature rely on a mapping between some arbitrary response function (e.g., some specific motor imagery task, or focused attention on some specific stimulus) and the answer to a question (e.g., yes or no). As pointed out in [191], a patient is required to perform at least two different processes in this case, namely finding the answer to the question being asked, and to map this particular answer to the abstract response function. A patient with memory deficits for example may not be able to think of the answer to a question, or to maintain the abstract link between response function and answer word in the short-term memory. Also the delay range of responses in non-responsive patients is usually not known, in contrast to healthy controls. For these reasons, some patients may show responses to command following, but fail to do so in real communication tasks [191]. Reducing the mental workload, more intuitive BCI paradigms as proposed in recent studies [105, 125, 192, 190] where no intermediate mapping is required but the patients directly pay attention to what they want to communicate are promising future directions to be used in non-responsive patients.

Since the group of patients with DOCs is very heterogeneous, only few assumptions about their abilities can be made. It is therefore important to develop different BCIs based on various brain signals and modalities, and to select the most reliable and robust response individually for each patient. A promising option is also to combine multiple brain patterns, multimodal signals, or multisensory stimuli within one hybrid or multimodal BCI system [154, 182, 186, 219]. In this way, the overall performance may be increased, the susceptibility to artifacts reduced, the BCI may be applicable to a broader range of patients, and multiple independent control signals may be available. However, as demonstrated within this thesis, hybrid BCIs need to be carefully designed, to avoid unintended interaction effects between different stimulation or brain signals. As also highlighted in a recent review paper about multimodal BCIs [154], it is therefore essential to investigate in more detail the underlying mechanisms of inter- and cross-modal interaction and integration in the brain so that effective hybrid or multimodal BCIs can be designed in future. Moreover, individually identifying the optimal combination of brain patterns and modalities, and the integration of multimodal feedback may be required for the successful use of such BCIs in non-responsive patients.

3.5. Conclusion

Within this thesis, important steps towards communication with non-responsive patients were made. Different BCI approaches based on SSSEP, tactile P300, and auditory P300 were developed to be used with patients in clinical environments. Using a hybrid BCI setup, interaction effects between different types of combined stimulation signals were demonstrated, revealing new insights which may be important for the future development of hybrid BCIs. In recent years, various other approaches for assessment of and communication with DOC patients which can be found in literature were developed. The BCIs developed within this thesis fit very well in this range of novel methods and extend the range of potential tools for bedside assessment and communication with DOC patients. These tools may one day be incorporated into the standard home and clinical setting of DOC patients and may not only improve diagnoses and treatment options, but increase quality of life by providing a means of communication.

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Appendix

Appendix A.

Publications

A.1. A Tactile Stimulation Device for EEG Measurements in Clinical Use

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A Tactile Stimulation Device for EEG Measurements in Clinical Use

Christoph Pokorny, Christian Breitwieser, and Gernot R. Müller-Putz

***Abstract*—A tactile stimulation device for EEG measurements in clinical environments is proposed. The main purpose of the tactile stimulation device is to provide tactile stimulation to different parts of the body. To stimulate all four major types of mechanoreceptors, different stimulation patterns with frequencies in the range of 5–250 Hz have to be generated. The device provides two independent channels, delivers enough power to drive different types of electromagnetic transducers, is small and portable, and no expensive components are required to construct this device. The generated stimulation patterns are very stable, and deterministic control of the device is possible. To meet electrical safety requirements, the device was designed to be fully galvanically isolated. Leakage currents of the entire EEG measurement system including the tactile stimulation device were measured by the European Testing and Certifying Body for Medical Products Graz (Notified Body 0636). All measured currents were far below the maximum allowable currents defined in the safety standard EN 60601–1:2006 for medical electrical equipment. The successful operation of the tactile stimulation device was tested during an EEG experiment. The left and right wrist of one healthy subject were randomly stimulated with seven different frequencies. Steady-state somatosensory evoked potential (SSSEPs) could successfully be evoked and significant tuning curves at electrode positions contralateral to the stimulated wrist could be found. The device is ready to be used in clinical environment in a variety of applications to investigate the somatosensory system, in brain-computer interfaces (BCIs), or to provide tactile feedback.**

***Index Terms*—Biomedical electronics, electrical safety, electroencephalography (EEG), leakage current, steady-state somatosensory evoked potential (SSSEP), tactile stimulation.**

I. Introduction

TACTILE stimulation applied to different parts of the body is commonly used to study the human somatosensory system [1]–[11]. By repetitive tactile stimulation with a sufficiently high rate, steady-state somatosensory evoked potentials (SSSEPs) can be evoked and measured using electroencephalography (EEG) [12]. In healthy subjects, SSSEPs were investigated in several studies to find "resonance-like" frequencies of the somatosensory system [2]–[4], modulation effects due to attention [6]–[8] and interaction effects between simultaneous stimuli [11]. The influence of the stimulation waveform on the resulting SSSEP amplitude was also explored [13]. Beyond that, a brain-computer interface (BCI) based on SSSEPs was successfully realized by simultaneously stimulating the left and right index finger while the subjects had to focus attention on either of them modulating the resulting SSSEPs [14]. Bypassing the natural muscular output, a BCI can provide a means of communication and control for patients with severe neurological deseases or injuries [15], [16]. In most patients, the somatosensory system is assumed to remain functional thus offering a possible channel for stimuli and feedback presentation usable for BCI control [14], [17].

Usually, in studies involving tactile stimulation, some kind of stimulation device is required to generate tactile stimuli. In many studies investigating SSSEPs, custom-built stimulation devices [2], [3], [18] or computers with amplifiers [4], [6]–[8], [14], mostly driving some electromagnetic transducer are mentioned. Commonly used stimulation patterns are sinusoidal signals [6]–[9] or amplitude-modulated stimulation patterns with carrier frequencies up to 200 Hz [2], [3], [14], [18], [19]. Other approaches involve air-puff stimulation [20], [21], pneumatically [5], [22] or hydraulically [23] driven stimulators, or monofilaments [24]. These other approaches, however, are mostly intended for magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) studies, providing rectangular stimulation patterns with low repetition rates only and are thus hardly suitable to evoke SSSEPs. Commercially available stimulation devices, such as Eval.2.0 Tactor Controller (Engineering Acoustics, Inc., Casselberry, Florida, USA) or g.STIMbox (g.tec medical engineering GmbH, Schiedlberg, Austria) are also not capable of generating sinusoidal or modulated stimulation patterns. The QS Piezostimulator (QuaeroSys Medical Devices, Schotten, Germany) which is capable of generating such waveforms is, however, not portable and only drives Braille-like pin matrix transducers which cannot be mounted to different body parts very easily.

Consequently, to overcome these limitations, the aim of our work was to develop a flexible, low-cost tactile stimulation device. The device should reliably evoke SSSEPs and should be used during EEG or similar neurophysiological measurements. The device should be capable of generating sinusoidal and modulated waveforms and of driving different kinds of electromagnetic transducers which can be attached to various parts of the body. The idea was to develop a portable and safe device which can be used not only under laboratory conditions but also with

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patients with severe neurological diseases or injuries in clinical environments.

II. Materials and Methods

In the first part of this section, some important requirements for the tactile stimulation device are specified. Then, the design of the device is shown in detail. Finally, the methods of testing the performance and safety of the device are described.

A. Requirements

The design of the tactile stimulation device is subject to two main requirements, namely generation of proper stimulation patterns and safety.

1) Stimulation Pattern: The main purpose of the tactile stimulation device is to provide tactile stimulation to different parts of the body. Based on neurophysiological considerations, the required stimulation patterns can be specified. From literature [25]–[27] it is known that there are four major types of mechanoreceptors in the human glabrous skin. These are Ruffini endings, Merkel cells, Meissner and Pacinian corpuscles, the first two being slowly adapting, the latter two rapidly adapting mechanoreceptors. Ruffini endings are sensitive to streching of the skin whereas Merkel cells respond to static pressure and skin indentation with extremely low frequencies (5–15 Hz [25]). Meissner corpuscles are mostly sensitive to dynamic pressure and vibrations with mid-range frequencies (20–50 Hz [25]). Pacinian corpuscles respond to vibrations with higher frequencies (60–400 Hz [25]) and have their maximum sensitivity around 200–250 Hz [25], [27]. Therefore, to be capable of stimulating all four types of mechanoreceptors, the tactile stimulation device is required to cover the whole frequency range of 5–250 Hz. To be maximally flexible and to use the device in a variety of applications, possible stimulation patterns should include sinusoidal and rectangular waveforms. Beyond that, amplitude modulation of a high-frequency carrier with a mid- or low-frequency stimulation signal should be possible whenever needed.

2) Safety: The tactile stimulation device is regarded as medical device. Since the electromagnetic transducers are in direct contact with the person being stimulated, the stimulation device must meet certain safety requirements. To ensure electrical safety for patients and users, leakage currents must not exceed the maximum allowable currents defined in the safety standard EN 60601–1:2006 for medical electrical equipment. Not only the stimulation device but the entire system consisting of all functionally connected components has to be taken into account due to the increased risk of interference and hazardous couplings among devices [28]. This means that all applied parts (i.e., electromagnetic transducers) and intended accessories (e.g., power supply) must be included in the safety considerations. If the device is not used stand-alone, this may also involve an external computer or EEG measurement system the device is connected to. In such cases, leakage currents of the whole setup have to be measured and must not exceed the maximum allowable limits.

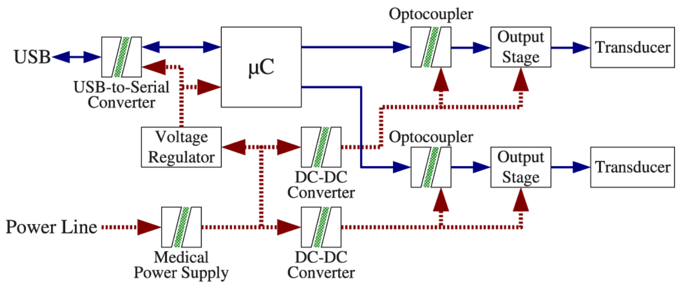

Fig. 1. Schematic diagram of the tactile stimulation device. The core element is a microcontroller that generates the stimulation signals. These signals are filtered and amplified in the output stage and used to drive the transducers. For safety reasons, the device and each transducer are fully galvanically isolated. The power supply (red thick dashed lines) and signal paths (blue thin solid lines) are shown with all isolation barriers (green hatched areas).

B. Design

1) Architecture: The overall architecture of the tactile stimulation device is depicted in Fig. 1. The core element of the device is a microcontroller that generates the stimulation signals. Two independent stimulation channels are available to stimulate different body locations (e.g., left and right index finger). Each stimulation signal is filtered and amplified in an output stage and used to drive an electromagnetic transducer, converting electrical to tactile stimulation signals. Communication to a computer can be established via USB (Universal Serial Bus) by means of a USB-to-Serial converter. The tactile stimulation device is powered by a medical power supply. For safety reasons, the device and each transducer are fully galvanically isolated.

2) Signal Generation: A low-cost 8-bit microcontroller ATmega328 (Atmel, San Jose, California, USA) clocked with 16 MHz is used to generate two independent stimulation signals. For this purpose, two analog output channels of the microcontroller based on 8-bit pulse width modulation (PWM) with 5 V output voltage and 62.5 kHz PWM frequency are used. The desired stimulation patterns are generated by means of direct digital synthesis (DDS) with a clock frequency of 7.8 kHz. In this way, rectangular, sinusoidal or similar waveforms in the frequency range of 5–250 Hz, also amplitude-modulated when needed, can be generated. To reconstruct the analoge output signals from the PWM signals, a low-pass filter is applied in the subsequent output stage.

3) Output Stage: The PWM output signals from the microcontroller need to be filtered with a reconstruction low-pass filter to remove the high-frequency components introduced by the PWM. Furthermore, the signals need to be amplified to be strong enough to drive electromagnetic transducers. Therefore, for each channel, an output stage consisting of a filter and amplifier, as shown in Fig. 2, was designed. A Sallen-Key filter topology consisting of the resistors R1, R2, the capacitors C1, C2 and a rail-to-rail operational amplifier OP1 was chosen to realize a 2nd-order Butterworth low-pass filter. A push-pull output driver with low distortions using bipolar transistors T1 and T2 and negative feedback (unity gain) is used to drive the transducers. The capacitor C3 is used to eliminate DC components in the stimulation signal. Each output stage is powered with 12 V operating voltage by a 2W DC-DC converter, providing

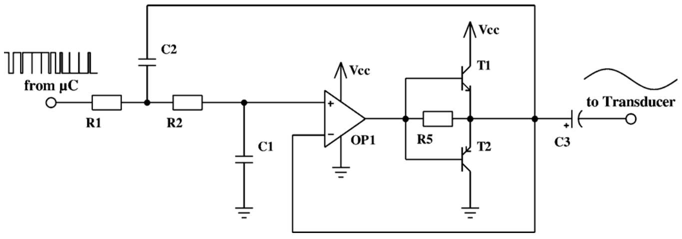

Fig. 2. Schematic of the output stage. Within this stage, the stimulation signals are reconstructed from the PWM signals generated by the microcontroller (μC), and amplified to drive an electromagnetic transducer. This stage consists of a Sallen-Key low-pass filter together with a push-pull output driver with negative feedback (unity gain).

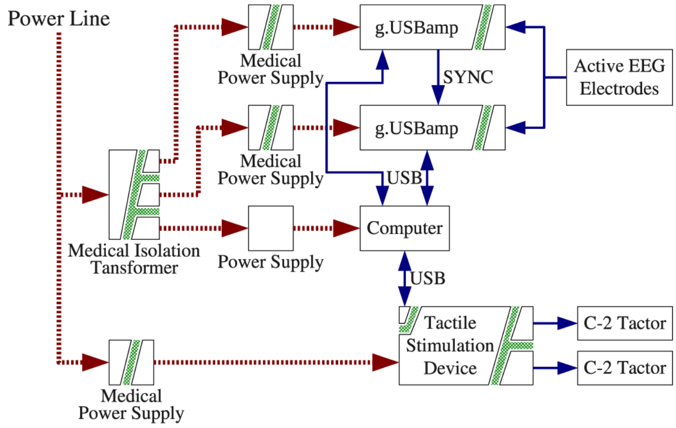

Fig. 3. Schematic diagram of the test setup used during an EEG experiment. The system consisted of a computer, two synchronized g.USBamp EEG amplifiers with active electrodes and the tactile stimulation device with two C-2 tactors. The power supply (red thick dashed lines) and signal paths (blue thin solid lines) are shown with all isolation barriers (green hatched areas).

enough power to drive commonly used electromagnetic transducers, such as C-2 tactors (Engineering Acoustics, Inc., Casselberry, Florida, USA) which are recommended to be typically driven by a 0.5 W amplifier [29].

4) Communication: The device is designed to be used standalone, meaning that when switching on the device, some preprogrammed stimulation pattern is immediately generated on its outputs. Whenever needed, a USB connection, realized using a USB-to-Serial converter, is available to connect the device to a computer. The computer can take control over the device by sending a certain serial command to enter the communication mode. Once entered the communication mode, device settings, such as stimulation frequency or magnitude of a certain channel, can be changed. The device, on the other hand, can transmit status messages back to the computer. When in communication mode, all stimulation outputs are disabled. When leaving the communication mode, all new settings are applied and all outputs are enabled again. Using the Boost.Asio low-level C++ library to access the serial port, fast and deterministic control of the device is possible (cf. Section III-A).

5) Safety: To meet safety requirements, the stimulation device is fully galvanically isolated. More precisely, the device is galvanically isolated from the power line and from any possibly connected computer, reducing earth leakage and touch currents. Each electromagnetic transducer which is intended to be in direct contact with a patient is galvanically isolated too, reducing hazardous patient leakage and auxiliary currents. In Fig. 1, the power supply and signal paths including all isolation barriers can be seen. The tactile stimulation device is powered by an isolated 12 V medical power supply (FRIWO MPP 15 Medical). A 5 V voltage regulator is used to power the microcontroller and the USB-to-serial converter which is optically isolated by optocouplers (Fairchild 6N137). Isolated DC-DC converters (RECOM R12P212S) and optocouplers (Fairchild H11L1M) are used to isolate the signal path and power supply of each electromagnetic transducer.

C. Testing

The first part of this section specifies the setup the device was tested in. Then, the procedures to test different characteristics of the stimulation device are described.

1) Test Setup: The newly designed tactile stimulation device was tested in practice in a setup typically used in EEG experiments (see Fig. 3). The core component of this setup was a computer used to control the whole experiment. To generate tactile stimuli, the tactile stimulation device with two C-2 tactors (Engineering Acoustics, Inc., Casselberry, Florida, USA) was connected via USB to this computer. C-2 tactors are linear actuators which provide strong point-like sensation, have a peak displacement of 1 mm and a nominal impedance of 7 Ω[29]. C-2 tactors were selected since they turned out to be very useful in practice and can be attached to different body parts very easily (e.g., using elastic wrist bands or finger clips). To acquire EEG data, two g.USBamps (g.tec medical engineering GmbH, Schiedlberg, Austria) with 32 active electrodes were connected via USB to this computer as well. Both g.USBamps were synchronized by means of a sync cable. Galvanically isolated medical power supplies were used to power the tactile stimulation device and the g.USBamps. Since the computer with its power supply was not a medical device, a medical isolation transformer (Toroid ISB-100 W) which also powered the power supply of the g.USBamps established galvanic isolation.

2) Communication: The communication delay between the computer dispatching a serial command and the stimulation device receiving the command was measured. The point in time when dispatching a command was marked by toggling an output pin of the computer's parallel port. The point in time when receiving the command was marked by toggling one of the I/O pins of the device's microcontroller. The signals of the parallel port and the I/O pin were recorded using the data acquisition device NI 6031E (National Instruments, Austin, TX, USA) with a sampling rate of 50 KHz. Time differences between both signals were extracted and statistically analyzed.

3) Stimulation Pattern: The stimulation device was programmed to generate two different stimulation patterns: (i) Sine tap stimuli were realized using a 200 Hz sinusoidal carrier signal modulated with a rectangular signal of the respective stimulation frequency. The modulated signal was generated in such a way that the carrier signal always started and stopped at phase zero. The duty cycle of the rectangular modulation signal was chosen greater than or equal 50%, exactly matching multiple integers of the period time of the carrier signal. (ii) Sine AM (amplitude modulation) stimuli consisted of a 200 Hz sinusoidal carrier signal which was amplitude modulated with a sinusoidal signal. The modulated signal was generated in such a way that the carrier signal always started at phase zero.

The amplitude and frequency stability of the output signals generated by the tactile stimulation device were tested under load. For both stimulation patterns, a stimulation (i.e., modulation) frequency of 23 Hz was chosen. The stimulation pattern of one output channel with a C-2 tactor connected was recorded using the same data acquisition device and sampling rate as in the communication test. Additionally, to facilitate analysis of the recorded data and proper alignment of the recorded modulated waveforms, an internal trigger signal was recorded from one of the I/O pins of the device's microcontroller.

4) Safety: To test the electrical safety of the tactile stimulation device used in the EEG setup, leakage current measurements were conducted by the European Testing and Certifying Body for Medical Products Graz (Notified Body 0636). Not only the stimulation device alone but the entire EEG measurement system including all functionally connected components was taken into account. Earth leakage currents, touch currents, patient leakage currents and patient auxiliary currents of the entire system were measured under normal condition, single fault condition and with an external voltage applied on the patient connection. The measurements were conducted with 1 ground and 1 reference electrode, all 32 active electrodes and two C-2 tactors connected, which are all applied parts of type BF (Body Floating). The applied parts were grouped by connecting all applied parts of the same type, resulting in one group with electrodes and one with tactors. Patient leakage currents were measured for each group separately and patient auxiliary currents were measured between both groups of applied parts. Total patient leakage currents were measured by connecting all applied parts of both groups.

5) Neurophysiological Experiment: To test the correct operation of the device, an EEG experiment was conducted. The aim of this experiment was to test whether SSSEPs can reliably be evoked using the tactile stimulation device. Sine tap stimuli (see Section Section II-C.3), which are commonly used in EEG studies intended to evoke SSSEPs [14], [18], [19], were used as stimulation pattern. One healthy subject voluntarily participated in this experiment. The experiment was approved by the Ethics Committee of the Medical University of Graz and was conducted in accordance with the Declaration of Helsinki.

In this experiment, a screening procedure commonly used to find the individual "resonance-like" frequencies, i.e., the frequencies yielding the highest SSSEP response of the somatosensory system [4], [14], [18], was conducted. The subject was sitting in an armchair with the hands comfortably placed on armrests. The two C-2 tactors were attached to the left and right volar wrist using elastic wrist bands (see Fig. 4). In general, tactile stimuli on the wrists can be perceived and localized very well, especially when mounting just one transducer on each wrist [30], [31]. Both the left and right wrist of the subject were stimulated with seven frequencies ranging from 14 to 32 Hz in steps of 3 Hz. As shown in Fig. 5, each trial started with a reference interval without stimulation (length 2.5 s) followed by seven stimulation intervals (length 2 s each). Within each trial,

Fig. 4. Tactile stimulation device with two C-2 tactors connected. The tactors can be attached to the left and right wrist using elastic wrist bands.

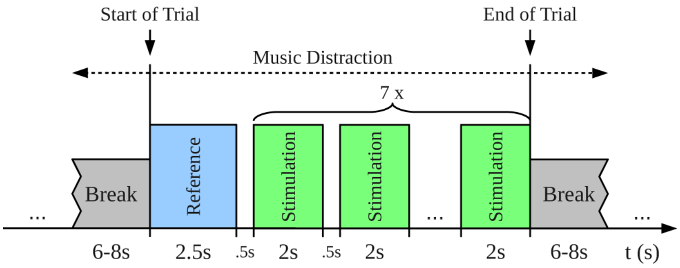

Fig. 5. Screening paradigm. Each trial started with a reference interval without stimulation (length 2.5 s) followed by seven stimulation intervals (length 2 s each) with random stimulation frequencies and wrists. As distraction, a relaxing music was presented during the whole experiment.

the stimulation frequencies and wrists were chosen randomly, but the same frequency and wrist was never used twice in succession. The subject was not supposed to focus attention on the stimuli to avoid attentional modulation of the SSSEPs during the screening procedure. Therefore, relaxing music was presented via headphones to distract the subject during the whole experiment. The subject was instructed to just relax and listen to the music without paying any attention to the tactile stimuli. In total, the paradigm consisted of 40 repetitions per frequency and wrist, divided into 8 runs with 10 trials each. The whole experiment lasted around 40 minutes.

In this experiment, only 14 EEG channels covering the primary somatosensory cortex were actually recorded. The electrode setup (according to the international 10–20 system) can be seen in Fig. 6. The ground electrode was connected to the right mastoid, the reference electrode was attached to the left earlobe. EEG data were acquired with a sampling rate of 512 Hz.

To analyze the recorded EEG data, seven bipolar channels covering the primary somatosensory cortex were derived, namely FC5-CP5, FC3-CP3, FC1-CP1, FCz-CPz, FC2-CP2, FC4-CP4 and FC6-CP6. Mean fast Fourier transform (FFT) spectra (zero-padded, window length 16 s) were computed to detect SSSEPs elicited by the tactile stimulation. Additionally, tuning curves showing the percentage band power increase [4] of the stimulation intervals relative to the reference intervals were computed separately for all seven bipolar channels. These percentage band power values were averaged across trials. To identify statistically significant results, 95% confidence intervals were estimated by bootstrapping using 1000 bootstrap samples. Band power values with non-overlapping confidence

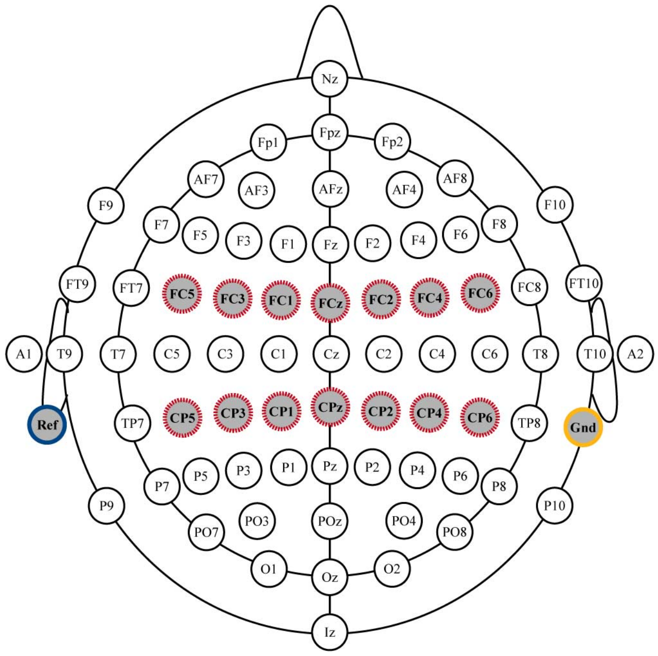

Fig. 6. Electrode setup (according to the international 10–20 system) of the EEG experiment. The EEG was recorded at electrode positions marked with bold dashed circles. The right mastoid was used as ground (Gnd), the left earlobe as reference (Ref).

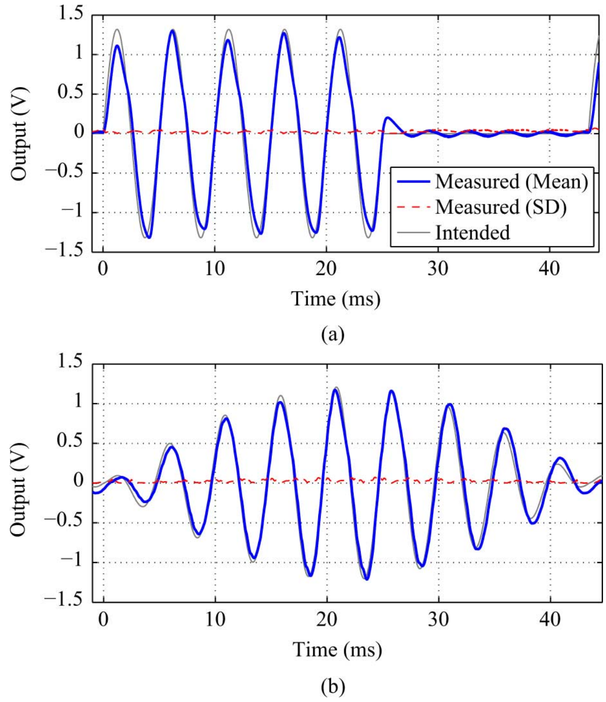

Fig. 7. Measured simulation patterns for (a) sine tap stimuli and (b) sine AM stimuli. The output voltage of the stimulation device (23 Hz stimulation frequency) was recorded with a C-2 tactor connected. The mean signals (blue solid line) averaged over 1960 periods together with the standard deviations (SD; red dashed line) are shown. The intended patterns are drawn in the background (gray thin line).

intervals are considered as statistically significant band power increases.

III. Results

A. Communication

The communication delay was computed based on 9758 serial commands transmitted from the computer to the stimulation device. The mean delay was found to be 293 μs (median 300 μs) with a standard deviation of 20 μs. The minimum and maximum values were 260 μs and 400 μs respectively, which yields a maximum communication jitter of 140 μs. In general, when averaging signals in the time domain (e.g., somatosensory evoked potentials (SEPs) evoked by tactile stimulation) which are temporally misaligned due to some communication jitter, a low-pass filter effect can be observed [32]. Based on the measured values of the communication delay, the 3 dB cutoff frequency of this low-pass filter effect was computed to be at 8081 Hz.

B. Stimulation Pattern

To analyze the amplitude and frequency stability of the stimulation signal, roughly 1.5 minutes (1960 periods) of each of the modulated stimulation patterns were recorded. In Fig. 7, the averaged waveforms, aligned to the rising edges of the trigger channel, together with the standard deviations are shown. Additionally, the intended patterns are drawn in the background of the figures. It can be seen that the actually measured waveforms have very small standard deviations and look very similar to the intended patterns.

The mean period of the sine tap stimulation signal, shown in Fig. 7(a), was found to be 43.53 ms (median 43.52 ms) with a standard deviation of 66 μs. The minimum and maximum values were 43.44 ms and 43.72 ms respectively, which yields a maximum jitter of 280 μs. Based on these measurements, a mean stimulation frequency of 22.97 Hz and a frequency jitter of 147 mHz can be computed. To assess the amplitude stability of this pattern, the amplitude of the first period of the sinusoidal carrier signal (i.e., the first peak) was analyzed. The mean amplitude was found to be 1.113 V (median 1.112 V) with a standard deviation of 2.3 mV. The minimum and maximum values were 1.112 V and 1.120 V respectively, which yields a maximum amplitude jitter of 8.5 mV.

The mean period of the sine AM stimulation signal, shown in Fig. 7(b), was found to be 43.72 ms (median 43.68 ms) with a standard deviation of 90 μs. The minimum and maximum values were 43.66 ms and 43.98 ms respectively, which yields a maximum jitter of 320 μs. Based on these measurements, a mean stimulation frequency of 22.87 Hz and a frequency jitter of 167 mHz can be computed. To assess the amplitude stability of this pattern, the amplitude of the fifth period of the sinusoidal carrier signal (i.e., the highest peak in the middle) was analyzed. The mean amplitude was found to be 1.175 V (median 1.175 V) with a standard deviation of 2.0 mV. The minimum and maximum values were 1.17 V and 1.180 V respectively, which yields a maximum amplitude jitter of 10.1 mV.

C. Safety

In Table I, the results of the leakage current measurements together with the maximum allowable values defined in the safety standard EN 60601–1:2006 are summarized. Where specified,

TABLE I
MEASURED AND MAXIMUM ALLOWABLE CURRENTS OF THE ENTIRE EEG MEASUREMENT SYSTEM UNDER NORMAL CONDITION (NC), SINGLE FAULT CONDITION (SFC), AND WITH AN EXTERNAL VOLTAGE ON THE PATIENT CONNECTION (EXT). THE MEASUREMENTS WERE CONDUCTED BY THE EUROPEAN TESTING AND CERTIFYING BODY FOR MEDICAL PRODUCTS GRAZ

Current	Condition	Measured (μA)	Allowable (μA)
Earth leakage current	NC	73	5000
Earth leakage current	SFC	116	10000
Touch current	NC	3	100
Touch current	SFC	73	500
Patient leakage current DC	NC	<1	10
Patient leakage current DC	SFC	<1	50
Patient leakage current AC	NC	<1	100
Patient leakage current AC	SFC	17	500
Patient leakage current	EXT	50	5000
Patient auxiliary current DC	NC	<1	10
Patient auxiliary current DC	SFC	4	50
Patient auxiliary current AC	NC	<1	100
Patient auxiliary current AC	SFC	3	500
Total patient leakage current DC	NC	<1	50
Total patient leakage current DC	SFC	<1	100
Total patient leakage current AC	NC	<1	500
Total patient leakage current AC	SFC	18	1000
Total patient leakage current	EXT	53	5000

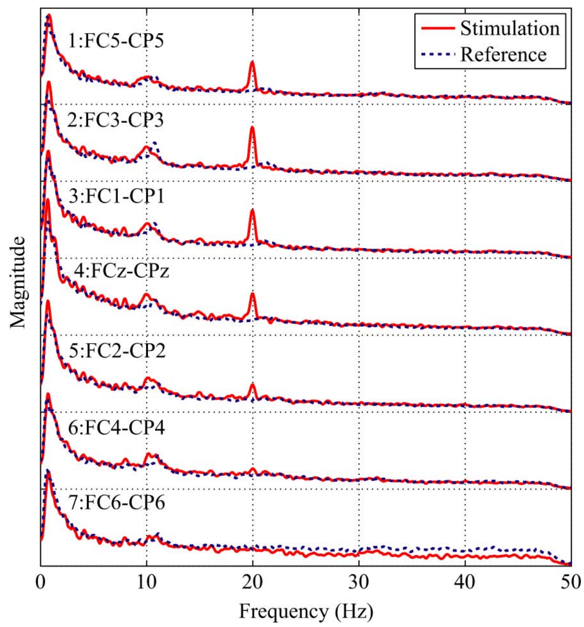

Fig. 8. FFT spectra of all seven bipolar EEG channels. The mean spectra of the reference intervals (blue dashed line) and the stimulation intervals with 20 Hz stimulation of the right wrist (red solid line) can be seen. The emergence of an SSSEP at 20 Hz is clearly visible on channels contralateral to the stimulated wrist.

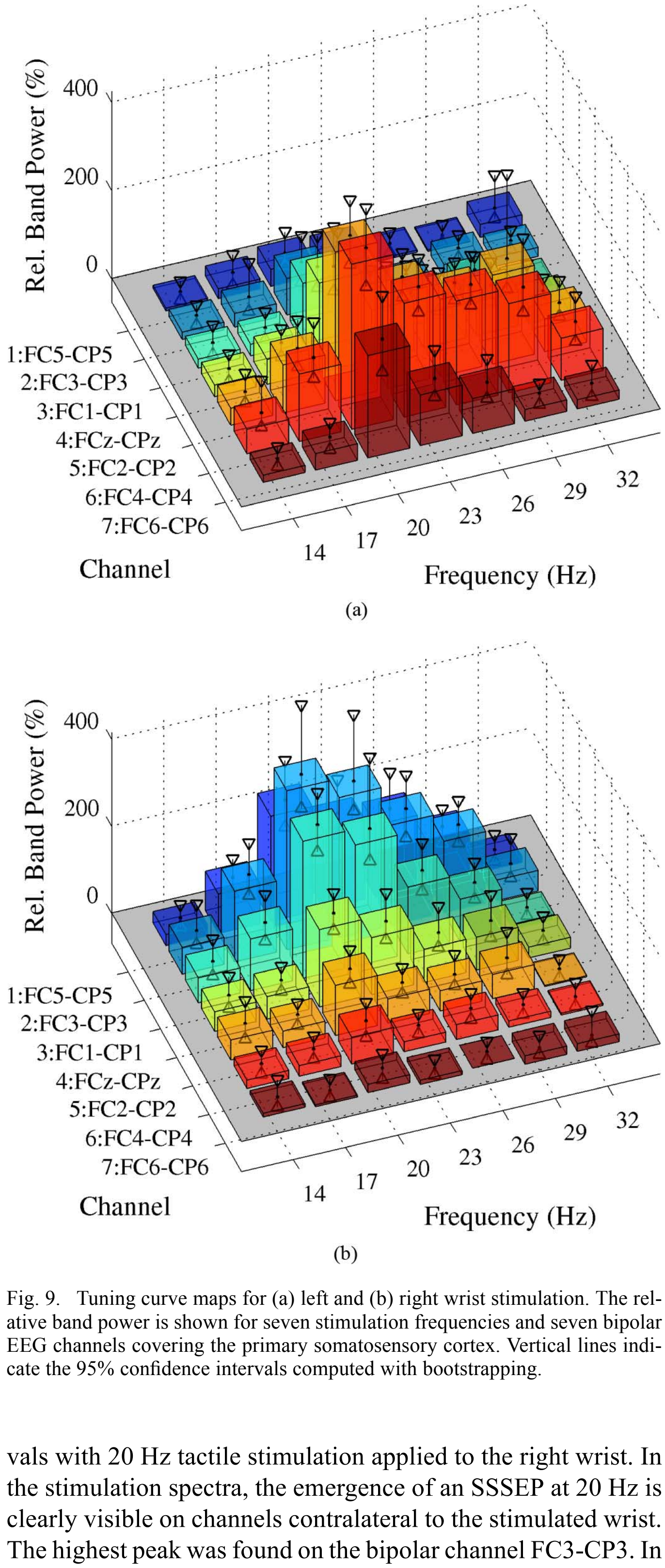

Fig. 9. Tuning curve maps for (a) left and (b) right wrist stimulation. The relative band power is shown for seven stimulation frequencies and seven bipolar EEG channels covering the primary somatosensory cortex. Vertical lines indicate the 95% confidence intervals computed with bootstrapping.

separate measurements were taken for DC and AC. Otherwise, the values may be DC or RMS (root mean square) values. Only the measured maximum values of each category are reported.

As it can be seen in Table I, all measured currents of the entire EEG measurement system including the tactile stimulation device were found to be far below the maximum allowable currents defined in EN 60601–1:2006.

D. Neurophysiological Experiment

As an example, Fig. 8 shows the mean reference and stimulation FFT spectra of all seven bipolar EEG channels for intervals with 20 Hz tactile stimulation applied to the right wrist. In the stimulation spectra, the emergence of an SSSEP at 20 Hz is clearly visible on channels contralateral to the stimulated wrist. The highest peak was found on the bipolar channel FC3-CP3. In contrast, in the reference spectra, no magnitude increase could be found.

In Fig. 9, the entire results of the screening procedure are summarized. Tuning curve maps showing the percentage band power increase of the stimulation intervals relative to the reference intervals can be seen. The relative band power is shown for all seven stimulation frequencies and all seven bipolar channels for both left and right wrist stimulation. The tuning curve maps are shown together with 95% confidence intervals. Both for left and right wrist stimulation, the emergence of significant tuning curves with clear peaks at channels contralateral to the stimulated wrist can be seen. In contrast, channels on the ipsilateral side show no or just a slight increase in band power. The confidence intervals of the tuning curves on the contralateral and ipsilateral side are clearly non-overlapping. Therefore, the tuning curves can be considered to be statistically significant. Maximum values were reached for both wrists at a stimulation frequency of 20 Hz. The maximum relative bandpower increase for left wrist stimulation could be found at the bipolar channel FC4-CP4 (374%) whereas the maximum increase for right wrist stimulation could be found at the bipolar channel FC3-CP3 (365%).

IV. Discussion

Within our work, a tactile stimulation device for EEG measurements has been proposed. When designing the device, the two main requirements could be fulfilled. First, the device was tested to be electrically safe and is ready to be used for EEG measurements in clinical environments. In case the device is used in other setups than the tested one, leakage currents have to be remeasured though. Second, it could be shown that the device can generate different stimulation patterns which are very stable in terms of frequency and amplitude. Moreover, it was possible to reliably evoke SSSEPs during a practical EEG experiment using a modulated stimulation pattern commonly used in EEG studies investigating SSSEPs. This EEG experiment was conducted with a healthy subject rather than with patients since the expected brain response of healthy subjects is well-known from previous studies and literature. In a screening procedure, the emergence of significant tuning curves at electrode positions contralateral to the stimulated wrist could be found which was not the case at positions ipsilateral to the stimulated wrist. These results are both pysiologically meaningful and consistent with literature since sensory information is known to be processed on the contralateral side of the cortex [25], [26]. Moreover, also other studies showed the emergence of tuning curves with greatest SSSEP amplitudes on the contralateral side of the stimulated hand [2]–[4], [18], [19]. In our study, the maxima of the tuning curves of both wrists were found at 20 Hz. Similar findings were also reported in other studies although other parts of the hands were stimulated. Narrow tuning curves with their maxima between 17 and 31 Hz were reported when stimulating the tips of the fingers [4], [18], [19], and at 21 Hz when stimulating the palmar surface of a hand [2], [3]. Therefore, in our EEG experiment, screening results from previous studies could basically be replicated, which can be regarded as a validation of the correct operation of the stimulation device.

The tactile stimulation device was designed to be used in a variety of applications. The device provides two independent channels and delivers enough power to drive different types of electromagnetic transducers. Obviously, the architecture of the device allows for easy expansion to more than two channels. The device may not only be used for EEG but also during similar neurophysiological measurements, such as functional near-infrared spectroscopy (fNIRS). The device is small and portable, and no expensive components are required to construct this device. Whenever needed, modulated sinusoidal or rectangular stimulation patterns can be realized by reprogramming the microcontroller. Possible applications could be to use the device to investigate the somatosensory system, specifically the effects of different stimulation patterns or interaction effects between different body locations. Moreover, since the communication jitter was shown to be very small, evoked signals can also be averaged and analyzed in the time domain, which is particularly important for SEP recordings. Additionally, the device could be used in BCI applications based on SSSEPs [14], [18], in multimodal BCIs [33], and to realize oddball paradigms needed in P300-based BCIs [34]. Beyond that, the device could be used as a tactile feedback channel for BCIs [35], [36]. The tactile modality has some advantages over other forms of sensory inputs, such as the auditory or visual modality. Tactile transducers can be attached to different body parts hidden under the user's clothes, providing tactile stimuli unnoticeable to others [34]. Another advantage of tactile stimulation is that eyes and ears of the user are kept free [34]. Also, since patients with severe neurological diseases or injuries may lose volitional control of their gaze [14], they might be unable to use vision-based BCIs. In such a case, tactile stimuli could be an alternative since the somatosensory system is expected to remain functional [14], [17]. The idea was to use the stimulation device not only under laboratory conditions but also in clinical environments directly at the patient's bedside. Patients who may be included in future investigations are patients with amyotrophic lateral sclerosis and patients in a minimally conscious or vegetative state. Certainly, very few assumptions about the brain response of patients with severe neurophysiological diseases or injuries to tactile stimuli can be made. Therefore, using the stimulation device may open up new directions for clinical research and may provide new insights into the cerebral processing of severly impaired patients.

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A.2. Towards a Single-Switch BCI Based on Steady-State Somatosensory Evoked Potentials

C. Pokorny, C. Breitwieser, C. Neuper, and G. R. Müller-Putz. Towards a single-switch BCI based on steady-state somatosensory evoked potentials. In *Proc. Int. BCI Conf.*, pages 200–203, 2011 [222]

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Towards a Single-Switch BCI Based on Steady-State Somatosensory Evoked Potentials

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Abstract

A single-switch Brain-Computer Interface (BCI) based on steady-state somatosensory evoked potentials (SSSEPs) was designed with the aim to provide non-responsive patients with a means of communication. The main focus of this study was to investigate, whether a single-switch BCI can be realized at all based on SSSEP. First, two different stimulation frequencies were selected using a screening procedure. Then, tactile stimuli with the selected frequencies were applied to the thumb and the middle finger of the subjects' right hand. The subjects were instructed to randomly focus attention on one of the fingers. Both classes were classified against the reference period using lock-in analyzer system (LAS) features and two linear discriminant analysis (LDA) classifiers. The offline classification results were compared and the class with the higher classification accuracy was selected to be used to activate a brain switch. Thirteen out of fourteen healthy subjects performed above chance level for at least one class. This study shows that a single-switch BCI can be realized based on SSSEP in healthy subjects.

1 Introduction

A Brain-Computer Interface (BCI) can provide a means of communication for non-responsive patients. Non-responsive patients are patients who have lost all motor functions due to a severe neurological disease, such as amyotrophic lateral sclerosis (ALS). Several studies showed that patients suffering from ALS are able to operate different kinds of BCIs [1, 2]. Patients with severe neurological diseases may also lose volitional gaze control, making them unable to use vision-based BCIs [3]. To overcome this problem, BCIs based on auditory or tactile stimuli can be used as alternatives. In healthy subjects, a tactile two-class BCI based on steady-state somatosensory evoked potentials (SSSEPs) was successfully applied [3]. In that study, the index fingers of the left and right hand were simultaneously stimulated with different frequencies found in a screening procedure. Two out of four subjects learned to modulate the elicited SSSEPs by focusing attention on one of the fingers.

For patients with severe neurological diseases operating a two-class BCI might be too demanding. However, using a single-switch BCI, only one single brain response that can reliably be detected is sufficient to activate a switch. Eventually, the single-switch BCI can be connected to assistive technology devices that can be controlled by a conventional single switch in order to provide patients with means of communication and control.

The focus of the present study was to investigate, if it is possible to realize a single-switch BCI based on SSSEP in healthy subjects. Starting point of this investigation was a two-class BCI based on SSSEP with two fingers of one hand simultaneously stimulated with different frequencies, individually selected for each subject. The two classes were compared in an offline analysis to find the more responsive class which can be used to activate a brain switch.

2 Methods

Fourteen healthy subjects participated in this study. The subjects were informed about the purpose of the study and were paid for participation. All subjects participated voluntarily and gave informed consent.

Tactile stimuli were applied to the thumb and the middle finger of the subjects' right hand. The fingers were stimulated using C2 tactors [Engineering Acoustics, Inc., Casselberry, Florida, USA]. The tactors were attached to the subjects' fingers using finger clips. The stimulation patterns were created using a self-made stimulation device and consisted of a 200 Hz sinusoidal signal modulated with a rectangular signal (duty cycle 50%) of the respective stimulation frequency [3].

The EEG was recorded using three g.USBAmps [Guger Technologies OG, Graz, Austria] with 48 Ag/AgCl electrodes. The ground electrode was attached to the tip of the nose. Linked mastoids were used as reference. All impedances were kept below 5 kΩ. A sampling rate of 2.4 kHz was used and all EEG measurements were done in a shielded room. For further analyses, the exact electrode positions were measured using the electrode positioning system ELPOS [zebris Medical GmbH, Isny, Germany].

2.1 Experimental Paradigms

The first paradigm of this study was a screening procedure (similar as proposed in [4]) to identify the subjects' "resonance-like" frequencies together with a tuning curve. After the screening procedure, two stimulation frequencies were individually selected for each subject to be used in the single-switch paradigm.

2.1.1 Screening Paradigm

The thumb of each subject was randomly stimulated with twelve frequencies ranging from 13 Hz to 35 Hz in steps of 2 Hz, with 60 trials per frequency. Only the thumb was stimulated assuming that the tuning curves of all fingers are similar [5]. Each trial started with a reference period without stimulation followed by twelve stimulation periods with random stimulation frequencies, as shown in Figure 1. To avoid the subjects to focus attention on the stimuli during the screening procedure, the subjects had to perform a distracting mental arithmetic task.

After the screening procedure, the fast Fourier transform (FFT) was computed and two stimulation frequencies were manually selected for each subject to be used in the single-switch paradigm. The two stimulation frequencies with the highest peaks in the spectrum (compared to the reference period) which were similarly high and separated by at least one other stimulation frequency were selected.

2.1.2 Single-Switch Paradigm

The subjects' thumb and middle finger were simultaneously stimulated using the two frequencies selected after the screening procedure. The subjects were instructed to randomly focus attention on one of the fingers. In order to make it easier to focus attention on one of the fingers, short twitches (i.e., amplitude attenuations similar as proposed in [3]) were inserted in the stimuli of both fingers at random time points. As shown in Figure 2, each trial started with a reference period during which the subject was instructed to just look at the center of a blank screen. After that, a text faded in on the screen instructing the subject to focus attention on one of the fingers. Tactile stimulation was applied on both fingers during the whole trial. In total, the paradigm consisted of 80 trials per class.

2.2 Analysis

EMG (electromyogram) artifacts were manually selected in all data sets and trials containing artifacts were excluded from data analysis. As a first attempt, only the bipolar channel FC3-CP3 that had the highest FFT magnitude across most subjects was selected for classification.

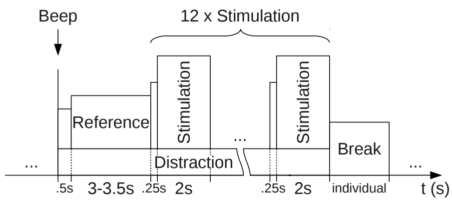

Figure 1: Screening paradigm. After a beep tone, each trial started with a reference period without stimulation (random length 3 s to 3.5 s) followed by twelve stimulation periods (length 2 s each) with random stimulation frequencies. A distracting mental arithmetic task was presented during the whole trial.

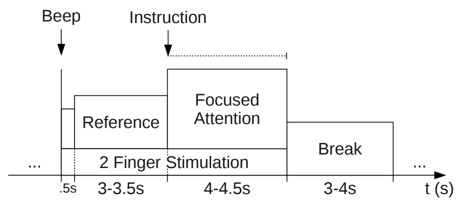

Figure 2: Single-switch paradigm. After a beep tone, each trial started with a reference period (random length 3 s to 3.5 s) followed by a period of focused attention on one of the fingers (random length 4 s to 4.5 s). Tactile stimulation was applied on both fingers during the whole trial.

Magnitude features were extracted at the two stimulation frequencies using a lock-in analyzer system (LAS) [3]. The resulting two time series were smoothed with a moving average filter (length 1 s) and logarithmized. Two linear discriminant analysis (LDA) classifiers (Fisher's LDA) were trained using 10x10 cross-validation. Both classes (focused attention on the thumb and on the middle finger) were separately classified against the reference period (no focused attention). The classification results were compared and the class with the higher classification accuracy was selected and can in principle (i.e., when being above chance level) be used to activate a switch.

3 Results

As an example, Figure 3 shows the offline classification accuracies of both classes (focused attention on the thumb and on the middle finger) against the reference period (no focused attention) for subject s7 (randomly chosen). While the classification accuracy for the thumb remains at chance level, the classification accuracy for the middle finger starts increasing after around 1 s and reaches a maximum value of 65% after around 2 s. The maximum accuracy for the middle finger is above chance level (significance level $\alpha = 5\%$) [6]. Because of removed trials due to EMG artifacts, the number of used trials was varying. Therefore, also the confidence limit of the chance level is different across classes and subjects. Table 1 shows the classification accuracies of the single-switch paradigm for all subjects. The time points with the highest classification accuracy were chosen.

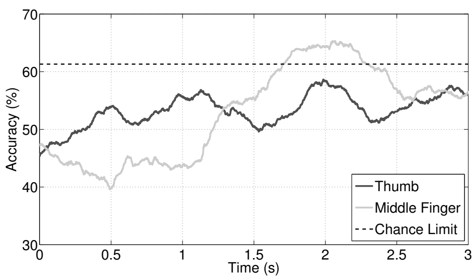

Figure 3: Offline classification accuracies for focused attention on the thumb (dark gray curve) and on the middle finger (light gray curve) against reference for subject s7. The dashed horizontal line at 61% indicates the confidence limit of the chance level ($\alpha = 5\%$).

Subject	s1	s2	s3	s4	s5	s6	s7
Cl1 (%)	**74**	**72**	64*	76	**69**	**70**	58*
Cl2 (%)	73	64	**65**	**78**	64	68	**65**
Subject	s8	s9	s10	s11	s12	s13	s14
Cl1 (%)	**74**	65	**67**	**63**	60*	**64**	57*
Cl2 (%)	72	**66**	66	58*	**68**	**64**	59*

* Below chance limit ($\alpha = 5\%$).

Table 1: Maximum offline classification accuracies for focused attention on the thumb (Cl1) and on the middle finger (Cl2) against reference. The class with the higher accuracy (marked bold) was selected and can be used to activate a switch.

4 Discussion

This study shows that a single-switch BCI can be realized based on SSSEP in healthy subjects. Thirteen out of fourteen healthy subjects performed above chance level for at least one class, nine out of fourteen even for both classes. The class (i.e., the finger) with the higher accuracy can in principle be used to activate a brain switch. Within this study, the transition from a two-class BCI to a single-switch BCI based on SSSEP was demonstrated when two fingers of one hand are simultaneously stimulated with two different frequencies. The frequencies used for stimulation were individually selected by a screening procedure where similar effects as described by Müller-Putz et al. [4] could be observed.

So far, only offline measurements were carried out. To activate a switch in an online paradigm, the output of the classifier with the higher classification accuracy together with a threshold can be used. To increase classification accuracy, investigations about the optimal electrode positions and channel combinations (among all recorded 48 channels) are necessary. According to Burton et al. [7], also regions other than the primary somatosensory cortex are involved in vibrotactile attention. Moreover, higher harmonics of the stimulation frequencies have not yet been taken into account for classification. If a single-switch BCI can be realized with stimuli applied to just one single finger remains an open question and needs to be further investigated, too.

In summary, this study shows that a single-switch BCI can be realized based on SSSEP in healthy subjects. This study is the first step towards a single-switch BCI that eventually may provide non-responsive patients with an alternative means of communication and control.

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A.3. Steady-State Somatosensory Evoked Potentials in Minimally Conscious Patients – Challenges and Perspectives

C. Pokorny, G. Pichler, D. Lesenfants, Q. Noirhomme, S. Laureys, and G. R. Müller-Putz. Steady-state somatosensory evoked potentials in minimally conscious patients – Challenges and perspectives. In *Proc. Int. BCI Conf.*, number 055, 2014. doi: 10.3217/978-3-85125-378-8-55 [226]

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Steady-State Somatosensory Evoked Potentials in Minimally Conscious Patients – Challenges and Perspectives

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Abstract

In the present study, we aimed to detect the "resonance-like" frequencies of the somatosensory system in patients in a minimally conscious state using a screening paradigm. EEG measurements were conducted in seven patients during tactile stimulation of their left and right wrist. A significant tuning curve could be found in one of the patients. Various reasons that could explain the inconclusive outcome of most measurements, as well as future perspectives are discussed.

1 Introduction

A brain-computer interface (BCI) based on electroencephalography (EEG) can provide severely brain-injured people with a new output channel for communication and control [8]. BCIs may also be used as an objective and motor-independent diagnostic tool for patients with disorders of consciousness (see [1] for a review). For patients with impaired hearing or vision, BCIs based on tactile stimuli could be one possible alternative since the somatosensory system is expected to remain functional [4]. By repeatedly applying tactile stimuli with a sufficiently high rate, steady-state somatosensory evoked potentials (SSSEPs) can be evoked and measured using EEG [7]. SSSEPs can intentionally be modulated by attention [2] and, therefore, are one possible way to realize a tactile BCI [4].

As a first step to realize such an SSSEP-based BCI in patients with severe neurological diseases or brain injuries, the "resonance-like" frequencies, i.e. the frequencies with the highest SSSEP response of the somatosensory system [3] need to be identified. Within our work, a well-established screening paradigm was adapted for this purpose to be applied to patients in a minimally conscious state (MCS), i.e. to patients showing non-reflexive behavior but being unable to communicate. Challenges, problems, and results of this attempt are presented. Possible improvements and reasons why the results are not as promising as expected are discussed.

2 Materials and Methods

2.1 Screening Paradigm

Two C-2 tactors (Engineering Acoustics, Inc., USA) were attached to the left and right volar wrist using elastic wrist bands. The wrists were stimulated with seven frequencies ranging from

14 to 32 Hz (3 Hz steps). A modulated stimulation pattern (200 Hz sine carrier), generated by a self-made, medically approved stimulation device [5], was used.

Each trial started with a 2.5 s reference interval without stimulation, followed by seven 2 s stimulation intervals with frequency and wrist randomly chosen (without using the same frequency and wrist twice in a row). To avoid attentional modulation effects of the SSSEPs, relaxing music was presented via headphones to distract the participants. The whole paradigm lasted around 40 minutes and consisted of 40 repetitions per frequency and wrist.

The EEG was recorded with two g.USBamps (g.tec medical engineering GmbH, Austria) using 32 active electrodes. The reference electrode was connected to the left earlobe, the ground electrode to the right mastoid. Bipolar channels were derived at three frontal, seven central, and four parietal positions (international 10-20 system). Tuning curves showing the percentage band power increase of the stimulation intervals relative to the reference intervals [3] were computed. For statistical validation, 95 % confidence intervals were estimated by bootstrapping using 1000 bootstrap samples.

2.2 Participants

Seven patients in an MCS participated in this study (one or two sessions) at the Albert Schweitzer Clinic (Graz, Austria) and the Liège University Hospital (Liège, Belgium). The patients were either sitting in a wheelchair or lying in bed with the upper part of their body slightly elevated. Before or after each EEG measurement, the patients were behaviorally assessed using the Coma Recovery Scale-Revised (CRS-R). Table 1 provides clinical and demographic data together with the CRS-R scores of all patients. Informed consent was obtained from the patients' legal representatives. The study was approved by the Ethics Committees at the participating institutions and was conducted in accordance with the Declaration of Helsinki.

Patient no.	Location	Age (years)	Sex	Etiology	CRS-R s1	CRS-R s2
PA_{01}	Graz	28	male	Traumatic	9	11
PA_{02}	Graz	58	female	Anoxia	8	10
PA_{03}	Graz	67	male	Traumatic	17	17
PA_{04}	Liège	22	male	Traumatic	6	–
PA_{05}	Liège	15	male	Hemorrhagic stroke	15	–
PA_{06}	Liège	51	female	Hemorrhagic stroke	4	–
PA_{07}	Liège	45	female	Traumatic	7	–

Table 1: Clinical and demographic data of the patients, together with the CRS-R scores of the first (s1) and, where applicable, second (s2) session.

3 Results

Fig. 1 shows the SSSEP screening results of all patients and sessions from three representative EEG channels contralateral to the stimulated wrist. Only in one patient, PA_{05}, a significant tuning curve could be found for right wrist stimulation at the bipolar channel F3-C3. The frequency with the highest relative bandpower increase (140 %) was found to be 20 Hz. In all other patients, no significant tuning curves were found at any of the channels contra- or ipsilateral to the stimulated wrist. To demonstrate that the screening paradigm is suitable to identify the individual "resonance-like" frequencies, the results of a healthy control were included (same tactor location; reduced channel set only), showing high tuning curve peaks at 23 Hz for left (373 %) and right (363 %) wrist stimulation.

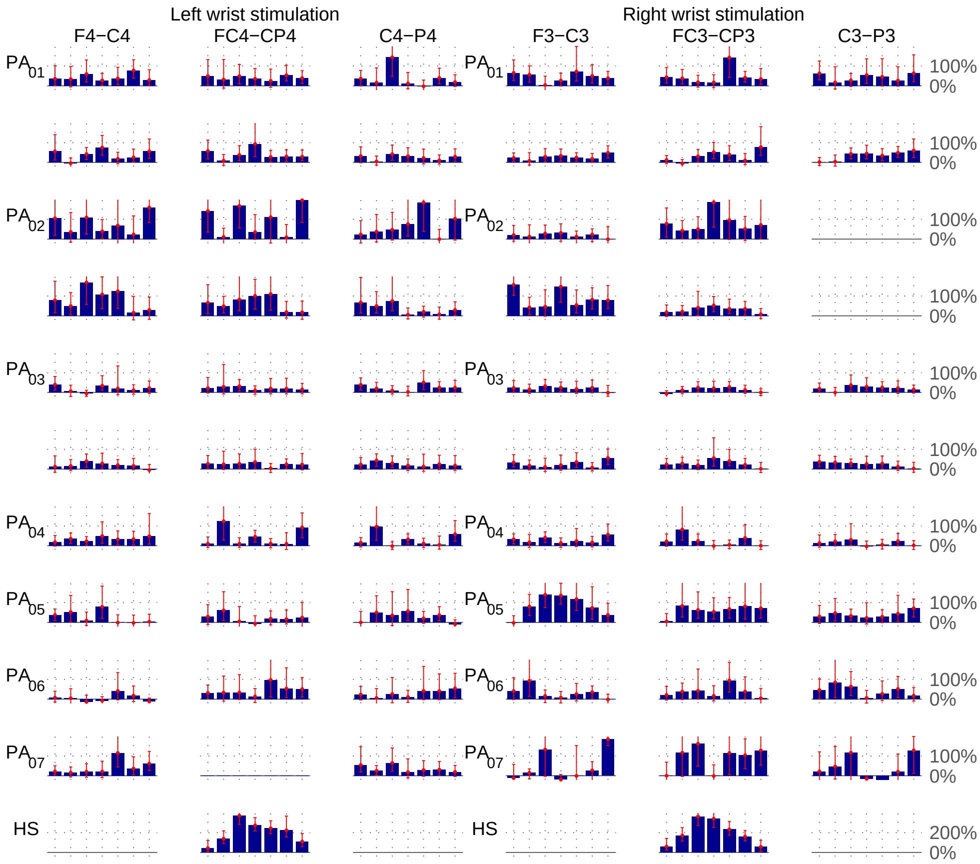

Figure 1: Screening results of all patients and sessions (rows) from three representative (bipolar) EEG channels contralateral to the stimulated wrist (columns). The bars show the relative bandpower increase (in %) with 95 % confidence intervals of all seven stimulation frequencies. The last row shows the results of a healthy subject (HS), using a different y axis scaling.

4 Discussion

Within this work, a screening paradigm was developed with regard to the specific needs and capabilities of patients in an MCS. The wrists were selected as target location, since some of the patients suffered from hand spasticities, making it not easily possible to use more sensitive locations like finger tips. Screening results obtained from a healthy control were totally in accordance with literature (e.g. [3]). However, only in one of the seven patients, a significant tuning curve could be found. In all other patients, stable SSSEPs were not present. In some patients, an increase in band power of only certain single frequencies could be found. However, it is not yet known if perhaps such frequencies could intentionally be modulated and thus be sufficient to realize a BCI. While technical problems seem unlikely (as shown by the control experiment), various other reasons could explain the inconclusive outcome of most patient measurements. First, uncontrolled body movements of the patients resulted in a huge amount of biological (EOG, EMG) and technical (cable movements, electrodes touching the pillow) artifacts. Even though trials containing strong artifacts were manually remove, outliers and huge confidence intervals were still present in the screening results. Second, it was not clear if the position and contact pressure of the tactors allowed the patients to perceive the stimuli strong enough at all, as they could not be simply asked about their perception of the stimuli. Spasticities may have also had a severe influence on the SSSEPs, since the tendons of the finger flexors are located at the volar side of the hand. Third, maybe SSSEPs were not present because of an impaired somatosensory system, or could simply not be measured with EEG due to alterations in the brain topology. Interestingly, the one patient showing significant results was a stroke survivor with a CRS-R score of 15. In comparison to the others, this patient had a high score and no traumatic injury. This could be evidence that the structures in his brain were not that damaged and therefore SSSEPs could be measured.

Similar difficulties regarding a paradigm transition from healthy subjects to patients in an MCS were already reported in [6]. In future, better artifact avoidance or rejection methods, longer stimulation intervals, or other target body locations could be beneficial. Moreover, a thorough neurophysiological examination prior to SSSEP measurements may be helpful.

5 Acknowledgments

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A.4. The Role of Transient Target Stimuli in a Steady-State Somatosensory Evoked Potential-Based Brain–Computer Interface Setup

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The Role of Transient Target Stimuli in a Steady-State Somatosensory Evoked Potential-Based Brain–Computer Interface Setup

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In earlier literature, so-called twitches were used to support a user in a steady-state somatosensory evoked potential (SSSEP) based brain–computer interface (BCI) to focus attention on the requested targets. Within this work, we investigate the impact of these transient target stimuli on SSSEPs in a real-life BCI setup. A hybrid BCI was designed which combines SSSEPs and P300 potentials evoked by twitches randomly embedded into the streams of tactile stimuli. The EEG of fourteen healthy subjects was recorded, while their left and right index fingers were simultaneously stimulated using frequencies selected in a screening procedure. The subjects were randomly instructed by a cue on a screen to focus attention on one or none of the fingers. Feature for SSSEPs and P300 potentials were extracted and classified using separately trained multi-class shrinkage LDA classifiers. Three-class classification accuracies significantly better than random could be reached by nine subjects using SSSEP features and by 12 subjects using P300 features respectively. The average classification accuracies were 48.6% using SSSEP and 50.7% using P300 features. By means of a Monte Carlo permutation test it could be shown that twitches have an attenuation effect on the SSSEP. Significant SSSEP blocking effects time-locked to twitch positions were found in seven subjects. Our findings suggest that the attempt to combine different types of stimulation signals like repetitive signals and twitches has a mutual influence on each other, which may be the main reason for the rather moderate BCI performance. This influence is originated at the level of stimulus generation but becomes apparent as physiological effect in the SSSEP. When designing a hybrid BCI based on SSSEPs and P300 potentials, one has to find an optimal tradeoff depending on the overall design goals or individual subjects' performance. Our results give therefore some new insights that may be useful for the successful design of hybrid BCIs.

Keywords: brain–computer interface (BCI), steady-state somatosensory evoked potential (SSSEP), P300, electroencephalography (EEG), tactile stimulation, transient target stimulus

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1. INTRODUCTION

Brain–computer interfaces (BCIs) can provide a means of communication for persons who have lost all their motor control due to a severe neurological disease or brain injury (Wolpaw et al., 2002). In cases where the visual or auditory system is not functional, a BCI based on tactile stimuli might be the only way to provide a communication channel for such persons. One promising way to realize a tactile BCI is to use steady-state somatosensory evoked potentials (SSSEPs). SSSEPs can be evoked by repetitive tactile stimuli of sufficiently high rate (Regan, 1989). In healthy subjects, a two-class BCI based on SSSEPs could successfully be realized for the first time (Müller-Putz et al., 2006). On the one hand, users of such a BCI have to learn to focus attention on one of several stimulus locations, thereby modulating the respective SSSEP. On the other hand, the BCI needs to be trained to reliably detect such attention-modulated changes in the SSSEPs and translate them into an output channel for communication and control.

In several studies, attention modulation effects of SSSEPs and BCIs based on SSSEPs were investigated (Giabbiconi et al., 2004, 2007; Müller-Putz et al., 2006; Adler et al., 2009; Breitwieser et al., 2011; Severens et al., 2013; Pang and Mueller, 2014). In all of these studies, the use of some kind of randomly appearing transient target stimuli with increased or decreased amplitude which were embedded in the streams of repetitive tactile stimuli was reported. In our work, we follow the nomenclature of Müller-Putz et al. (2006) and refer to these transient target stimuli as "amplitude twitch" or simply "twitch." Typically, the subjects were instructed to actively recognize (e.g., to silently count) these twitches, in order to force the subjects to focus maximal attention on the desired stimulation site. Otherwise, keeping attention focused on one of different simultaneous streams of stimuli over some period of time would be a virtually impossible task. In most of these studies, trials with twitches were included in the data analysis without treating them in a particular way (Giabbiconi et al., 2004, 2007; Müller-Putz et al., 2006; Breitwieser et al., 2011), whereas, Adler et al. (2009) and Pang and Mueller (2014) excluded them from further analyses in order to investigate pure SSSEPs. In the study of Severens et al. (2013), a successful attempt was made to explicitly include transient event-related potentials (ERPs) caused by twitches in the analyses and to directly compare the BCI performance using transient and steady-state responses for the first time.

However, in none of these studies, the effects of twitches on the stimulation signal and subsequently, on the SSSEP itself were explicitly analysed from a signal processing point of view in terms of intended or unintended temporal or spectral changes of the stimulation signal. Arguably, a transient change in the repetitive stimulation signal will have some impact on the SSSEP. Here, an important question is, if such effects are negligible or may cause some undesired physiological effects, such as degraded classification performance in a BCI. In some cases, as shown by Xu et al. (2013) in the context of steady-state visually evoked potentials (SSVEPs), seemingly negative effects may even be turned to some new kind of features ("blocking features") which can even be beneficial for classification.

The aim of our work is to ask this question again and to critically revisit the use of twitches in an SSSEP-based BCI. For this purpose, a hybrid BCI based on tactile stimuli was designed to throw some new light on the use of twitches. In general, the idea of a hybrid BCI is to combine different brain signals in a meaningful way in order to improve the performance and to make the BCI applicable to a broader range of subjects or patients (i.e., lower number of illiterates) (Pfurtscheller et al., 2010; Müller-Putz et al., 2015). Similar as Severens et al. (2013), we investigate in our study a BCI which combines SSSEPs and P300 potentials evoked by twitches embedded into the streams of tactile stimuli. However, these two brain signals are somehow mutually exclusive, since the former is a frequency-domain signal whereas the latter is a time-domain signal. According to the Fourier uncertainty principle (Gabor limit) a signal cannot be both time-limited and band-limited at the same time (Gabor, 1946). We therefore investigate the role of twitches in the context of SSSEPs and address the questions if SSSEPs and P300 potentials can be evoked concurrently and under what conditions the performance of a hybrid BCI may be improved by combining SSSEPs and P300 potentials.

2. METHODS

The impact of twitches on SSSEPs was investigated in a real-world BCI setup. For this purpose, we designed an online BCI following the standards for open interfaces for communication (TiA, TiD) described by Müller-Putz et al. (2011). For the online BCI and all offline analyses, Matlab/Simulink (The MathWorks, Inc., MA, USA) together with the EEGLAB (Delorme and Makeig, 2004) and BCILAB (Kothe and Makeig, 2013) toolboxes were used.

2.1. Experimental Paradigms

Within this study, EEG (electroencephalogram) measurements were conducted in three successive parts using experimental paradigms for (i) EOG (electrooculogram) recording needed for EOG artifact removal, (ii) screening for subject-specific "resonance-like" frequencies of the somatosensory system (Müller et al., 2001), and (iii) a cue-based online BCI paradigm.

2.1.1. EOG Recording

The first part of each measurement was to record 2 min of induced EOG artifacts. Following the procedure described by Schlögl et al. (2007), each subject was instructed to perform 1 min of eye movements and 1 min of blinking only. Using this recording, parameters for an autoregressive model were estimated which was then used to automatically remove EOG artifacts from online BCI recordings.

2.1.2. Screening

As demonstrated in various experiments in literature, each person shows a characteristic tuning curve and reacts with specific "resonance-like" frequencies of the somatosensory system in response to repetitive tactile stimuli (Tobimatsu et al., 1999, 2000; Müller et al., 2001; Breitwieser et al., 2012). "Resonance-like" frequencies are frequencies with maximal SSSEP amplitude and reflect resonance phenomena of the underlying frequency-selective neuronal networks. In SSSEP-based BCIs, the use of subject-specific stimulation frequencies with strongest SSSEP responses is assumed to yield higher BCI performance compared to when using the same standard frequencies for all subjects (Müller-Putz et al., 2006; Breitwieser et al., 2011; Severens et al., 2013). Therefore, a screening procedure similar as described by Breitwieser et al. (2012) was applied to identify these subject-specific "resonance-like" frequencies, and to select two frequencies for left and right index finger stimulation to be used in the subsequent BCI paradigm.

The left and right index finger tips were randomly stimulated with 10 frequencies ranging from 17 to 35 Hz in steps of 2 Hz. As shown in **Figure 1A**, each trial started with a reference period (length 3–3.5 s) without stimulation, followed by 10 stimulation intervals (length 2.3 s; only the last 2 s were used for analysis). In each stimulation interval, frequency and index finger were randomly chosen. The only restriction was that the exact same frequency and finger could not be selected twice in succession. Short pauses (length 0.25 s) were added between different stimulation intervals. To avoid attention modulation effects during screening, the subjects were not supposed to focus attention on the stimuli. Therefore, subjects had to perform a distracting mental arithmetic task during the whole trial (Breitwieser et al., 2011). They had to continuously add or subtract random numbers appearing on the screen in front of them. At the end of each trial, they were asked for their calculation results in order to monitor their distraction. The whole screening was divided into eight runs with 10 trials each. In total, 40 repetitions per frequency and index finger were recorded, resulting in a total amount of 800 repetitions per subject.

After screening, tuning curve maps showing the percentage band power increase of the stimulation intervals relative to the reference intervals (Müller et al., 2001) were computed for seven bipolar channels above the somatosensory cortex. Two stimulation frequencies with the highest and most similar responses in the tuning curve maps were manually selected for each subjects. The only restriction was that the selected frequencies had to be separated by at least one other stimulation frequency in between. The selected frequencies were then used in the subsequent BCI paradigm for left and right index finger stimulation.

2.1.3. BCI Paradigm

The left and right index fingers were simultaneously stimulated using the two frequencies selected after the screening procedure. The subjects were randomly instructed by a cue on the screen to focus attention on one or none of the fingers. The target finger was indicated by an arrow pointing to the left ("Focus left" class) or right ("Focus right" class). In one third of all trials, no arrow was shown and the subjects were instructed to avoid focusing attention on any finger ("Idle" class). Since the repetitive stimulation signals are usually just perceived as continuous vibrations, it is generally very difficult to focus attention and keep attention focused on the target finger. In order to make the focusing attention task easier, short twitches were inserted in the stimulation patterns of both fingers at random time points (see Section 2.2 for more details). Such twitches were short interruptions in the repetitive stimulation signals and could be perceived as rare, discrete events in the repetitive streams of stimuli. So, to keep attention focused on the target finger, the subjects were instructed to actively recognize and silently count the twitches appearing on the target, and to ignore twitches on the non-target finger. During the whole trial, the subjects were also instructed to avoid shifting their gaze and to just look at the center of the screen indicated by a cross.

As shown in **Figure 1B**, each trial started with a beep tone and the cross appearing on the screen. After 0.2 s, the stimulation of the left and right index fingers started. After a waiting time of 0.5 s after trial start, there was a reference period with a random length between 1 and 1.5 s without focused attention, where the subjects just had to look at the cross on the screen. Then, an arrow faded in on the screen instructing the subjects on which finger to focus attention on, or no arrow appeared for idle trials. The length of such a focus attention or idle period respectively was randomly chosen between 9.5 and 10 s. Twitches were presented only during this period and not during the reference interval. Each trial ended with a double beep followed by a discrete feedback appearing for 2 s on the screen. The feedback indicated if the target class was correctly detected (green circle), wrongly detected (red circle), or if no decision could be made (yellow circle). After the feedback, a random break between 3 and 4 s was added before the start of the next trial. Class decisions were made by two combined classifiers, one for SSSEPs and one for P300 potentials evoked by twitches (see Section 2.5 for details).

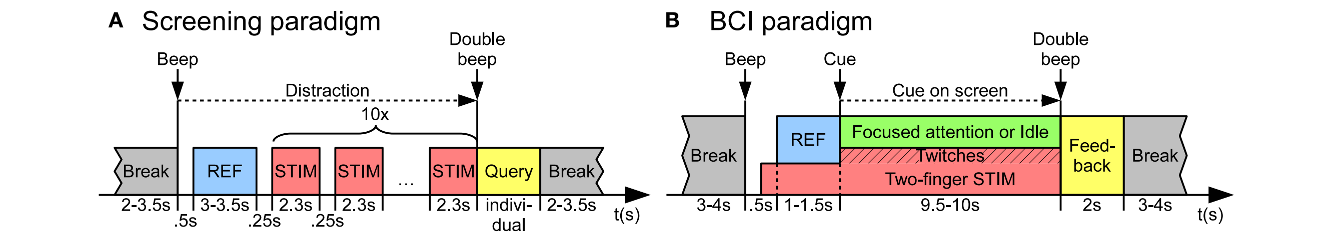

FIGURE 1 | Experimental paradigms. (A) In the screening paradigm, each trial started with a reference (REF) period, followed by 10 stimulation (STIM) intervals with frequency and index finger randomly chosen. Subjects had to perform a distracting mental arithmetic task during the whole trial. At the end of each trial, they were asked for their calculation results. **(B)** In the online BCI paradigm, both index fingers were simultaneously stimulated. Each trial started with a reference period, followed by a focused attention or idle period, as indicated by a cue appearing on the screen. Twitches were only presented during this period (hatched area). At the end of each trial, a discrete feedback was given on the screen.

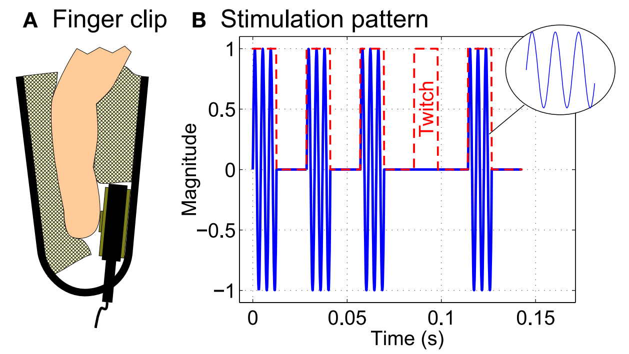

FIGURE 2 | Tactile stimulation. (A) Two C-2 tactors were attached to the left and right index finger using finger clips. **(B)** The tactile stimulation pattern consisted of a 237 Hz sinusoidal carrier signal which was amplitude modulated with a rectangular stimulation signal (red dashed line) of the respective stimulation frequency (here: 35 Hz). Twitches were implemented as complete interruption of the stimulation signal for exactly one stimulation period.

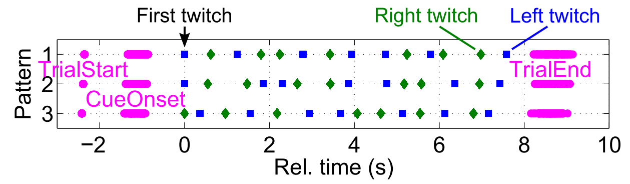

FIGURE 3 | Pseudo-randomized twitch patterns. To ensure that twitches would not occur closer than 250 ms, three different randomized twitch patterns were generated beforehand for all possible stimulation frequency combinations (here: 33 and 27 Hz). In each trial, one of these three pattern was randomly chosen. Left (blue squares) and right (green diamonds) twitch positions, as well as trial start, cue onset, and trial end (magenta bullets) are shown for individual trials, aligned to the first twitch's positions ($t = 0$ s).

The whole online BCI paradigm was divided into eight runs with 10 trials per class each. The following classifier update strategy was chosen: During the first two runs, data were just recorded and no feedback was given. After two runs, the classifiers were trained based on data from the first two runs and used to provide feedback in the following two runs. After four runs, the classifiers were retrained again based on data from all four previous runs and used to provide feedback in the remaining four runs of the measurement. The data from all eight runs (80 trials per class) were altogether used in the offline analyses.

2.2. Tactile Stimulation

Two C-2 tactors (Engineering Acoustics, Inc., Casselberry, Florida, USA) were attached to the left and right index finger. In order to have constant contact pressure betweeen tactors and fingers, finger clips as depicted in **Figure 2A** were used for this purpose. The prototype of a self-made tactile stimulation device (Pokorny et al., 2014) was used to generate the complex repetitive and transient stimulation patterns needed to evoke SSSEPs as well as P300 potentials. The stimulation pattern consisted of a 237 Hz sinusoidal carrier signal which was amplitude modulated with a rectangular signal of the respective stimulation frequency (see **Figure 2B**), similar as used in previous studies involving SSSEPs (Müller-Putz et al., 2006; Breitwieser et al., 2011, 2012; Pokorny et al., 2014). The duty cycle was chosen close to 50% in such a way that the carrier signal always started and stopped at phase zero.

During the online BCI runs, seven twitches per finger and trial were pseudo-randomly embedded into the stimulation patterns. As visible in **Figure 2B**, twitches were implemented as complete interruption (100% attenuation) of the repetitive stimulation signal for exactly one period of the respective stimulation frequency. This was done to have a strong and clearly defined effect when explicitly investigating the role of twitches. In contrast, in previous studies, e.g., by Breitwieser et al. (2011) and some pilot studies (unpublished), we realized twitches only as moderate attenuation of the stimulation signal. However, in those studies, twitches were generally reported by the subjects to be hardly perceivable and almost impossible to recognize or count.

Twitch positions were distributed in such a way that they would occur as rare, random events, suitable to evoke P300 potentials when the subjects actively focus attention on them. To ensure that twitches would not occur too close after each other within and across hands, three different randomized twitch patterns were generated beforehand for all possible combinations of left and right stimulation frequencies. In each trial, one of these three pattern was randomly chosen. The minimal inter-stimulus interval between consecutive twitches at the same hand and across hands was 250 ms each. Twitch onsets were precisely (in the order of μs) recorded by means of two additional (optically isolated) trigger channels from the stimulation device to the EEG amplifier. **Figure 3** shows an example of three different twitch patterns generated for stimulation frequencies of 33 and 27 Hz respectively. Twitch positions, as well as trial start, cue onset, and trial end positions are shown as separate markers for individual trials. All positions within trials were aligned to the corresponding first twitch's positions. Due to random reference and focus attention period lengths, this results in variable trial start, cue onset, and trial end positions relative to the first twitch.

2.3. Participants

Fifteen healthy subjects voluntarily participated in this study. They were paid for participation and were informed in detail about the aims of this study. None of them reported any neurological disease. All subjects gave written informed consent, and the study was conducted in accordance with the local ethics regulations (Medical University Graz) and the Declaration of Helsinki. The measurement of one subject was aborted since he or she did not follow the instructions given by the experimenter. The remaining fourteen subjects (seven male/female) were aged between 20 and 39 years [mean 26.3 ± 6.2(SD) years].

2.4. EEG Recording

The EEG was recorded from 29 channels together with 3 EOG channels, as shown in **Figure 4**. The channel Fpz was used as reference, the right mastoid as ground. Data were recorded using two g.USBamp biosignal amplifiers (g.tec medical engineering

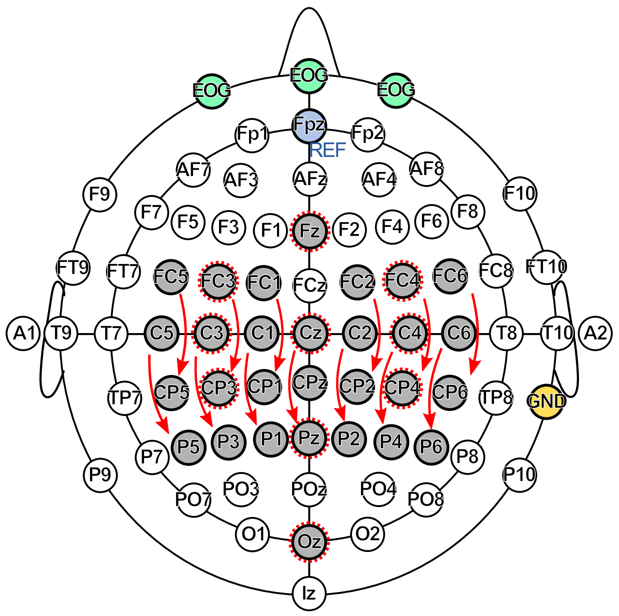

FIGURE 4 | Electrode setup. The EEG was recorded at 29 channels (gray), the EOG at 3 channels (green). The Fpz electrode (blue) was used as reference (REF), the right mastoid (yellow) as ground (GND). The SSSEP channel set consisted of 13 bipolar channels indicated by arrows, the P300 channel set of 10 monopolar channels indicated by dashed circles.

GmbH, Austria) with active electrodes and a sampling rate of 600 Hz. A bandpass filter between 0.5 and 200 Hz, and a notch filter at 50 Hz were applied. All measurements were conducted in a shielded room. The subjects were seated in an armchair in front of a computer screen with their hands comfortably placed on armrests during the measurements.

For SSSEP investigations, 13 bipolar channels above the somatosensory cortex indicated by arrows in **Figure 4** were preselected and are referred to as SSSEP channel set. Similarly, 10 monopolar channels indicated by dashed circles in **Figure 4** were preselected for investigating P300 effects and are referred to as P300 channel set.

2.5. Data Analysis

2.5.1. Artifact Removal

EEG channels with obviously bad signal quality found after visual inspection of the EEG signals during measurements were excluded from data analysis (five channels in total). EOG artifacts were removed based on autoregressive parameters estimated from the EOG recording (Schlögl et al., 2007). Trials contaminated with EMG (electromyogram) and other types of strong artifacts were removed using a simple theshold-based artifact detection method (Delorme et al., 2007). Artifact thresholds of 90 and 60 μV were used for monopolar and bipolar channels respectively.

2.5.2. Brain–Computer Interface

Feature for SSSEPs and P300 potentials were extracted and classified using separately trained classifiers. For SSSEPs, logarithmic lock-in amplifier system (LAS) features (Müller-Putz et al., 2006) were extracted from the 13 bipolar channels from the SSSEP channel set. A filter bandwidth of 2 Hz around each stimulation frequency was used and a moving average (MAV) filter with 1 s length was applied. The mean SSSEP strength was estimated by averaging the LAS features over time within an interval from 1 to 8.5 s after cue onset and used for classification.

For P300 potentials, the 10 monopolar channels from the P300 channel set were selected and low-pass filtered using a 3rd-order Butterworth filter at 10 Hz. Time segments from 0 to 800 ms after each twitch onset (read out from trigger channels) were extracted, resulting in seven twitch segments for each of the index fingers per trial. The seven segments of each finger were linearly detrended, averaged, downsampled by a factor of ten, and used for classification. The influence of the number of averages on the P300 performance was separately investigated by using different numbers of averages ranging from one to seven. For numbers of twitches lower than seven, random subsampling was used to select subsets of twitches within trials. The whole procedure was repeated 10 times in order to get a reliable estimate.

For both types of features, multi-class shrinkage LDA classifiers (Schäfer and Strimmer, 2005) based on the one-vs-all strategy were used to predict the target class. The overall BCI performance was estimated using 10 $\times$ 10 cross-validation to avoid overfitting. To identify classification results that were significantly better than a random classifier, we compared our results to the real chance level (Müller-Putz et al., 2008) instead of to the theoretical one (33.3%). The real chance level takes a confidence interval at significance level $\alpha = 1\%$ into account and was computed based on the total number of trials per class to be 40.8%. So all classification results exceeding this level can be regarded as significantly better (at $\alpha = 1\%$) than just random results. For online feedback presentation, the decisions from both classifiers were combined in order to arrive at a final decision. Together with the class prediction, each classifier returned a linear score which was mapped to a class probability value, representing a measure of certainty (0–100%) about their decisions. The result from the classifier with the higher probability value was selected as final decision. If none of the classifiers reached a probability threshold of at least 50%, no decision was made.

2.5.3. Effects of Twitches on the SSSEP

To investigate the effects of twitches on the SSSEP, different visualization and analysis methods were implemented. A time-frequency representation was chosen which is capable of visualizing steady-state as well as transient signals. For this purpose, spectrograms were computed based on the short-time Fourier transform (STFT) showing the power spectral densities (PSD) at different frequencies over time. The STFTs were computed using a 4096-point fast Fourier transform (FFT). As already mentioned (see Section 2.2), in each trial, one of three pseudo-randomized twitch patterns was randomly chosen. Separate spectrograms were computed by averaging the PSDs of all trials belonging to the same twitch pattern. Before averaging, the corresponding time axes were aligned either to the trial start or first twitch's position as needed. Since spectrograms are subject to the Fourier uncertainty principle, the choice of the window has a strong impact on their time-frequency resolution. Long time windows result in better frequency but poor time resolution, whereas short time windows result in good time but poor frequency resolution. Minimizing the Fourier uncertainty principle, the best simultaneous time-frequency resolution can be achieved with a Gaussian window function (Gabor, 1946) which was used in our analysis. Gaussian windows with two different lengths were applied: (i) To visualize the (steady-state) frequency content, a fixed window length of 3 s and an overlap between consecutive window segments of 2.95 s was chosen. (ii) To visualize transient effects, a fixed window length of 1 s and a window overlap of 0.95 s was chosen.

To specifically reveal potential transient effects of twitches on the SSSEP, the idea was to extract LAS features from both stimulation frequencies and test them for significant changes (decreases) at twitch locations. Since the settling time of the LAS is inverse proportional to its bandwidth, a bandwidth of 4 Hz around each stimulation frequency was chosen for this purpose. Additionally, the MAV filter was omitted, resulting in a much faster LAS setting. **Figure 5** shows an example of how this method is capable of extracting short transient disruptions caused by twitches from an ideally simulated stimulation signal with 35 Hz. Effects of twitches are clearly visible as attenuations of the LAS amplitude at the twitch locations. In comparison, LAS features extracted with the standard setting (2 Hz bandwidth, 1 s MAV filter) are not capturing such transients.

To test if such attenuations caused by twitches are not only present in the stimulation signal but also in the resulting SSSEPs (referred to as SSSEP blocking) a Monte Carlo permutation test (Nichols and Holmes, 2001) was applied. Since this is a non-parametric approach, no assumptions about the distribution of values being tested were required. The permutation test was based on the null hypothesis that no significant decrease in SSSEP amplitude caused by twitches was present and therefore, twitch pattern labels (i.e., fixed twitch positions within each trial) would be interchangeable across trials. So, twitch patterns were randomly permuted, changing the assignment of twitch patterns to trials, without changing the overall distribution of twitch positions. As test statistic, the average SSSEP amplitude over all trials and twitches extracted from 50 ms time intervals around twitch onsets (positions according to real or permuted twitch pattern assignment) was computed. In this way, a null distribution of average SSSEP amplitude values was generated based on the real assignment and $N = 100,000$ permutations. The false positive probability (FPP) that an observed decrease in SSSEP amplitude is just a random effect was estimated as percentage of values in the null distribution that were lower than or equal the actually observed one. Since the actually observed value was always part of the null distribution, the resulting FPP could never be smaller than $1/(N + 1)$. The FPP was estimated in steps of 50 ms from -500 to $+500$ ms around twitch onsets, in order to identify intervals of significant blocking effects. An FPP below some significance level α was then considered as significant SSSEP blocking effect. An α-level of 1%, Bonferroni corrected for multiple testing based on the number of time intervals, stimulated fingers, and observed channels was applied. Only two bipolar channels above the somatosensory cortex (FC3-CP3 and FC4-CP4), where the highest SSSEP responses and therefore, the strongest effects were expected, were included in this significance test.

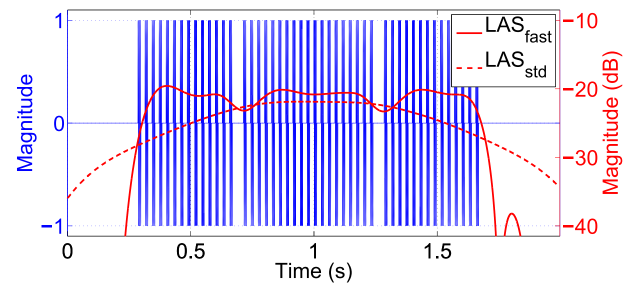

FIGURE 5 | Effect of twitches in an ideally simulated 35 Hz stimulation signal. Logarithmic LAS features were extracted at the stimulation frequency using a fast setting (4 Hz bandwidth, no MAV filter; red solid line) or standard setting (2 Hz bandwidth, 1 s MAV filter; red dashed line). With the fast setting, effects of twitches are clearly visible as attenuations of the LAS amplitude at twitch locations.

This significance test was intended to identify significant SSSEP blocking effects disregarding any class information. As a next step, we investigated if potential SSSEP blocking effects were modulated by attention and could, therefore, be beneficial features for classification, similar as shown by Xu et al. (2013) in the context of SSVEPs. For this purpose, we extracted SSSEP features at both stimulation frequencies using the fast LAS setting from intervals of 0 to 400 ms after twitch onsets. Segments from all seven twitches per finger and trial were averaged over time for different channels and used as blocking features for classification. All 13 bipolar channels from the SSSEP channel set were used for this purpose. Again, a multi-class shrinkage LDA classifier together with 10×10 cross-validation was applied for performance estimation.

3. RESULTS

3.1. Steady-State Somatosensory Evoked Potentials

SSSEP responses could be found in all subjects after screening for subject-specific "resonance-like" frequencies of the somatosensory system. In **Figure 6**, the grand average tuning curve maps over all subjects obtained after the screening procedure can be found. The relative bandpower increase is shown at 10 stimulation frequencies and seven bipolar channels above the somatosensory cortex for left and right index finger stimulation. Vertical markers indicate the grand average of the 95% confidence intervals estimated with bootstrapping based on 1000 bootstrap samples. As expected, the tuning curve maps show largest bandpower increases at channels contralateral to the stimulated finger.

Table 1A summarizes the individual screening results of all subjects. The manually selected stimulation frequencies for left

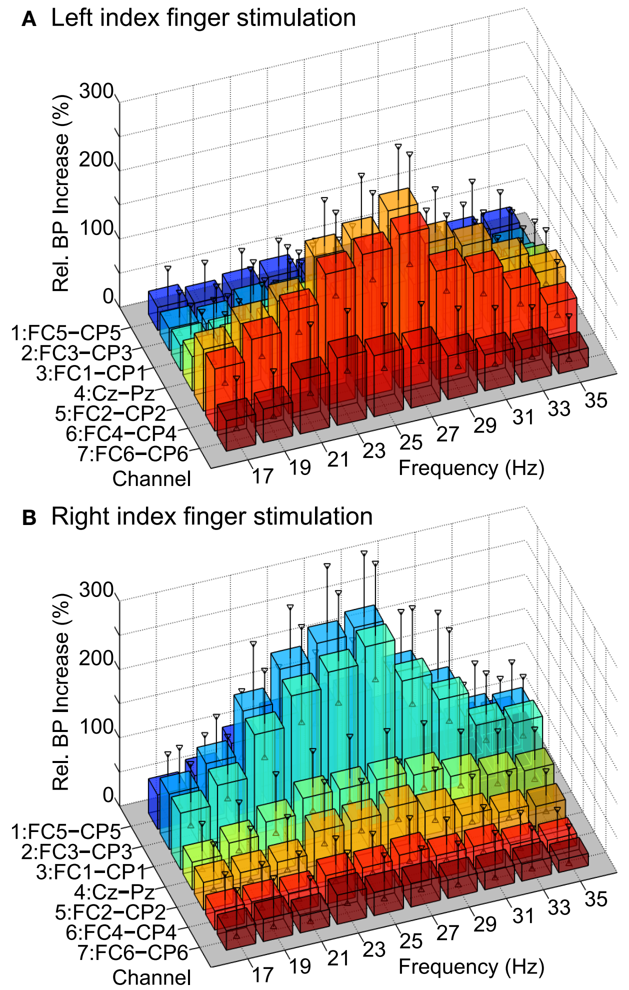

FIGURE 6 | Grand average tuning curve maps over all subjects. The relative bandpower increase is shown at 10 stimulation frequencies and seven bipolar channels above the somatosensory cortex for **(A)** left and **(B)** right index finger stimulation. Vertical markers indicate grand average confidence intervals (α = 95%) estimated with bootstrapping.

and right index finger stimulation to be used in the BCI paradigm are shown, which were in the range of 21 to 35 Hz. Additionally, the relative bandpower increases at bipolar channels contralateral to the stimulated hand, namely FC4-CP4 for left and FC3-CP3 for right index finger stimulation can be found. Relative bandpower increases at these channels were in the range of 53–536%. On average, relative bandpower increases of 235±133(SD)% for left and 269±127(SD)% for right index finger stimulation could be found.

To visualize SSSEPs at the selected stimulation frequencies during the online BCI runs, spectrograms with a window length of 3 s and an overlap between consecutive window segments of 2.95 s were computed. As an example, in **Figure 7**, spectrograms of subject s01 showing the PSD during simultaneous left and right index finger stimulation with 25 and 21 Hz respectively can be found. Spectrograms are shown for the bipolar channels FC3-CP3 and FC4-CP4 during the course of a trial. Trials belonging to only one of the three twitch patterns were averaged, and individual trials were aligned to each trial's start position. SSSEPs are clearly visible at the respective channel contralateral to the stimulated hand.

3.2. P300 Potentials

By embedding twitches at random positions into the streams of repetitive tactile stimuli, P300 potentials could be evoked. **Figure 8** shows the grand average P300 response over all subjects divided into different twitch locations (left or right hand) and target classes (left cue, right cue, or idle cue). Averaged time segments from 0 to 800 ms after twitch onsets are shown for the monopolar channels Fz, Cz, and Pz. A P300 response can be seen around 300–400 ms in response to left and right target twitches (i.e., at left twitch locations for left classes and at right twitch locations for right classes), most pronounced at channel Cz. After non-target twitches, no clear P300 potentials can be found.

Additionally, in **Figure 9**, grand average topographic plots show the spatial distribution over all subjects of the P300 component extracted from a 200–500 ms time window. It can be seen that the P300 component is most prominent after target twitches at central channel location above the somatosensory cortex. For the left target twitches, a shift toward contralateral channels can be observed while for right target twitches, a bilateral activation can be found.

3.3. Effects of Twitches on the SSSEP

To visualize transient effects in the SSSEP, spectrograms with a window length of 1 s and a window overlap of 0.95 s were computed. As an example, **Figure 10** shows spectrograms for the same subject and trials as in **Figure 7**. This time, individual trials were aligned to each corresponding first twitch's position, and positions of all twitch onsets are drawn in the spectrograms. Moreover, the color axes were individually scaled to highlight PSD variations over time at the stimulation frequencies. Interestingly, SSSEP blocking effects, namely an attenuation of roughly 2–3 dB of the SSSEPs time-locked to the corresponding twitch onsets can be observed. In more detail, attenuations at the left stimulation frequency seem to be time-locked to left-hand twitches (visible at channel FC4-CP4). Similarly, attenuations at the right stimulation frequency seem to be time-locked to right-hand twitches (visible at channel FC3-CP3).

To statistically validate this visual impression, significant blocking time intervals were determined by means of a permutation test based on SSSEP amplitudes extracted with the fast LAS setting. As an example, **Figure 11** shows the estimated FPPs (i.e., the probabilities that the observed decreases in SSSEP amplitude are random effects) for subject s01 at the bipolar channels FC3-CP3 and FC4-CP4 in the interval from −500 to +500 ms around twitch onsets for left-hand and right-hand twitches. Significant SSSEP blocking effects can be seen in intervals where the FPP is below the α-level of 1% (Bonferroni corrected). For left-hand twitches, significant SSSEP blocking was found in the interval 50–150 ms after twitch onset at channel FC4-CP4. For right-hand twitches, significant SSSEP blocking was found in the interval 150–200 ms after twitch onset at channel FC3-CP3. A full summary of significant results from all

TABLE 1 | Summary of individual screening, blocking interval estimation, and classification results.

Code	(A) SSSEP screening				(B) SSSEP blocking intervals		(C) Performance			
	f_L (Hz)	f_R (Hz)	$relBP_{L,c}$ (%)	$relBP_{R,c}$ (%)	$BLInt_{L,c}$ (ms)	$BLInt_{R,c}$ (ms)	SSSEP (%)	P300 (%)	BLFtr (%)	Combined (%)
s01	25	21	536	475	50–150	150–200	**47.1**	**47.3**	29.8	38.2
s02	23	27	356	482	–	100–150	**56.1**	**51.1**	**49.4**	**50.9**
s03	33	27	114	133	–	–	**45.5**	**58.1**	**46.0**	**64.3**
s04	31	35	291	288	50–150	–	39.5	**41.9**	35.7	39.8
s05	25	29	190	201	–	–	36.0	**45.7**	38.9	**47.8**
s06	27	23	291	315	200–250	–	**42.7**	**44.2**	**46.5**	**50.1**
s07	23	27	161	419	–	–	**46.0**	**42.3**	38.7	40.5
s08	33	27	376	291	50–100	50–100	**46.5**	39.2	**44.8**	**46.6**
s09	25	29	155	165	–	–	31.4	**42.4**	23.3	24.0
s10	29	25	53	101	–	–	9.2	36.0	16.0	10.8
s11	23	27	234	294	50–200	50–100	**44.4**	**65.5**	38.6	33.0
s12	23	27	120	123	–	–	**47.5**	**64.1**	**46.4**	**66.2**
s13	27	21	310	308	50–150	100–250	**61.8**	**57.5**	**44.2**	**62.9**
s14	21	25	101	165	–	–	39.5	**48.1**	32.6	33.6
Mean			235	269			48.6	50.7	46.2	55.5
SD			133	127			6.2	8.5	1.8	8.5

***(A)** SSSEP screening: Manually selected stimulation frequencies for left (f_L) and right (f_R) index finger stimulation; Relative bandpower increases at contralateral bipolar channels, FC4-CP4 for left ($relBP_{L,c}$) and FC3-CP3 for right ($relBP_{R,c}$) hand stimulation. **(B)** SSSEP blocking intervals: Significant blocking intervals (BLInt) for left and right index finger stimulation at the bipolar channels FC3-CP3 and FC4-CP4 contralateral to the stimulated hand. **(C)** Performance: Cross-validated BCI performance using SSSEP, P300, and blocking features (BLFtr) separately or combined for classification. Mean and SD were computed only over subjects with accuracies significantly better than random [40.8% at $\alpha = 1\%$ (Müller-Putz et al., 2008); bold values].*

subjects can be found in **Table 1B**. Significant blocking intervals could be found in seven subjects at channels contralateral to the stimulated hand. These intervals were found between 50 and 250 ms after twitch onsets, with interval lengths in the range of 50–150 ms. On ipsilateral channels, no significant blocking intervals were found (not shown in **Table 1**).

3.4. BCI Performance

The three-class BCI performance was evaluated by means of a 10 × 10 cross-validation when using SSSEP features, P300 features, or SSSEP blocking features. **Table 1C** summarizes the classification accuracies of all subjects. All classification results above the 1% chance level (Müller-Putz et al., 2008) are highlighted as bold values in the table. Accuracies better than random were found in 12 subjects using P300 features, in nine subjects using SSSEP features, and only in six subjects using blocking features. Mean and SD were computed only over subjects with accuracies significantly better than random. When comparing the accuracies of all three types of features one can see that the mean accuracies are in the range of 46.2 ± 1.8(SD)% for blocking feature classification, 48.6 ± 6.2(SD)% for SSSEP features, and 50.7 ± 8.5(SD)% for P300 features. Additionally, the hybrid BCI performance was computed when using the combined SSSEP, P300, and blocking features for classification, showing various results. In some subjects, an improvement in accuracy of the combined over the best single feature set could be found, whereas in some other subjects, no improvement or even a drop in performance to chance level could be observed. Classification accuracies better than random could be found in seven subjects, with a mean accuracy of 55.5 ± 8.5(SD)%. One subject, s10, did not reach accuracies above chance level using any feature set. This can be explained by the fact, that in s10, unexpectedly strong alpha waves were present in the EEG throughout all measurements, interfering with the actual features used for classification and leading to a rejection of around two thirds of the trials. Over all other subjects (s10 excluded), the mean rejection rate of trials due to artifacts was 7% using SSSEP features and 6% using blocking features. When using P300 features, no trials at all were rejected but the number of averaged segments per trial was reduced accordingly (on average, 6.997 ± 0.07(SD) averaged segments per hand and trial).

When extracting P300 features, all seven twitch segments per trial and hand were averaged. **Figure 12** shows the grand average classification accuracies (10 × 10 cross-validated) for different numbers of averages ranging from one to seven. The P300 accuracy is monotonically increasing with the number of averages per trial from 36% (one segment only, i.e., no averaging) to 49% (seven segments averaged). The actual 1% chance level (Müller-Putz et al., 2008) of 40.8% is also shown in the figure.

4. DISCUSSION

Within our work, the impact of transient target stimuli on the SSSEP was investigated in a real-life BCI setup. SSSEPs could successfully be evoked by simultaneous left and right index

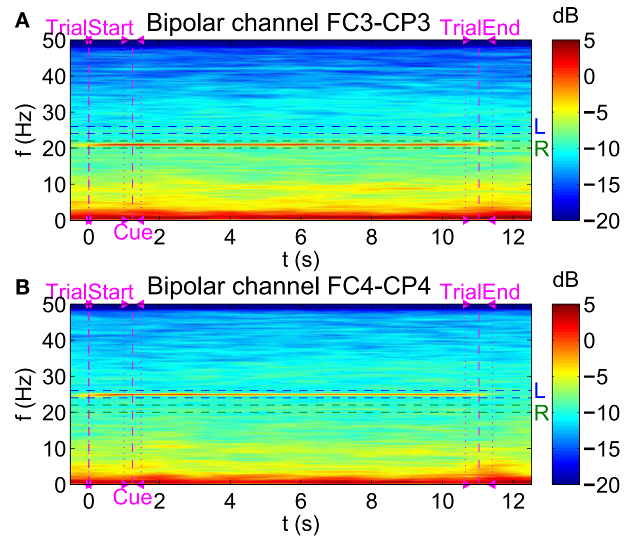

FIGURE 7 | Visualization of SSSEPs. Spectrograms (4096-point FFT, 3 s window length, 2.95 s window overlap) of subject s01 showing the PSD (in dB) during simultaneous left (25 Hz) and right (21 Hz) index finger stimulation can be seen for the bipolar channels **(A)** FC3-CP3 and **(B)** FC4-CP4.

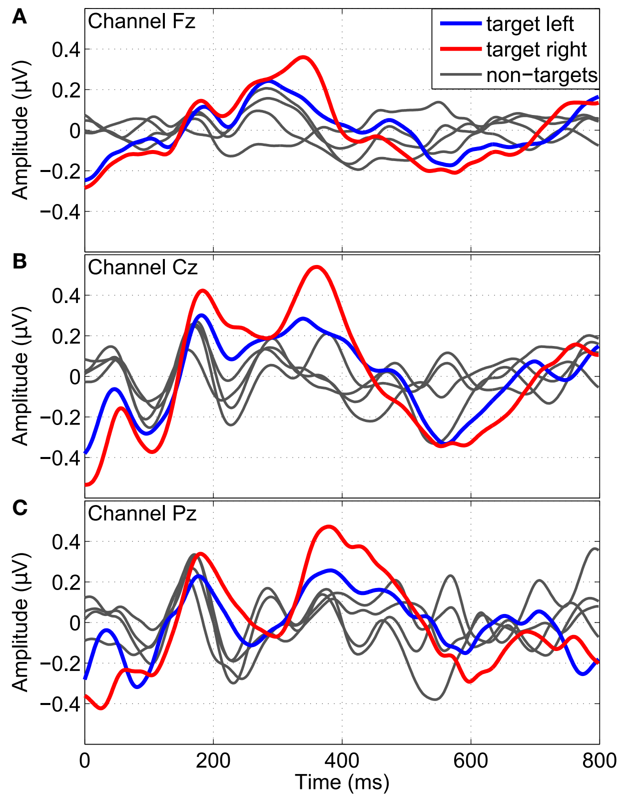

FIGURE 8 | P300 response evoked by twitches randomly embedded into the stream of repetitive stimuli. Grand average time segments (0–800 ms) after twitch onsets over all subjects are shown for the channels Fz, Cz, and Pz **(A–C)**. Separate segments are shown for left (bold blue) and right (bold red) target twitches, as well as for all remaining non-target conditions (gray).

finger stimulation with repetitive tactile stimuli. Subject-specific stimulation frequencies were determined by means of a screening procedure in order to maximize the individual SSSEP responses. The overall screening results showed grand average tuning curves with peaks at 27 Hz, which is fully in line with previous findings by Müller et al. (2001). Moreover, the subject-specific stimulation frequencies which were selected after screening are in a similar range as the individual tuning curve maxima reported in previous studies (Breitwieser et al., 2011, 2012).

By embedding twiches at random positions into the repetitive stimulation signals, P300 potentials could successfully be evoked in addition to the steady-state response. The P300 component is usually defined as ERP with a positive deflection with a latency of about 300 ms (Farwell and Donchin, 1988). In our study, the grand average P300 response at channel Cz was found between 300 and 400 ms which is in line with this definition. Moreover, the latency and shape of the P300 component are fully in agreement with the results reported in other studies involving pure tactile P300 (Brouwer and van Erp, 2010; van der Waal et al., 2012). However, in our study, the P300 component was most prominent at central channel location above the somatosensory cortex, with an activation bilateral or contralateral to the stimulated hand, which was not reported in any other of these studies. Yet another transient response, namely a positive deflection with shorter latencies and at a more frontal location than the standard P300 response was found by Severens et al. (2013). These various results may be explained by the use of different tactile stimulators, stimulation patterns, and target body locations. In the study of Severens et al. (2013) for example, the index, middle, and ring finger tips were stimulated simultaneously per hand by means of Braille stimulators with complex stimulation characteristics involving different pins of the Braille stimulators. In contrast, in our study, we only used a single stimulator for each index finger tip but complex temporally modulated stimulation patterns. Moreover, due to the short inter-stimulus intervals between twitches, it is possible that some kind of overlapping ERPs instead of pure P300 potentials may have been evoked, which may explain the differences in our results. Some overlapping effects were already observed in the auditory domain using two concurrent tone streams with randomly appearing deviant tones (Pokorny et al., 2013).

The main focus of our work was to investigate the impact that twitches may have on the SSSEP. By means of a fast LAS feature extraction setting and statistical validation methods it could be shown that twitches have an attenuation effect on the SSSEP which usually cannot be captured with standard analysis methods. Significant SSSEP blocking effects time-locked to twitch positions were found in seven subjects. This shows that the attempt to combine different types of stimulation signals like repetitive signals and twitches has a mutual influence on each other. As demonstrated in an ideally simulated stimulation signal, this influence is originated at the level of stimulus generation but becomes apparent as physiological effect in the SSSEP. Similar results were also presented by Xu et al. (2014) who found out that SSVEPs and ERPs were not two absolutely independent features in their study. However, our significance test only proved the presence of significant attenuations of the SSSEP, but no conclusions about the actual blocking strength–full interruption or just attenuation of SSSEPs–can be made. Moreover, the exact positions of reported blocking intervals need not necessary coincide with real physiological effects. The reason for this are fundamental limitations in the simultaneous time-frequency resolution referred to as Gabor limit (Gabor, 1946) which prevents a more detailed characterization of the observed blocking effects in the time or frequency domain.

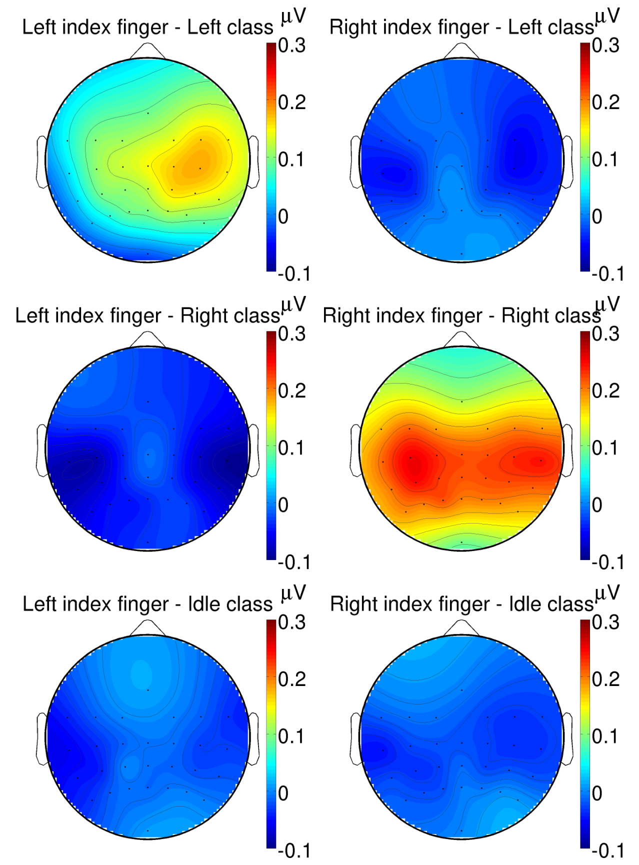

FIGURE 9 | Grand average topographic plots of the P300 response. The spatial distribution of the P300 component extracted from a 200–500 ms time window is shown for different twitch locations (left/right column: left/right hand) and target classes (from top to bottom: left/right/idle cue).

The general principle of an SSSEP-based BCI is that users intentionally modulate the SSSEP by focusing attention on one of the stimulated target locations (Müller-Putz et al., 2006). However, the SSSEP blocking effects found in our work may prevent subjects from effectively modulating the target SSSEP. According to Müller-Putz et al. (2006), time points of best class separability were generally reached only after a few seconds after cue onset. So, such time points of highest separability may have never been reached in our study due to repeated interruptions of the steady-state potential. We therefore investigated the information content about the target class that is contained in different feature sets by means of a classifier. In the SSSEP feature set, we wanted to reduce any transient effects and used the mean SSSEP strengths averaged over a long time interval of 7.5 s. In contrast, in the P300 feature set, short time segments after twitch onsets were used. Using a third feature set, we also investigated if SSSEP blocking effects may contain additional information useful for classification, similar as reported by Xu et al. (2013) in the visual domain.

When looking at the three-class BCI performance, classification accuracies significantly better than random could be reached by nine subjects using SSSEP features and by 12 subjects using P300 features respectively. The average classification accuracies (counting subjects with accuracies better than random only) were on similar performance levels, namely 49% for SSSEP features and 51% for P300 features. Using blocking features, accuracies significantly better than random could be reached only by six subjects, with an average performance of 46%. When using the combined feature set for classification, an improvement in accuracy could be found only in some subjects, whereas in others, no improvement or even a drop in performance to chance level could be observed. The main reason for this may be that the number of combined

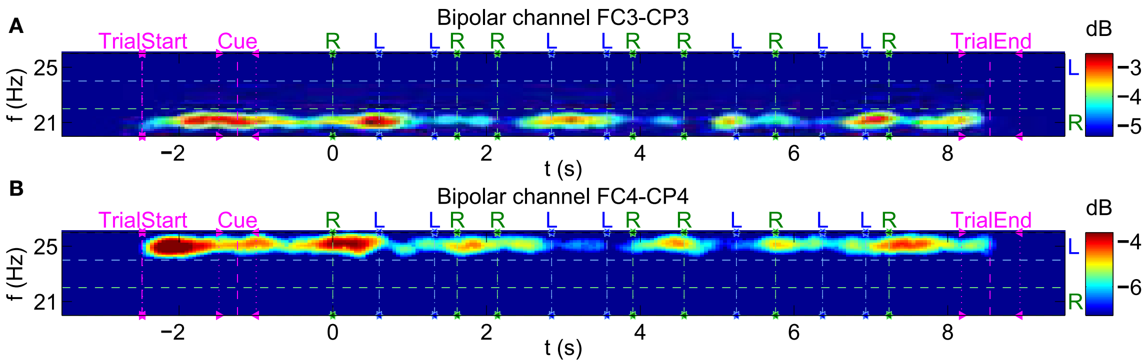

FIGURE 10 | Visualization of transient effects in the SSSEP. Spectrograms for the bipolar channels **(A)** FC3-CP3 and **(B)** FC4-CP4 of subject s01 as in **Figure 7**, but with shorter time windows (1 s window length, 0.95 s window overlap) and individual trials aligned to each first twitch's position. The color axes were scaled to highlight variations at each stimulation frequency. Twitch onsets at left (L) and right (R) index fingers are drawn as vertical dashed lines.

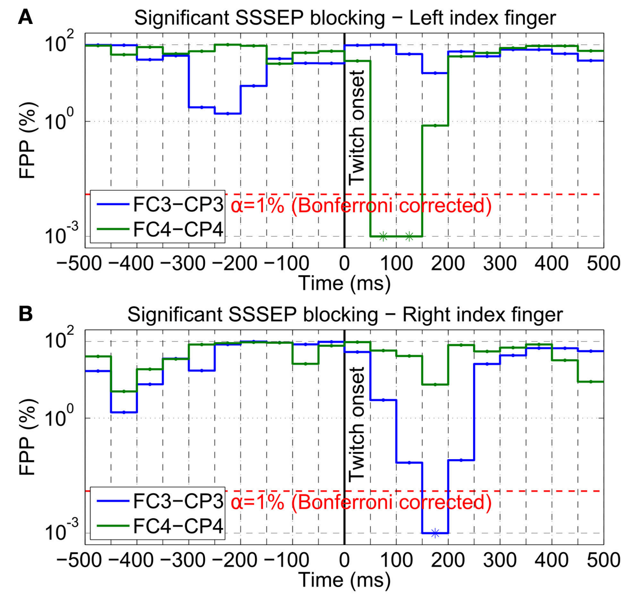

FIGURE 11 | Blocking interval estimation of subject s01. SSSEP blocking effects of **(A)** left-hand and **(B)** right-hand twitches were statistically validated using a permutation test (100, 000 repetitions; 4 Hz LAS bandwidth; no MAV filter). The FPP (in %; log y-axis) was estimated in steps of 50 ms from −500 to +500 ms around twitch onsets for two bipolar channels (blue: FC3-CP3; green: FC4-CP4). Significant blocking effects (indicated by asterisks) can be found in intervals where the FPP is below the indicated significance level ($\alpha = 1\%$; Bonferroni corrected; red dashed line).

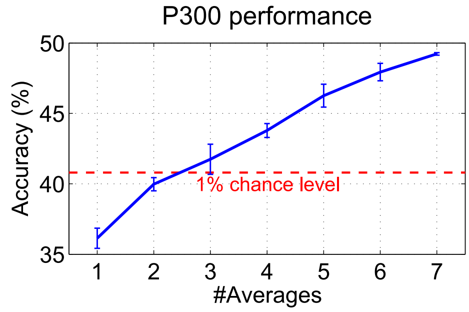

FIGURE 12 | Influence of the number of averages on the P300 performance. The grand average of the classification accuracies (10 × 10 cross-validated) over all subjects is shown when averaging different numbers of twitch segments per trial (1–7). Random subsampling was used to select different numbers of twitches within trials. The whole procedure was repeated 10 times in order to get a more reliable estimate (mean±SD are shown).

features (in the order of 1350) was simply too high compared to the number of trials (80 trials per class) so that even a shrinkage-based classifier could not extract all useful information any more. Moreover, the respective numbers of features within the combined feature set were highly different between SSSEP (2%), P300 (71%), and blocking (27%) features so that their relative importance may be biased toward P300 features. Further optimizations, such as reducing the total number of combined features and balancing their relative numbers in the combined feature set may therefore be required. So, unlike in the study of Xu et al. (2013), blocking features could not successfully be used to increase classification performance. However, they used a completely different BCI setup, namely a visual matrix speller with only one repetitive stimulation (flicker) frequency. In our work, blocking feature classification performance was above chance level only in subjects where SSSEP performance was also significant, and could never improve classification in cases where SSSEP classification was below chance level. This indicates that blocking features did not contain any additional information about the intended class but simply reflected SSSEP features extracted from shorter time intervals within the whole focus attention period. Moreover, a direct relationship between significant SSSEP blocking effects and reduced SSSEP accuracies could not be observed in our results. However, for blocking feature classification, all channels from SSSEP channel set were included whereas the blocking intervals reported in **Table 1B** only reflect significant results from two channels.

Even though accuracies better than random were reached by most subjects, the overall BCI performance was rather moderate and presumably hardly sufficient for communication purposes. The minimum performance level of 70% usually required for communication (Kübler et al., 2004) could not be reached by any of the subjects. However, this performance level was defined for a two-class BCI and, therefore, cannot be directly applied to our three-class BCI setup. The main reason for the rather moderate BCI performance could be that both types of brain signals—SSSEP and P300—cannot be evoked at the same time, since one is detrimental to the other. Also Severens et al. (2013) found no boost in performance when combining SSSEP and ERP features. On the one hand, the use of many twitches would be beneficial for P300, since as shown in **Figure 12**, averaging of many twitch segments increases the P300 accuracy. On the other hand, many twitches within short time may cause overlapping ERPs and many interruptions of the SSSEP, presumably lowering SSSEP and P300 performance. One obvious solution would be to increase the trial durations, so that many twitches could be embedded with large inter-stimulus intervals into the repetitive stimulation signal. The disadvantages of longer trial durations are of course lower information transfer rates and higher susceptibility to EEG artifacts. Another reasons for only moderate P300 performance may be that in some subjects a P300 was present not only after target but also after non-target twitches (not visible in the grand average response), possibly due to too strong (100% attenuation) twitches which drew attention toward the non-target hand. The same reason may also contribute to decreased SSSEP performance in some subjects, as non-target twitches may have prevented them from keeping attention focused on the target finger, thereby reducing attention modulation of the SSSEP (as opposed to SSSEP blocking effects which were caused by twitches irrespective of the target finger). As demonstrated by Adler et al. (2009), the distracting influence of non-target events in sustained somatosensory attention is mediated by perceptual load. In that study, distractors pulled attention toward to-be-ignored body locations in an easy detection task (low perceptual load), which was not the case in a challenging discrimination task (high perceptual load). Therefore, our results indicate that even though twitches were reported by most subjects as difficult to recognize and count, the perceptual load may have been too low since it was only a detection task. So, a more challenging discrimination task using different types of twitches could be beneficial in future. Moreover, in some subjects, only weak SSSEPs were present, even though individual stimulation frequencies were determined by a screening procedure. However, it is not yet known if there is some relationship between relative bandpowers from screening and SSSEP classification accuracies and if selecting the frequencies with highest bandpowers is even the best choice for strongest attention modulation effects.

5. CONCLUSION

Within our work, the role of transient target stimuli was investigated in an SSSEP-based BCI setup. Our findings suggest that different types of combined stimulation or brain signals such as SSSEP and P300 may not be regarded separately but have a mutual influence on each other. When designing a hybrid BCI based on SSSEPs and P300 potentials, one has to find an optimal tradeoff depending on the overall design goals or individual subjects' performance. Our results give therefore some new insights that may be useful for the successful design of hybrid BCIs.

AUTHOR CONTRIBUTIONS

CP, CB, GM designed the study. CP, CB conducted all measurements. CP, CB analyzed the data. CP, CB, GM interpreted and discussed the results. CP wrote the manuscript.

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A.5. The Auditory P300-Based Single-Switch Brain-Computer Interface: Paradigm Transition from Healthy Subjects to Minimally Conscious Patients

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The auditory P300-based single-switch brain–computer interface: Paradigm transition from healthy subjects to minimally conscious patients

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ABSTRACT

Objective: Within this work an auditory P300 brain–computer interface based on tone stream segregation, which allows for binary decisions, was developed and evaluated.
Methods and materials: Two tone streams consisting of short beep tones with infrequently appearing deviant tones at random positions were used as stimuli. This paradigm was evaluated in 10 healthy subjects and applied to 12 patients in a minimally conscious state (MCS) at clinics in Graz, Würzburg, Rome, and Liège. A stepwise linear discriminant analysis classifier with 10×10 cross-validation was used to detect the presence of any P300 and to investigate attentional modulation of the P300 amplitude.
Results: The results for healthy subjects were promising and most classification results were better than random. In 8 of the 10 subjects, focused attention on at least one of the tone streams could be detected on a single-trial basis. By averaging 10 data segments, classification accuracies up to 90.6% could be reached. However, for MCS patients only a small number of classification results were above chance level and none of the results were sufficient for communication purposes. Nevertheless, signs of consciousness were detected in 9 of the 12 patients, not on a single-trial basis, but after averaging of all corresponding data segments and computing significant differences. These significant results, however, strongly varied across sessions and conditions.
Conclusion: This work shows the transition of a paradigm from healthy subjects to MCS patients. Promising results with healthy subjects are, however, no guarantee of good results with patients. Therefore, more investigations are required before any definite conclusions about the usability of this paradigm for MCS patients can be drawn. Nevertheless, this paradigm might offer an opportunity to support bedside clinical assessment of MCS patients and eventually, to provide them with a means of communication.

1. Introduction

Traditional means of assistive technologies (AT), such as joystick or button-based systems rely on residual muscular output from the user. In contrast, a brain–computer interface (BCI) is a technology that utilizes neurophysiological signals directly from the brain to control external devices, bypassing the natural muscular output [1]. Currently, BCI systems based on electroencephalography (EEG) can provide severely motor-disabled people with a new output channel to voluntarily control applications for communication and environmental control [2–8].

In addition, different neuroimaging and electrophysiological techniques have revealed signs of intact cortical processing and awareness in unresponsive patients diagnosed with vegetative state (VS) and minimally conscious state (MCS) [9,10]. MCS is a disorder of consciousness (DOC) that is clinically identified on the basis of behavioral assessment that shows the presence of non-reflexive responses to visual and auditory stimulation [11,12]. Severe motor impairment might, however, prevent the disclosure of awareness even during a careful repeated examination, leading to a rate of misdiagnosis of approximately 40% [10]. To overcome this problem, EEG-based BCI systems might offer a unique

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opportunity in supporting the bedside clinical assessment of unresponsive patients and eventually, in providing them with a means of communication. When considering BCI-based communication for unresponsive patients, the main goals of development should be to implement simple and robust devices. Both requirements can be fulfilled by using a single-switch BCI (ssBCI) which reliably detects one specific brain pattern of the patient [13,14]. Consequently, any kind of assistive technology (AT) can be controlled by simple binary yes/no commands provided by the ssBCI [15].

When designing an ssBCI for unresponsive patients, the specific needs and capabilities of the target patient group need to be taken into account. One promising way to realize a BCI in unresponsive patients is to use an auditory paradigm [16–18]. While vision might be considerably impaired, the auditory system is usually preserved in unresponsive patients [19–21] or might even be the only remaining channel usable for BCI-based communication [22]. One brain signal often used to realize a BCI is the P300 component of the event-related potential (ERP). The P300 component is a positive deflection in the EEG that can be elicited by a so-called oddball paradigm and occurs about 300 ms after a rare stimulus event in a stream of standard stimuli [23–26]. Previous studies have shown the applicability of auditory P300-based paradigms, allowing a user to make a binary decision by focusing attention on one of two concurrent tone streams [27–29]. Hill et al. [27,28] presented the tone streams separately to the left and the right ear. In contrast, Kanoh et al. [29] showed that focusing attention on one of the tone streams is even possible when both streams are presented to the right ear only. These studies showed promising results, but only in healthy subjects.

Based on these considerations, the aim of our current work was to develop an auditory P300 paradigm similar to [29] which just allows for binary decisions and which does not rely on binaural hearing. Such a paradigm is considered to be simpler than other P300 paradigms (e.g., auditory matrix speller [4]) since only two classes (i.e., two tone streams) exist. It is, therefore, assumed to be suitable for unresponsive patients. This paradigm was evaluated in healthy subjects and then applied to MCS patients. Our work, therefore, shows the transition of a paradigm from healthy subjects to MCS patients. Our main question was, whether a paradigm that is promising in healthy subjects can also successfully be applied to MCS patients. Some preliminary results of this work have already been presented in [30].

2. Materials and methods

2.1. Auditory stimulation

In order to create an oddball paradigm similar to [29], two tone streams with infrequently appearing deviant tones at random positions were used as stimuli. Both tone streams were composed of short beep tones with a length of 60 ms and a rise and fall time of 7.5 ms each. The beep tones were arranged according to the tone stream pattern LHL_LHL_... (‘L’ = low tone, ‘H’ = high tone, ‘_’ = silent gap). In this way, the low tone stream (LTS) was twice as fast as the high tone stream (HTS). This was an attempt to make the streams more distinguishable. Based on our own experience when listening to the tone streams we considered the tone streams to be better distinguishable if the tones would not only differ in frequency (low/high) but also in the presentation rate (fast/slow). In the LTS, the inter-stimulus interval (ISI) was 300 ms and the standard low tones had a frequency of 396 Hz, whereas the low deviants had a frequency of 297 Hz. In the HTS, the ISI was 600 ms and the standard high tones had a frequency of 1900 Hz, whereas the high deviants had a frequency of 2640 Hz. Both tone streams were intermixed

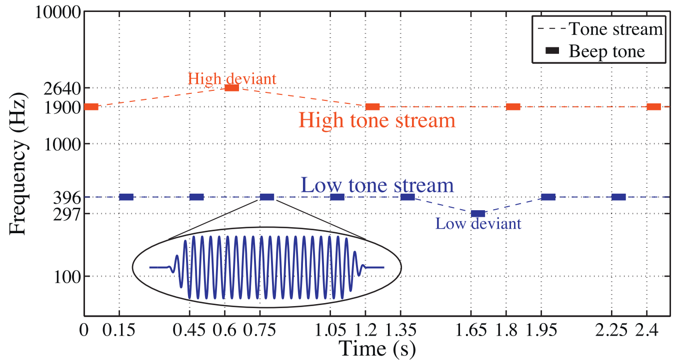

Fig. 1. Schematic representation of the two intermixed tone streams used as stimuli. Both the high and the low tone stream (dashed lines) consisted of short beep tones (short bars) with randomly placed deviants. In the high tone stream, every other tone is omitted corresponding to silent gaps in the tone stream pattern. The waveform of one standard low tone is also shown in magnified view.

with an offset of 150 ms. In Fig. 1, a schematic representation of the tone streams can be seen.

Since the frequency separation between both tone streams was large enough and the presentation rate was sufficiently high, the beep tones could be perceived as two segregated tone streams [31]. Therefore, it was possible to intentionally shift attention from one stream to the other and thus to modulate the P300 response elicited by the deviant tones in the attended tone stream [27–29,32]. The modulated P300 amplitude could then be used to infer which tone stream the participants paid attention to. Both tone streams were presented binaurally using in-ear headphones, making the paradigm usable for patients with only monaural hearing capabilities.

The percentage of deviant tones was 20% in the HTS (slow) and 10% in the LTS (fast) respectively, resulting in the same absolute number of deviants in both streams. The deviants were randomly distributed with some restrictions. In the LTS, between 5 and 13 standard low tones (uniform distribution; 9 tones on average) always appeared between two deviants. In the HTS, between 2 and 6 standard high tones (uniform distribution; 4 tones on average) always appeared between two deviants. Additionally, across streams, high and low deviants could not appear consecutively.

A regular computer with Matlab/Simulink together with a custom-made C++function to ensure high-speed and low-delay audio output was used to play the beep tones. The beep tones were generated with a sampling rate of 44,100 Hz. To ensure that all four types of beep tones (low/high standard tones, low/high deviant tones) were perceived equally loud, the loudness of the tones was adjusted according to the normal equal-loudness-level contours defined in the ISO standard ISO 226:2003 [33] (see Fig. 2). In this way, bias effects toward one of the streams were reduced.

2.2. Participants

This multi-centered study was conducted in two parts, one part with healthy subjects and another with MCS patients which was conducted approximately one year later. In the first part, 10 healthy subjects (3 female, 7 male) aged between 24 and 33 years (mean age 27.6 ± 3.0 (SD) years) participated in this study. They were informed in detail about the aims of the study, gave informed consent and were paid for participation. One participant reported a slight tinnitus in both ears, but had no problems hearing the beep tones or perceiving the two tone streams separately. All other participants did not report any hearing problems. All EEG measurements with healthy subjects were conducted at Graz University of Technology.

The second part of this study was conducted with 12 MCS patients (4 female, 8 male) aged between 14 and 66 years (mean

Table 1
Characteristics of all MCS patients who participated in this study.

Patient no.	Location	Age (years)	Sex	Cause of DOC	Time since event (months)
PA_1	Graz	45	Male	Traumatic brain injury	19
PA_2	Graz	66	Male	Traumatic brain injury	9
PA_3	Graz	21	Male	Hypoxic brain injury	37
PA_4	Graz	28	Male	Traumatic brain injury	49
PA_5	Würzburg	59	Female	Hypoxic brain injury	41
PA_6	Würzburg	59	Male	Traumatic brain injury	30
PA_7	Würzburg	55	Male	Ischemic stroke	27
PA_8	Rome	62	Male	Hemorrhagic stroke	5
PA_9	Rome	47	Female	Hemorrhagic stroke	38
PA_{10}	Rome	64	Female	Hemorrhagic stroke	13
PA_{11}	Rome	14	Male	Traumatic brain injury	7
PA_{12}	Liège	29	Female	Traumatic brain injury	89

age 45.8 ± 18.2 (SD) years) at four different locations. EEG measurements were conducted in Graz (Albert Schweitzer Clinic), Würzburg (Intensive Care Hospital Schwaig), Rome (Fondazione Santa Lucia) and Liège (CHU University Hospital). All patients were selected by the medical stuff in the respective clinics. Patients diagnosed with MCS between 14 and 80 years who were not in intensive care and in an overall stable medical condition were included. Exclusion criteria were gravidity, infections, and participation in other studies. Table 1 provides background and disease related data of all patients. Informed consent was obtained from the patients' legal representatives. The patients participated in a different number of sessions. The idea was that each patient, if possible, would participate in two session on different days to compensate for possible fluctuations in responsiveness. For patients who participated in more than one session, the follow-up sessions were carried out between 1 and 12 weeks later. The patients were behaviorally assessed using the Coma Recovery Scale-Revised (CRS-r) [11] within 24 h before or after each EEG measurement in order to keep track of their fluctuations in responsiveness.

This study was approved by the local Ethics Committees at all participating institutions and was conducted in accordance with the Declaration of Helsinki.

2.3. EEG recording

The EEG was recorded with a sampling rate of 512 Hz using active electrodes. A band-pass filter between 0.5 Hz and 100 Hz and a notch filter at 50 Hz were activated. The ground electrode was connected to the right mastoid, the reference electrode was attached to the left earlobe.

In healthy participants, the EEG was recorded at 15 positions (F3, Fz, F4, T7, C5, Cz, C6, T8, TP7, CP5, CP6, TP8, P3, Pz, and P4; see Fig. 3) according to the international 10-20 system. Positions covering the auditory cortices were included. All EEG measurements were conducted in a shielded room where the subjects were sitting in a comfortable armchair, with a computer screen placed in front of them.

With the patients, a reduced channel set was used to facilitate measurements in a clinical environment. The EEG was recorded at 9 positions only (F3, Fz, F4, C3, Cz, C4, P3, Pz and P4; see Fig. 3). Given the rather high effort of mounting electrodes, due to some patients unintentionally moving their head or lying in bed with the electrode cap constantly touching the pillow, a reduced channel set was considered to be acceptable. All measurements were conducted in a silent room in a clinical environment. The patients were either lying in bed with the upper part of their body slightly elevated or sitting in a wheelchair, with a screen placed in front of them.

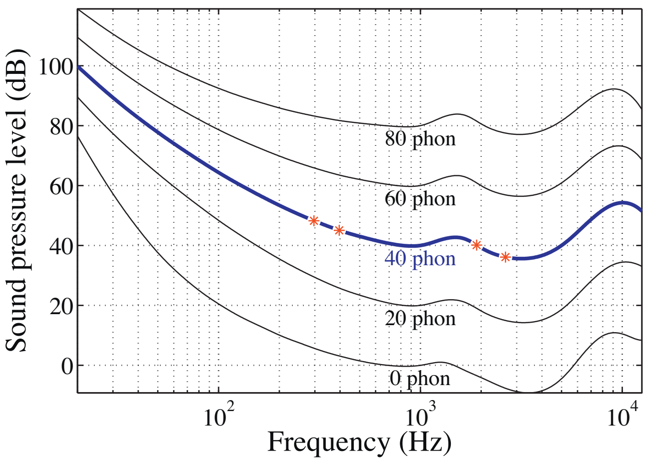

Fig. 2. Normal equal-loudness-level contours defined in ISO 226:2003 [33]. The loudness of the beep tones at the four frequencies 297 Hz, 396 Hz, 1900 Hz, and 2640 Hz (asterisks) was corrected along the 40-phon curve (bold line) in order to be perceived equally loud.

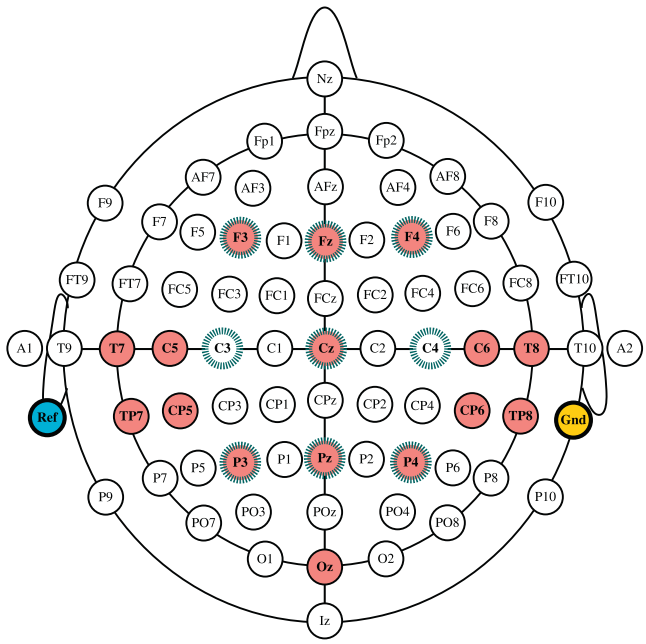

Fig. 3. Electrode setup according to the international 10-20 system. In healthy participants, the EEG was recorded at the 15 shaded electrode positions. In MCS patients, the EEG was recorded at 9 postions marked with dashed circles. The left earlobe was used as reference (Ref), the right mastoid as ground (Gnd).

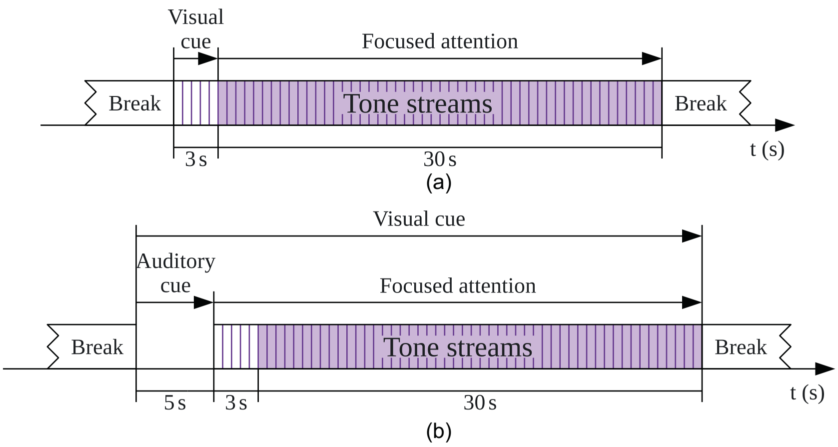

Fig. 4. Experimental paradigms. (a) Paradigm used with healthy participants. At the beginning of each trial, a visual cue instructing the subject to focus attention on one of the streams was shown on a screen. At the same time, the tone streams (vertical hatching) were presented, but without any deviant tones. After 3 s, deviant tones were randomly inserted (shaded area). (b) Paradigm used with MCS patients. Before the tone streams began, an auditory cue was presented. The visual cue was shown on the screen during the whole trial.

2.4. Experimental paradigms

2.4.1. Healthy subjects

The paradigm for healthy participants consisted of cue-based trials with a length of 33 s (see Fig. 4(a)). During the first 3 s of a trial, a visual cue randomly indicated which stream to focus attention on. This is referred to as the target stream. The other stream is referred to as the non-target stream. The cue was shown on the screen which was placed in front of the subjects. During this instruction period, the tone streams were presented (5 high beep tones, 10 low beep tones), but without any deviant tones. This is expected to make it easier to focus attention on the target stream. After 3 s, the cue disappeared and a fixation cross was displayed in the middle of the screen. During the next 30 s, 50 high beep tones and 100 low beep tones were presented, containing 10 deviant tones randomly distributed in each stream. The subjects were instructed to keep their attention focused on the target stream and ignore the non-target stream. Moreover, they were instructed to silently count and intentionally recognize any occurrence of a deviant tone in the stream they were focusing on. After 33 s, a random break between 8 s and 12 s was inserted before the next trial started. The whole experiment consisted of 8 runs with 10 trials each and lasted around 1 h (without breaks). The lengths of the breaks between runs were determined by the participant. In total, 80 trials were recorded, 40 trials for each stream as target. Within 40 trials, 4000 standard and 400 deviant tones in the LTS and 1800 standard and 400 deviant tones in the HTS were presented.

2.4.2. MCS patients

With MCS patients, each session started with a simple version of the paradigm where either the LTS or the HTS only was presented. Then, the complex paradigm with both tone streams was presented to the patients. The simple paradigm was added to find out whether the presence of a P300 in the simple paradigm is related to the presence of a P300 in the complex paradigm. Furthermore, the patients should have more time to get accustomed to the experimental conditions. Due to the limited concentration time of the patients, only one of the streams was selected (randomized across patients) to be presented in the simple paradigm. If an equal number of trials had been recorded for each of the streams, the measurement time for the simple paradigm would have doubled. Since the main goal of our work was to develop a communication paradigm for binary decisions, it was considered to be more important to record as many trials as possible using the complex paradigm. Only in the follow-up sessions of two (random) patients, was an attempt made to use each of the streams in the simple paradigm. In the simple paradigm, the patients were instructed to listen to the presented tone stream and to silently count the occurrences of deviant tones. This instruction was provided to facilitate focusing attention in the following complex paradigm. In total, 4 runs with 5 trials each were recorded with random breaks between all trials (between 8 s and 12 s). Between the runs, breaks were longer according to the patients' needs. Information about the patients' needs was obtained by visual assessment of their condition (e.g., possibly asleep, not focused, moving a lot). In the complex paradigm, random cues seemed to be too demanding for the patients. Therefore, blocks of 5 consecutive trials with the same target stream were recorded. The first target stream was always the same as used in the simple paradigm. At least two blocks, one with the LTS and one with the HTS as target, were recorded. When the patients' condition allowed it, a second turn with one block for each target was recorded. In the complex paradigm, individual breaks were taken after each single trial according to the patients' needs.

For MCS patients, the course of the paradigm was also slightly modified (see Fig. 4(b)). One trial had a length of 38 s, and during the additional 5 s at the beginning, an auditory cue (presented via headphones like the tone streams) indicated which stream to focus attention on. Additionally, patients were also instructed by the experimenter prior to each trial. This was possible because the cues were known in advance because of the block-based design instead of random cues. The same information was also shown as a visual cue which was presented during the whole trial instead of the fixation cross. The visual cue was presented on the screen which was placed in front of the patients' head. After 5 s, the tone streams were presented for 33 s like in the paradigm for healthy participants. Again, during the first 3 s, the streams did not contain any deviants. In addition, to make it easier for the patients to identify the target stream and focus attention on it, asynchronous stream onsets were used. This means that during this first 3 s, only the target stream was presented.

2.5. Data analysis

Data recordings from healthy subjects and patients were analysed exactly in the same way except for one difference. The EEG recordings from some patients contained a large amount of artifacts due to uncontrolled movements of their head, eyes, and extremities. Therefore, EOG (electrooculogram), EMG (electromyogram),

Table 2
SWLDA classification accuracies (with 10 × 10 cross-validation) for all healthy subjects together with the mean and standard deviation (SD). P300: To detect the P300, the deviant tones were classified against the standard tones. Attention: To investigate the attentional modulation, the target deviants were classified against the non-target deviants. The results are shown with (w/) and without (w/o) averaging (10 segments), separately for the LTS and HTS as target. All results better than random [34] are designated with asterisks.

Subject no.	Classification accuracies							
	P300				Attention			
	w/o averaging		w/ averaging		w/o averaging		w/ averaging	
	LTS	HTS	LTS	HTS	LTS	HTS	LTS	HTS
HS_{01}	57.3**	61.2**	74.0**	72.4**	55.2*	57.8**	59.0	68.5*
HS_{02}	70.7**	61.8**	84.7**	81.3**	62.6**	62.8**	78.0**	81.4**
HS_{03}	77.2**	72.0**	97.7**	94.9**	69.5**	70.4**	90.6**	90.2**
HS_{04}	62.2**	57.2**	81.0**	71.3**	56.9**	53.5	64.2	62.5
HS_{05}	63.9**	60.7**	82.5**	74.4**	63.5**	61.0**	76.9**	75.6**
HS_{06}	71.5**	64.4**	93.8**	82.4**	65.5**	65.5**	83.0**	83.0**
HS_{07}	61.9**	54.4	87.4**	66.4*	53.3	55.6*	58.2	59.6
HS_{08}	67.2**	59.7**	92.0**	74.2**	58.9**	60.2**	65.1*	80.8**
HS_{09}	56.8**	55.4*	68.6*	62.8	52.8	52.1	61.1	59.5
HS_{10}	56.0*	52.6	73.4**	56.5	51.4	50.6	54.0	57.6
Mean	64.5**	59.9**	83.5**	73.7**	59.0**	59.0**	69.0*	71.9**
SD	7.1	5.6	9.5	10.8	6.1	6.3	12.2	11.8

* Better than random ($\alpha = 5\%$).
** Better than random ($\alpha = 1\%$).

and technical artifacts (presumably due to cable movements and the head lying on some electrodes) were manually selected and data segments containing such artifacts were excluded from any further analyses. In the recordings from healthy subjects, artifact removal was considered to be not necessary.

All data were filtered with a 3rd-order Butterworth low-pass filter at 10 Hz and downsampled to a sampling rate of 64 Hz. Then, data segments from 0 to 1200 ms relative to the beep tone onsets were extracted. Only the EEG channels Fz, Cz and Pz were selected. These were included in both channel sets. For classification, a stepwise linear discriminant analysis (SWLDA) classifier was used with the enter criterion $p_{enter} = 0.1$, the removal criterion $p_{remove} = 0.15$ and the number of iterations $n_{iterations} = 10$, together with 10 × 10 cross-validation. The SWLDA classifier only used time points between 200 ms and 800 ms after beep tone onset as features. No baseline correction was performed since no suitable baseline interval could be defined because of the presence of overlapping auditory evoked potentials due to the high presentation rate of the beep tones. Each of the classification results was compared with the real level of chance [34] to identify random results.

For healthy subjects, in addition to the single-trial classification, a second classification approach was pursued. The idea was to use averaging to improve the signal-to-noise ratio (SNR) and thus to increase the classification accuracies. Therefore, 10 successive segments belonging to the same type of beep tone were averaged and used for classification, thereby reducing the effective number of segments by a factor of 10. This was possible since the total number of beep tones within the 80 recorded trials was sufficiently high. For patients, classification of averaged data segments could not be applied because of the small number of recorded trials.

The P300 classification was carried out under the following conditions: (i) The deviant tones were classified against the standard tones in the only tone stream used in the simple paradigm. This was only done for patients to investigate if a P300 was present. To account for the very different numbers of deviant and standard segments, random subsampling with 100 iteration was applied. (ii) The deviant tones were classified against the standard tones separately for each target stream used in the complex paradigm. This was done for healthy subjects as well as for patients to investigate if a P300 was present in either of the streams. Again, random subsampling was applied. (iii) The target deviant tones were classified against the non-target deviant tones separately for each stream used in the complex paradigm. Again, this was done for healthy subjects as well as for patients to investigate the attentional modulation of the P300 amplitude. Using this information it should be possible to infer which stream was attended. Usually, under this condition, the number of target and non-target segments should be equal (10 deviants in each stream per trial). If, however, due to artifacts, the number of segments differed by more than 25 %, random subsampling was also applied.

Statistical analysis comprised a Shapiro–Wilk test for testing normal distribution of the data and a multivariate analysis of variance (MANOVA) for evaluating differences in classification accuracy of P300 and attention results between tone streams (LTS versus HTS) and between analyzing methods (with averaging versus without averaging). All relevant data were normally distributed and Bonferroni correction was used to adjust p-values for multiple comparisons. Pearson's product moment correlation was used for evaluating possible relations between CRS-r scores and classification accuracies.

For visual inspection of the data, all data segments of each participant were averaged according to stimulus type and condition. These averaged segments were then tested for significant differences. To this end, confidence intervals with significance level $\alpha = 5\,\%$ were estimated using bootstrapping based on $n = 1000$ bootstrap samples. Similar to [35,36], only non-overlapping intervals with lengths $L \geq 60$ ms were regarded as significant differences whereas intervals with lengths $L \geq 30$ ms were regarded as weakly significant differences.

3. Results

3.1. Healthy subjects

Table 2 summarizes the SWLDA classification results of all 10 healthy subjects. The values in this table represent the mean classification accuracies over all cross-validation folds. The results are shown for two different conditions. The columns labeled with 'P300' contain the results when classifying the deviant tones against the standard tones. The columns labeled with 'Attention' contain the results when classifying target deviant tones against non-target deviant tones. All results are presented separately for the LTS and the HTS as target stream. Moreover, the results with and without averaging of 10 successive segments can be seen. The single

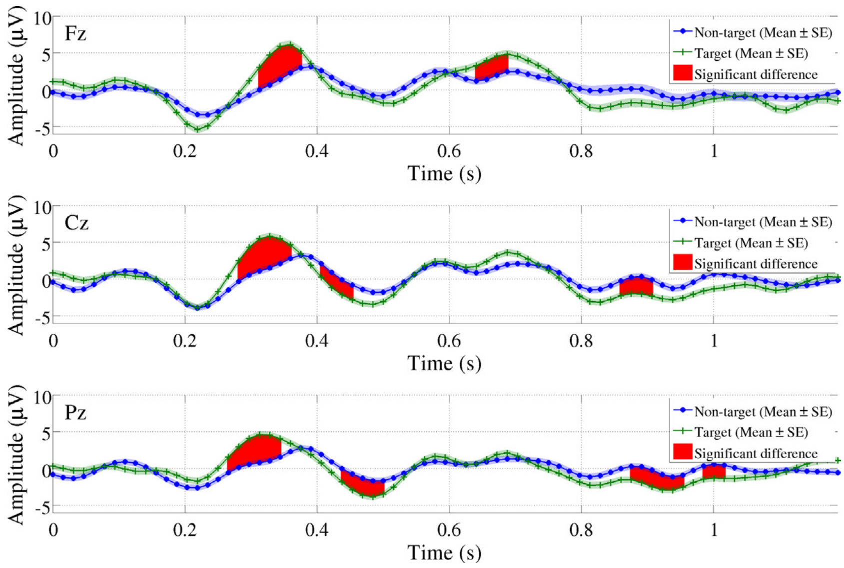

Fig. 5. Attentional modulation effect of the P300 amplitude for the healthy subject HS_{02} at the channels Fz, Cz, and Pz. The averaged data segments of the non-target low deviant tones (blue curve; marker type: •) versus the target low deviant tones (green curve; marker type: +) can be seen. Significant differences were computed using bootstrapping ($\alpha = 5\,\%$; red shaded areas). The standard error (SE) is plotted along with the curves (lightly shaded areas). (For interpretation of references to colour in this figure legend, the reader is referred to the web version of this article.)

results of all subjects as well as the mean and standard deviation across all subjects are shown. All results better than random [34] are designated with asterisks.

Most of the results are clearly better than random. Moreover, for all subjects and conditions, the classification accuracies could always be improved by averaging. However, after averaging, not all results were better than random because of the increased level of chance due to 10 times fewer effective data segments. The mean classification accuracies ranged between 59.0 % and 64.5 % without averaging and between 69 % and 83.5 % with averaging. In 8 of the 10 subjects, focused attention on at least one of the tone streams could be detected on a single-trial basis (i.e., without averaging of segments).

To evaluate any possible bias toward one of the two tone streams, classification accuracies were compared using MANOVA and revealed a significant difference in the P300 results. Subjects reached higher accuracies in the LTS than in the HTS ($p = 0.011$). No differences between LTS and HTS were found in the attention results. To evaluate the hypothesis that data averaging improves classification accuracies, a comparison between data with averaging and without averaging was conducted and revealed significant differences both in the P300 results ($p < 0.001$) and in the attention results ($p = 0.001$).

By way of example, Fig. 5 shows the attentional modulation effect of the P300 amplitude for one healthy subject HS_{02}. The averaged data segments belonging to the target low deviant tones (i.e., when focusing attention on the LTS) versus the non-target low deviant tones (i.e., when focusing attention on the HTS) can be seen. Significant differences (estimated using bootstrapping with $\alpha = 5\,\%$) could be found at all three channels Fz, Cz, and Pz. A significant enhancement of the P300 amplitude due to attention can be seen around 350 ms after stimulus onset. The standard error (SE) is plotted along with the curves.

3.2. MCS patients

Table 3 summarizes the SWLDA classification results of all 12 MCS patients. Again, the values in this table represent the mean classification accuracies over all cross-validation folds and are shown separately for the LTS and HTS as target. The results are also divided into the conditions labeled with 'P300' and 'Attention' in the complex paradigm as well as the condition 'P300' in the simple paradigm where only one tone stream at a time was presented. Information about sessions and CRS-r scores is also provided. Five patients participated in one session only, six patients in two sessions and one patient in three sessions. The number of sessions was not equal for all patients since the patients' conditions did not always allow successful EEG measurements. Due to the high logistic effort to carry out measurements in different clinics some sessions, unfortunately, could not always be repeated. The single results of all patients as well as the mean and standard deviation across all patients and sessions are shown. All results better than random [34] are designated with asterisks.

Table 3 shows that only a small number of results, mainly in the simple paradigm, were above chance. The mean classification accuracies were below chance level for all conditions. In 4 of the 12 patients, the presence of a P300 in the simple paradigm could be detected on a single-trial basis. Only in PA_{09}, a P300 in the complex paradigm could be classified above chance level. Not enough trials were recorded to use averaging to improve the SNR. Attentional modulation could not be detected in any of the patients on a single-trial basis.

To assess any possible relations between CRS-r scores and classification accuracies, Pearson's product moment correlation was computed but revealed no significant results. However, significant positive correlations were found between classification accuracies in the simple and complex paradigm in the HTS ($r = 0.56$, $p = 0.032$), indicating that the presence of a P300 in the simple paradigm is related to the presence of a P300 in the complex paradigm. Classification accuracies in one tone stream were also found to be correlated with the accuracies in the other tone stream in the complex paradigm ($r = 0.56$, $p = 0.012$). Due to the study protocol, only a few patients performed the simple paradigm with each of the tone streams. Nevertheless, a clear trend towards a significant correlation between both streams was present ($r = 0.99$, $p = 0.053$). In addition, a highly positive correlation between accuracies in the P300 results and the attention results was found in the HTS ($r = 0.58$, $p = 0.010$), but not in the LTS.

Although single-trial classification accuracies for patients were mainly below chance level, significant effects could be found after

Table 3
SWLDA classification accuracies (with 10 × 10 cross-validation) for all MCS patients together with the mean and standard deviation (SD). Information about sessions and CRS-r scores is also listed. P300: To detect the P300, the deviant tones were classified against the standard tones. Attention: To investigate the attentional modulation, the target deviants were classified against the non-target deviants. The results of the simple and complex paradigm are shown separately for the LTS and HTS as target. All results better than random [34] are designated with asterisks. Omitted values (–) indicate that no measurements were conducted.

Patient no.	Session	CRS-r	Classification accuracies (%)					
			Simple paradigm		Complex paradigm			
			P300		P300		Attention	
			LTS	HTS	LTS	HTS	LTS	HTS
PA_{01}	1	18	49.4	–	47.3	49.1	44.5	53.4
	2	18	–	57.2	54.9	47.1	58.2	52.6
PA_{02}	1	14	–	52.1	48.7	51.1	51.5	44.4
	2	15	49.7	–	49.2	49.6	43.5	52.5
PA_{03}	1	13	–	52.4	49.7	50.2	42.8	52.7
	2	12	51.4	–	54.2	49.5	49.4	47.4
PA_{04}	1	8	55.7	–	50.6	52.2	52.5	55.4
	2	8	–	50.0	50.1	51.2	52.7	48.6
PA_{05}	1	9	–	60.1*	52.9	56.7	49.4	58.6
	2	6	57.9	60.6*	49.4	50.2	48.3	49.7
PA_{06}	1	7	–	49.7	51.4	47.4	53.7	45.1
	2	6	50.2	48.8	–	–	–	–
	3	7	49.5	46.4	50.5	50.0	54.3	56.3
PA_{07}	1	21	–	49.6	53.4	47.2	58.1	45.9
PA_{08}	1	20	–	48.0	49.4	50.2	45.8	48.4
PA_{09}	1	18	–	59.6*	64.8*	63.0	47.0	60.1
PA_{10}	1	18	–	58.3*	57.7	51.5	65.5	51.1
	2	19	–	53.4	50.6	54.8	50.5	48.1
PA_{11}	1	20	–	59.1*	51.6	56.5	47.5	51.2
PA_{12}	1	4	–	50.1	49.2	50.1	49.3	49.8
Mean			52.0	53.5	51.9	51.5	50.8	51.1
SD			3.4	4.9	4.0	3.9	5.6	4.4

* Better than random (α = 5%).

averaging of all data segments belonging to one stimulus type and condition. In Table 4, significant differences (estimated using bootstrapping with α = 5 %) that could be found at any of the channels Fz, Cz, or Pz between 200 ms and 900 ms after stimulus onset are presented. Only significant differences with lengths $L \geq 60$ ms and weakly significant differences with $L \geq 30$ ms are listed. 'P' denotes a significant positive difference whereas 'N' denotes a significant negative difference. The approximate latency (in ms) is defined as

Table 4
Significant differences estimated using bootstrapping with α = 5 % for all patients and conditions. Only significant differences with lengths $L \geq 60$ ms (bold values) and weakly significant differences with $L \geq 30$ ms that could be found at any of the channels Fz, Cz, or Pz between 200 ms and 900 ms after stimulus onset are reported. 'P' denotes a significant positive difference whereas 'N' denotes a significant negative difference. The approximate latencies between stimulus onset and the mean time of the significant interval are given in ms. 'n.s.' means that no significant differences could be found. Omitted values (–) indicate that no measurements were conducted.

Patient no.	Session	Significant differences					
		Simple paradigm		Complex paradigm			
		P300		P300		Attention	
		LTS	HTS	LTS	HTS	LTS	HTS
PA_{01}	1	n.s.	–	n.s.	n.s.	n.s.	n.s.
	2	–	P230, **P520**	**P390**	n.s.	**P300**	n.s.
PA_{02}	1	–	P770	n.s.	n.s.	P680	n.s.
	2	n.s.	–	n.s.	n.s.	n.s.	n.s.
PA_{03}	1	–	P800	n.s.	n.s.	n.s.	n.s.
	2	P740	–	**N210**, P810	n.s.	n.s.	n.s.
PA_{04}	1	P440, **P690**	–	n.s.	n.s.	n.s.	**N730**
	2	–	n.s.	N760	N800	n.s.	n.s.
PA_{05}	1	n.s.	N250, **P370**	N360	n.s.	n.s.	n.s.
	2	**P460**	n.s.	n.s.	n.s.	n.s.	n.s.
PA_{06}	1	–	n.s.	n.s.	n.s.	n.s.	n.s.
	2	n.s.	n.s.	–	–	–	–
	3	n.s.	n.s.	N800	n.s.	n.s.	n.s.
PA_{07}	1	–	n.s.	n.s.	n.s.	n.s.	n.s.
PA_{08}	1	–	n.s.	n.s.	n.s.	n.s.	n.s.
PA_{09}	1	–	N240, **P390**, P880	**N260**, N530, P870	**N550**, **P760**	n.s.	n.s.
PA_{10}	1	–	**P490**, **N650**	**P420**	n.s.	n.s.	n.s.
	2	–	**P530**	P430	n.s.	n.s.	n.s.
PA_{11}	1	–	N360, **N590**, **N850**	N300	**P810**	n.s.	n.s.
PA_{12}	1	–	n.s.	n.s.	n.s.	n.s.	n.s.

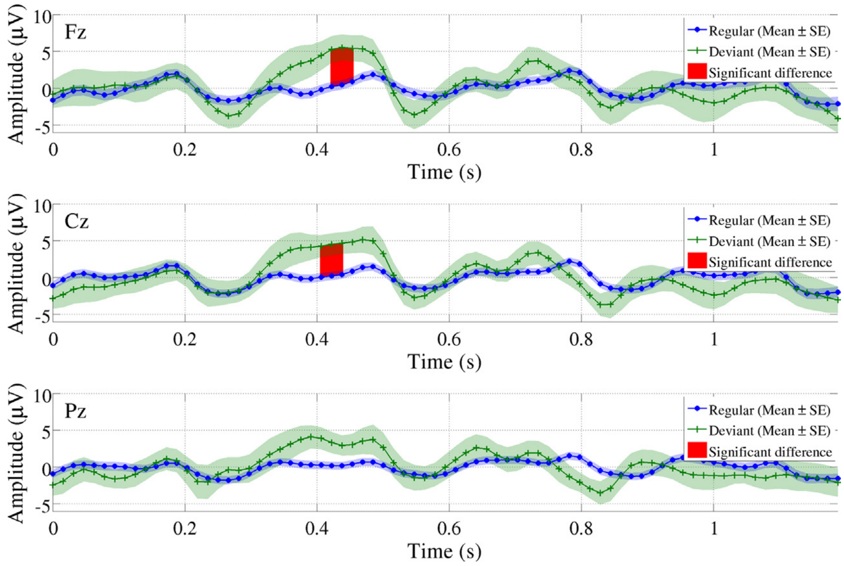

Fig. 6. Presence of a P300 in the complex paradigm for patient PA_{10} at the channels Fz, Cz and Pz. The averaged data segments of the low standard tones (blue curve; marker type: •) versus the low deviant tones (green curve; marker type: +) can be seen with the LTS as target stream. Significant differences were computed using bootstrapping ($\alpha = 5\,\%$; red shaded areas). The standard error (SE) is plotted along with the curves (lightly shaded areas). (For interpretation of references to colour in this figure legend, the reader is referred to the web version of this article.)

the period between stimulus onset and the mean time of the significant interval. Significant differences are reported separately for all patients and conditions.

Most patients showed significant differences between standard and deviant tones in the simple or complex paradigm in one of the sessions. Only a few patients also showed significant differences due to attention in one of the target tone streams. The significant results strongly varied across sessions and conditions.

By way of example, Fig. 6 shows the presence of a P300 in the complex paradigm for patient PA_{10}. The averaged data segments of the low standard tones versus the low deviant tones can be seen when the LTS was the target stream. A (weakly) significant P300 can be seen around 430 ms after stimulus onset. The standard error (SE) is plotted along with the curves.

4. Discussion

Within this work, an auditory P300 paradigm which allows for binary decisions was developed. As a first step, this paradigm was evaluated in 10 healthy subjects and finally, applied to 12 MCS patients at clinics in Graz, Würzburg, Rome, and Liège. The initial evaluation in healthy subjects showed promising results. Most of the classification results were clearly better than random. In 8 of the 10 subjects, focused attention on at least one of the tone streams could be detected on a single-trial basis. Statistical analyses revealed that both tone streams can be assumed to be equally salient, since, on average, no significant differences between the tone streams were found in the attention results. By averaging 10 data segments, the SNR could be increased and the classification accuracies could, thus, be improved, reaching mean accuracies between 69 % and 83.5 %. Therefore, in principle, the applicability of this paradigm in healthy subjects could be shown.

Our classification results were similar to the cross-validated classification accuracies reported in [29] but not as high as reported in other related studies which relied on dichotic listening tasks [27,28]. However, these studies are not directly comparable since different classification methods were used and some parameters of the tone streams (including ISI, beep tone frequencies, percentage of deviants, etc.) were different. Therefore, the impact of these parameters on the classification accuracy remains to be investigated in future studies. Moreover, some healthy subjects also reported difficulties focusing attention on the tone streams. It is possible the perceptual load involved in processing the auditory stimuli was not sufficiently high to remain focused on the target and to ignore the distracting non-target tone stream [37]. Furthermore, most subjects also reported that this paradigm was somehow monotonous and boring which might also have prevented them from remaining focused. Therefore, in future paradigms, more interesting sounds or even syllables or words could be used as stimuli.

Another possibility to facilitate focusing attention would be to present each tone stream exclusively to one ear, as in [27,28]. In this case, monaural hearing capabilities would no longer be sufficient to operate this paradigm. This, however, was a precondition when designing our paradigm. Since MCS or VS patients have different kinds of brain lesions, as few assumptions as possible about the patients' capabilities were made. According to a positron emission tomography (PET) study [38] comparing auditory processing in severely brain injured patients, activations in bilateral auditory cortices and associative areas similar to healthy controls were observed in MCS patients. Moreover, functional connectivity between auditory cortex and a larger network of temporal and prefrontal cortices was found in MCS patients. Such a high-order processing or functional integration could not be observed in persistent vegetative state (PVS) patients. In our study, at least some patients showed, on average, significant differences due to attention which also suggests that they must have preserved some degree of high-order processing and functional connectivity. Therefore, a binaural approach could be an alternative to improve the paradigm for some of the MCS patients. However, especially in VS patients, binaural hearing capabilities can no longer be assumed due to the lack of functional connectivity in the brain [19,38].

As a second step, the paradigm was modified according to the patients needs and capabilities and applied to MCS patients. Auditory cues were added rendering this paradigm applicable purely auditorily without relying on intact vision. Moreover, a block-based trial sequence instead of random cues was used. Asynchronous stream onsets were implemented to make it easier for the patients to identify the target stream. As a result, slightly different versions of the paradigm were applied to both groups of participants.

However, the key parameters such as the composition of the tone streams remained the same, allowing us to compare results from both groups. Since some healthy subjects reported difficulties focusing attention they could also have benefited from the modified version of the paradigm. However, unlike patients, healthy subjects were expected to understand the instructions and to be able to switch the target stream on a trial-by-trial basis. Therefore, asynchronous stream onsets and a block-based design were considered to be necessary only for patients.

Despite these modifications, only a few classification results of MCS patients were above chance level. Unfortunately, none of the results were sufficient for communication purposes. Usually, classification accuracies above 70% are considered as the performance level necessary for communication [39]. This could not be reached by any of the patients. Most healthy subjects did not reach this performance level on a single-trial basis either, but most of them, unlike patients, still performed clearly better than random. Possible reasons for low classification accuracies in patients could be that they were not able to understand or correctly follow the instructions, or the paradigm was simply too demanding for them.

Nevertheless, cue-directed attentional behavior could not be detected on a single-trial basis but after averaging all data segments. In most patients, significant differences between standard and deviant tones in the simple or complex paradigm could be found. Similarly to results described in [35,36], only significant differences exceeding a certain length were actually reported. In future analyses, more sophisticated statistical methods (such as for example an approach described in [40]) might be required to identify significant differences more reliably. It is not yet clear if these significant differences were really P300 potentials since, sometimes, the polarity was inversed and their occurrence was very much delayed. However, Perrin et al. [20] and Schnakers et al. [41] also reported P300 potentials with latencies between 600 ms and 800 ms in MCS patients. They concluded that MCS patients might have a slower processing speed than healthy subjects, an assumption that is also in line with Kotchoubey et al. [9]. There might have been some overlapping effects due to the short ISI the beep tones were presented with. This might also explain why the P300 occurred at later time points, an effect that could also be observed in some healthy subjects. Furthermore, the inversed polarity could indicate a (possibly delayed) mismatch negativity (MMN) instead of a P300 potential. Significant MMN effects could be found in most healthy subjects around 200 ms after stimulus onset followed by the P300 potential, and were also reported by Kanoh et al. [29].

Only 3 patients showed significant differences due to attention in one of the target tone streams. However, these findings indicate that these patients must have understood and adhered to the instructions. Therefore, this paradigm might offer an opportunity to support bedside clinical assessment of unresponsive patients and eventually, to provide them with a means of communication and control. Since time is not a crucial factor for unresponsive patients, communication could be established by simply averaging many trials and detecting significant differences due to attention. It may be acceptable to patients if the time needed to select a symbol or make a decision (e.g., yes or no) is in the order of minutes. In principle, detecting focused attention on one of the streams is sufficient to realize an ssBCI and thus, to control any kind of AT software or device that can be controlled by simple binary yes/no commands [15]. Therefore, since single-trial classification was not successful in patients but significant effects were found on average only, future modifications of the paradigm should aim at signal processing and classification methods involving averaging of many data segments. Also, our statistical results confirmed that averaging of data segments significantly improved classification accuracy and point out the importance of constructing paradigms in such a way that enough trials and data segments are available for averaging. In our current study, in contrast to healthy subjects, not enough trials could be recorded due to the short attention span of the patients and therefore, no averaging could be applied before classification.

In future studies, the impact of short ISIs on the brain response should be investigated in detail to address the problem of overlapping auditory evoked potentials. Moreover, paradigms in which stimuli may be easier to distinguish or elicit a stronger ERP response (as for example faces in the visual domain [42]) have to be developed. Another improvement could be to include EOG electrodes in the channel setup to facilitate artifact reduction. Furthermore, the inclusion of all recorded channels instead of only three pre-selected channels, together with automated channel selection algorithms, might also yield better classification results. The use of non-linear classifiers such as support vector machines (SVMs) that are superior to SWLDA [43] might also be beneficial. However, due to the low number of trials, there is a high risk of overfitting the data when using a non-linear classifier. In another comparison of classifiers for P300 [44], it was, therefore, suggested that linear classifiers are sufficient for P300 data and that the added complexity of non-linear methods is not necessary. Within this comparison, SWLDA was found to perform best in practice.

5. Conclusion

Within this work, an auditory P300 paradigm based on tone stream segregation was evaluated in healthy subjects and then, applied to 12 MCS patients in clinical environments in four different countries. Modifications of the paradigm were necessary to take into account the specific needs and capabilities of these patients. This work, therefore, shows the transition of a paradigm from healthy subjects to MCS patients. Clearly, such a paradigm transition from healthy subjects in the lab to patients in clinical environment involves some compromises. The resulting paradigms are, therefore, not fully comparable. Moreover, promising results with healthy subjects are no guarantee of good results with patients. More investigations are still required before any definite conclusions about the usability of this paradigm for MCS patients can be drawn. Nevertheless, this paradigm might offer an opportunity to support bedside clinical assessment of unresponsive patients and eventually, to provide them with a means of communication.

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Appendix B.

Curriculum Vitae

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Personal information

Born: November 12, 1982—Graz, Austria
Nationality: Austrian
Marital status: Married, 1 child

Areas of specialization

Computer Science; Electrical Engineering; Machine Learning; Brain-Computer Interfaces; Neural Circuits and Systems; Computational Neuroscience

Languages

German (native); English (fluent); Swedish (basic); French (basic); Italian (basic)

Professional experience

2013-Present	Research Assistant at the Institute for Theoretical Computer Science, Graz University of Technology, Graz, Austria
2010-2013	Research Assistant at the Laboratory of Brain-Computer Interfaces, Institute of Neural Engineering, Graz University of Technology, Graz, Austria
2008-2009	Hardware/Software Engineer at All Via Photonics, Grambach, Austria
2007	Software Engineer at GUEP Software, Graz, Austria
2005	Software Engineer at Sappi Austria, R&D Department, Gratkorn, Austria
2004	Printing Press Assistant at Raiffeisen Informatik, Vienna, Austria
2000	Software Engineer at dbs (daily business support), Graz, Austria

Education

2009-Present PhD Student in Computer Sciences, Graz University of Technology, Graz, Austria
Thesis: "Towards Communication with Non-Responsive Patients"
Advisor: Dr. Müller-Putz, Institute of Neural Engineering

2006-2009 MSc (with distinction) in Information and Computer Engineering, Graz University of Technology, Graz, Austria
Thesis: "Development of an Image Processing System for a Multi-Sensor System Based on Field Programmable Gate Arrays"
Advisors: Dr. Söser, Institute of Electronics; Dr. Aziz, All Via Photonics
Semester abroad: KTH Royal Institute of Technology, Stockholm, Sweden

2002-2006 BSc (with distinction) in Information and Computer Engineering, Graz University of Technology, Graz, Austria
Thesis: "Beamformer for Speaker Tracking"
Advisor: Dr. Feldbauer, Institute of Signal Processing and Speech Communication

Awards & scholarships

2016 IBRO/Allen Institute international travel grant (2016 Summer Workshop on the Dynamic Brain, Friday Harbor, WA, USA)

2012 BBCI Neurotechnology Poster Award: Erlbeck H, **Pokorny C**, Klobassa D, Lesenfants D, Real R, Risetti M, Kübler A, Mattia D, and Müller-Putz G (2012), "An auditory P300-based single-switch BCI for minimally conscious patients", *BBCI Workshop on Advances in Neurotechnology*, Berlin, Germany

2012 BBCI Neurotechnology Poster Award: Horki P, **Pokorny C**, Klobassa D, Pichler G, and Müller-Putz G (2012), "Detection of mental imagery and attempted movement in patients with disorders of consciousness using EEG", *BBCI Workshop on Advances in Neurotechnology*, Berlin, Germany

2003-2007 Merit scholarships of the Faculty of Computer Science, Graz University of Technology, in the academic years 2003/04, 2004/05, 2005/06 and 2006/07

Summer schools

2016 Summer Workshop on the Dynamic Brain, Allen Institute for Brain Science & University of Washington, Aug. 20-Sept. 4, Friday Harbor, WA, USA

2016 4th Baltic-Nordic Summer School on Neuroinformatics, Nencki Institute of Experimental Biology & University of Warsaw, June 15-18, Warsaw, Poland

Memberships

2015 Student member of the "Society for Neuroscience"

Publications

Journal articles

In prep. **Pokorny C**, Ison M, Legenstein R, Maass W (In preparation), "A model for the formation of associations between concepts in the brain", *Journal of Neuroscience*

In prep. Skreb V*, **Pokorny C***, Mayrhofer J, Garderes P-M, Maass W, Weber B, and Haiss F (In preparation), "Neuronal plasticity during whisker-dependent operant conditioning and the excitatory impact of behavioral engagement on online sensory processing in layer 2/3 of the barrel cortex", *Cerebral Cortex* (* co-first authorship)

2016 Breitwieser C, **Pokorny C**, and Müller-Putz G (2016), "A hybrid three-class brain–computer interface system utilizing SSSEPs and transient ERPs", *Journal of Neural Engineering* 13:066015

2016 **Pokorny C**, Breitwieser C, and Müller-Putz G (2016), "The role of transient target stimuli in a steady-state somatosensory evoked potential-based brain-computer interface setup", *Frontiers in Neuroscience* 10:152

2015 Horki P, Klobassa DS, **Pokorny C**, and Müller-Putz G (2015), "Evaluation of Healthy EEG Responses for Spelling through Listener-Assisted Scanning", *IEEE Journal of Biomedical and Health Informatics* 19:29-36

2014 **Pokorny C**, Breitwieser C, and Müller-Putz G (2014), "A Tactile Stimulation Device for EEG Measurements in Clinical Use", *IEEE Transactions on Biomedical Circuits and Systems* 8:305-312

2014 Horki P, Bauernfeind G, Klobassa DS, **Pokorny C**, Pichler G, Schippinger W, and Müller-Putz G (2014), "Detection of mental imagery and attempted movements in patients with disorders of consciousness using EEG", *Frontiers in Human Neuroscience* 8:1009

2014 Lesenfants D, Habbal D, Lugo Z, Lebeau M, Horki P, Amico E, **Pokorny C**, Gomez F, Soddu A, Müller-Putz G, Laureys S, and Noirhomme Q (2014), "An independent SSVEP-based brain-computer interface in locked-in syndrome", *Journal of Neural Engineering* 11:035002

2013 **Pokorny C**, Klobassa D, Pichler G, Erlbeck H, Real R, Kübler A, Lesenfants D, Habbal D, Noirhomme Q, Risetti M, Mattia D, and Müller-Putz G (2013), "The auditory P300-based single-switch brain-computer interface: Paradigm transition from healthy subjects to minimally conscious patients", *Artificial Intelligence in Medicine* 59:81-90

2013 Müller-Putz G, **Pokorny C**, Klobassa D, and Horki P (2013), "A single switch BCI based on passive and imagined movements: towards restoring communication in minimally conscious patients", *International Journal of Neural Systems* 23:1250037

Book chapters

2014 Guger C, Sorger B, Noirhomme Q, Naci L, Monti MM, Real R, **Pokorny C**, et al. (2014), "Brain-Computer Interfaces for Assessment and Communication in Disorders of Consciousness", In *Emerging Theory and Practice in Neuroprosthetics*, 1st ed., pp. 181-214.

Conference papers & presentations[1]

2015 Poster: **Pokorny C**, Griesbacher G, Jonke Z, and Legenstein R (2015), "Neural Computation with Assemblies and Assembly Sequences", *45th Annual Meeting of the Society for Neuroscience*, Chicago, USA

2014 Talk: **Pokorny C**, Pichler G, Lesenfants D, Noirhomme Q, Laureys S, and Müller-Putz G (2014), "Steady-State Somatosensory Evoked Potentials in Minimally Conscious Patients – Challenges and Perspectives", *6th International Brain-Computer Interface Conference*, Graz, Austria

2013 Talk: **Pokorny C**, Horki P, Klobassa D, Pichler G, and Müller-Putz G (2013), "Two Approaches to Communicate with Patients in Minimally Conscious State", *TOBI Workshop IV*, Sion, Switzerland

2012 Talk: **Pokorny C**, Breitwieser C, and Müller-Putz G (2012), "Impact of Channel Selection on the Classification Accuracy in a Brain-Computer Interface based on Steady-State Somatosensory Evoked Potentials", *1st International DECODER Workshop*, Boulogne-Billancourt, France

2011 Talk: **Pokorny C**, Breitwieser C, Neuper C, and Müller-Putz G (2011), "Towards a Single-Switch BCI Based on Steady-State Somatosensory Evoked Potentials", *5th International Brain-Computer Interface Conference*, Graz, Austria

[1] First author contributions only