Unlocking Communication:
Advancing Brain-Computer Interfaces for ALS Patients in Locked-In and Completely Locked-In States

Dissertation

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To my parents…

who are dearly missed.

To my colleages, past and present…

from whom I have learned.

To N. Birbaumer…

for his dedication.

To these patients…

for their inspiration.

Contents

Abbreviations

Abbreviation	Definition
ALS	Amyotrophic Lateral Sclerosis
ALSFRS	ALS Functional Rating Scale
BCI	Brain Computer-Interface
BOLD	Blood Oxygen Level-Dependent
CI	Cognitive Impairment
CLIS	Complete Locked-in Syndrome
CNS	Central Nervous System
ECoG	Electrocorticography
EEG	Electroencephalography
EPs	Evoked Potentials
ERPs	Event-Related Potentials
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
FTD	Frontotemporal Dementia
LFP	Local Field Potentials
LIS	Locked-in Syndrome
LMN	Lower Motor Neuron
MCS	Minimally Conscious State
MEG	Magnetoencephalography
MI	Motor Imagery
MUA	Multi-Unit Activity
PSD	Power Spectral Density
QoL	Quality of Life
REM	Rapid Eye Movement
SCP	Slow Cortical Potential
SMA	Supplementary Motor Cortex
SSVEP	Steady-State Visual Evoked Potential
SUA	Single-Unit Activity
SWS	Slow-Wave Sleep
UMN	Upper Motor Neuron

Summary

My participation in the current research program encompasses several critical investigations aimed at improving Brain-Computer Interface systems for individuals with advanced Amyotrophic Lateral Sclerosis, particularly those transitioning from Locked-In Syndrome to Completely Locked-In Syndrome.

Initial studies aim to gain a deeper understanding of the physiological changes during the progression of Amyotrophic Lateral Sclerosis using Electroencephalographic activity for monitoring brain function. Findings indicate significant frequency changes the in Electroencephalographic activity of Completely Locked-In Syndrome patients, which may impact the effectiveness of the Brain-Computer Interface. A validated and versatile Brain-Computer Interface software platform was developed, incorporating Electroencephalography, functional Near-Infrared Spectroscopy, and Electrooculography as modalities to enable communication for severely disabled users. This platform was used in a longitudinal study aimed at exploring communication performance during the transition from Locked-In Syndrome to Completely Locked-In Syndrome, highlighting the preference for Electrooculography-based control for this particular sample of patients.

Using the acquired knowledge, a groundbreaking case study was conducted involving a patient in Completely Locked-In Syndrome who utilized an intracortical Brain-Computer Interface system, resulting in sustained and successful spelling-based communication. This demonstrates that the correct methodological approach may have the potential to prevent the extinction of goal-directed voluntary thinking. This development has made a substantial contribution to enhancing the patient's Quality of Life. Lastly, the research program evaluated features of Quality of Life of severely paralyzed individuals, confirming the "disability paradox" and suggesting that neuroplastic changes as well as cognitive and behavioural adaptations, may contribute to their positive Quality of Life self-assessment.

Zusammenfassung

Meine Teilnahme am aktuellen Forschungsprogramm umfasst mehrere kritische Untersuchungen, die darauf abzielen, Brain-Computer Interface-Systeme für Personen mit fortgeschrittener Amyotropher Lateralsklerose zu verbessern, insbesondere für Personen, die vom Locked-In-Syndrom zum Completely Locked-In-Syndrom übergehen.

Erste Studien zielen darauf ab, ein tieferes Verständnis der physiologischen Veränderungen während des Fortschreitens der Amyotropher Lateralsklerose zu erlangen, indem die Elektroenzephalographie-Aktivität zur Überwachung der Gehirnfunktion genutzt wird. Die Ergebnisse deuten auf signifikante Elektroenzephalographie-Frequenzveränderungen bei Completely Locked-In-Syndrom-Patienten hin, die die Wirksamkeit von Brain-Computer Interface-Systeme beeinflussen können. Es wurde eine validierte und vielseitige Brain-Computer Interface-Systeme-Softwareplattform entwickelt, die Elektroenzephalographie-, funktionelle Nahinfrarotspektroskopie- und Elektrookulografie-Modalitäten einbezieht, um schwerbehinderten Menschen die Kommunikation zu ermöglichen. Diese Plattform wurde in einer Längsschnittstudie eingesetzt, um die Kommunikationsleistung während des Übergangs von Locked-In-Syndrom zu Completely Locked-In-Syndrom zu untersuchen, wobei die Präferenz für die Elektrookulografie-basierte Steuerung bei dieser speziellen Patientengruppe deutlich wurde.

Basierend auf den gewonnenen Erkenntnissen wurde eine wegweisende Fallstudie mit einem Patienten durchgeführt, der ein intrakortikales Brain-Computer Interface-System verwendete. Dies führte zu einer anhaltenden und erfolgreichen verbalen Kommunikation. Dies zeigt, dass der richtige methodische Ansatz das Potenzial hat, die Löschung des zielgerichteten Denkens, zu verhindern. Diese Entwicklung hat wesentlich dazu beigetragen, die Lebensqualität des Patienten zu verbessern. Schließlich wurden im Rahmen des Forschungsprogramms Merkmale der Lebensqualität schwerstgelähmter Personen bewertet, die das "Behinderungsparadoxon" bestätigen und darauf hindeuten, dass neuroplastische Veränderungen sowie kognitive und verhaltensbezogene Anpassungen zu ihrer positiven Selbsteinschätzung der Lebensqualität beitragen können.

List of publications

A. Accepted publications

Publication 1.

A. Malekshahi & U. Chaudhary, **A. Jaramillo-Gonzalez**, A. Lucas Luna, A. Rana, A. Tonin, N. Birbaumer, S. Gais (2019). Sleep in the Completely Locked-in State in Amyotrophic Lateral Sclerosis, *Sleep*, 42, 12, zsz185.
https://doi.org/10.1093/sleep/zsz185

Publication 2.

J. Martínez-Cerveró, M. Khalili-Ardali, **A. Jaramillo-Gonzalez**, S. Wu, A. Tonin, A. Tonin, N. Birbaumer, U. Chaudhary (2020). Open Software/Hardware Platform for Human-Computer Interface Based on Electrooculography (EOG) Signal Classification, *Sensors*, 20(9), 2443.
https://doi.org/10.3390/s20092443

Publication 3.

A. Tonin & **A. Jaramillo-Gonzalez**, A. Rana, M. Khalili-Ardali, N. Birbaumer, U. Chaudhary (2020). Auditory Electrooculogram-based Communication System for ALS Patients in Transition from Locked-in to Complete Locked-in State, *Nature Scientific Reports,* 10, 8452.
https://doi.org/10.1038/s41598-020-65333-1

Publication 4.

A. Secco, A. Tonin, A. Rana, **A. Jaramillo-Gonzalez**, M. Khalili-Ardali, N. Birbaumer, U. Chaudhary (2020). EEG power spectral density in locked-in and completely locked-in state patients: a longitudinal study, *Cognitive Neurodynamics*, 15, 473–480.
https://doi.org/10.1007/s11571-020-09639-w

Publication 5.

Y. Maruyama, N. Yoshimura, A. Rana, A. Malekshahi, A. Tonin, **A. Jaramillo-Gonzalez**, N. Birbaumer, U. Chaudhary (2020). Electroencephalography of completely locked-in state patients with amyotrophic lateral sclerosis, *Neuroscience Research*, 162, 45-51.
https://doi.org/10.1016/j.neures.2020.01.013

Publication 6.

A. Jaramillo-Gonzalez, S. Wu, A. Tonin, A. Rana, M. Khalili-Ardali, N. Birbaumer, U. Chaudhary (2021). A dataset of EEG and EOG from an auditory EOG-based communication system for patients in locked-in state, Nature Scientific Data, 8, 8.
https://doi.org/10.1038/s41597-020-00789-4

Publication 7.

U. Chaudhary, B. S. Chander, A. Ohry, **A. Jaramillo-Gonzalez**, D. Lulé, N. Birbaumer (2021). Brain-Computer Interfaces for assisted communication in paralysis and quality of life. *International Journal of Neural System*.
https://doi.org/10.1142/S0129065721300035

Publication 8.

U. Chaudhary, I. Vlachos, J. B. Zimmermann, A. Espinosa, A. Tonin, **A. Jaramillo-Gonzalez**, M. Khalili-Ardali, H. Topka, J, Lehmberg, G. M. Friehs, A. Woodtli, J. P. Donoghue, N. Birbaumer (2021). Spelling Interface using Intracortical Signals in a Completely Locked-In Patient enabled via Auditory Neurofeedback Training, *Nature Communications,* 13, 1236.

https://doi.org/10.1038/s41467-022-28859-8

B. Publications submitted and under revision

Publication 9.

Majid Khalili-Ardali, Jayro Martínez-Cerveró, Alessandro Tonin, **Andres Jaramillo-Gonzalez**, Shizhe Wu, Giovanni Zanella, Giulia Corniani, Alberto Montoya-Soderberg, Niels Birbaumer, Ujwal Chaudhary (2021). Framework of a binary EEG and fNIRS Brain Computer Interface. *SoftwareX,* in revision.

Personal contribution to the publications

Publication 1.

Sleep in the Completely Locked-in State in Amyotrophic Lateral Sclerosis

Azim Malekshahi: Study design/conceptualization, 20% of the BCI sessions/sleep recording sessions.
Ujwal Chaudhary: Study design/conceptualization, 65% of the BCI sessions/sleep recording sessions, project supervision, manuscript writing.
Andres Jaramillo-Gonzalez: 30% of the BCI sessions/sleep recording sessions, data analysis, data curation.
Alberto Lucas Luna: 35% of the BCI sessions/sleep recording sessions.
Aygul Rana: 35% of the BCI sessions/sleep recording sessions.
Alessandro Tonin: 35% of the BCI sessions/sleep recording sessions.
Niels Birbaumer: Study design/conceptualization, manuscript correction, project supervision.
Steffen Gais: Study design/conceptualization, data analysis, manuscript correction, project supervision.

Publication 2.

Open Software/Hardware Platform for Human-Computer Interface Based on Electrooculography (EOG) Signal Classification

Jayro Martínez-Cerveró: Study design/conceptualization, methodology, software development, data analysis, manuscript writing/review/editing.
Majid Khalili-Ardali: Methodology, manuscript writing.
Andres Jaramillo-Gonzalez: Methodology, validation.
Shihze Wu: Data curation, manuscript review/correction.
Alessandro Tonin: Manuscript review/correction.
Niels Birbaumer: Conceptualization, manuscript review/correction.
Ujwal Chaudhary: Conceptualization, methodology, manuscript writing/review/correction, project supervision.

Publication 3.

Auditory Electrooculogram-based Communication System for ALS Patients in Transition from Locked-in to Complete Locked-in State

Alessandro Tonin: 35% of the BCI sessions, data collection, data analysis, and manuscript writing.
Andres Jaramillo-Gonzalez: 35% of the BCI sessions, data collection, data analysis, and manuscript writing.
Aygul Rana: 35% of the BCI sessions, data collection.
Majid Khalili Ardali: Data analysis.
Niels Birbaumer: Study design/conceptualization, manuscript review/correction.
Ujwal Chaudhary: Study design, conceptualization, 65% of the BCI sessions, data collection, data analysis, manuscript writing/review/correction, and project supervision.

Publication 4.

EEG power spectral density in locked-in and completely locked-in state patients: a longitudinal study

Ariana Secco: Data analysis, manuscript writing
Alessandro Tonin: 40% of data collection, data analysis discussion.
Aygul Rana: 30% of data collection.
Andres Jaramillo-Gonzalez: Discussion.
Majid Khalili-Ardali: Discussion.
Niels Birbaumer: Study design/conceptualization, manuscript correction.

Ujwal Chaudhary: Study design/conceptualization, 70% of the data collection, data analysis, manuscript writing, and project supervision.

Publication 5.

Electroencephalography of completely locked-in state patients with amyotrophic lateral sclerosis

Yasuhisa Maruyama: Analysis, manuscript writing.
Natuse Yoshimura: Study design/conceptualization, manuscript writing/review/correction.
Aygul Rana: Data collection.
Azim Malekshahi: Data collection.
Alessandro Tonin: Data collection.
Andres Jaramillo-Gonzalez: Data collection.
Niels Birbaumer: Study design/conceptualization, manuscript review/correction.
Ujwal Chaudhary: Study design/conceptualization, data collection, manuscript review/correction.

Publication 6.

A dataset of EEG and EOG from an auditory EOG-based communication system for patients in locked-in state

Andres Jaramillo-Gonzalez: 35% of the auditory communication system (ACS) sessions, data collection, data curation, and manuscript writing.
Shihze Wu: Data curation, validation.
Alessandro Tonin: 35% of the ACS sessions, data collection.
Aygul Rana: 35% of the ACS sessions, data collection.
Majid Khalili Ardali: Discussion.
Niels Birbaumer: Study design/conceptualization, manuscript review/correction.
Ujwal Chaudhary: Study design/conceptualization, 65% of the ACS sessions, data collection, manuscript writing/review, and project supervision.

Publication 7.

Brain-Computer Interfaces for assisted communication in paralysis and quality of life

Ujwal Chaudhary: Review design/conceptualization, research, discussion, manuscript writing/reviewing.
Bankim Subash Chander: Research, discussion, manuscript writing/reviewing.
Avi Ohry: Review design/conceptualization, discussion, and manuscript reviewing.
***Andres Jaramillo-Gonzalez*:** Research, manuscript writing/reviewing.
Dorothée Lulé: Review design/conceptualization, manuscript writing/reviewing.
Niels Birbaumer: Review design/conceptualization, research, supervision/reviewing.

Publication 8.

Spelling Interface using Intracortical Signals in a Completely Locked-In Patient Enabled via Auditory Neurofeedback Training

Ujwal Chaudhary: Initiation, study design/conceptualization, ethics approval, 95% of sessions before/after implantation, figures, neurofeedback paradigm, manuscript writing.
Ioannis Vlachos: Software development/integration/testing, data analysis, neurofeedback paradigm implementation, 5% of sessions after implantation.
Jonas B. Zimmermann: Neurofeedback paradigm implementation, data analysis, figures, manuscript writing.
Arnau Espinosa: Software testing, EEG/EOG analysis, figures.
Alessandro Tonin: Speller software development, 30% of sessions before implantation, 20% of the sessions after implantation, EEG/EOG analysis, figures.
Andres Jaramillo-Gonzalez: EEG/EOG analysis, figures.

Majid Khalili Ardali: Graphical user interface.
Helge R. Topka: Ethics approval, medical patient care, clinical and diagnostic neurological procedures.
Jens Lehmberg: Ethics approval, neurosurgery, clinical care.
Gerhard M. Friehs: Neurosurgical training.
Alain Woodtli: Ethics approval, BfArM approval, neurosurgical training.
John P. Donoghue: Initiation, study design/conceptualization, manuscript writing/reviewing/editing.
Niels Birbaumer: Initiation, study design/conceptualization, coordination, clinical-psychological procedures and care, neurofeedback paradigm, 30% of the sessions with UC, ethics approval, BfArM approval, manuscript writing.

Publication 9.

Framework of a binary EEG and fNIRS Brain-Computer Interface

Majid Khalili Ardali: Software design/development/implementation, manuscript writing/reviewing.
Jayro Martínez-Cerveró: Software design/development/implementation/validation.
Alessandro Tonin: NIRS pipeline's software implementation, paradigm's software implementation, speller's software implementation, classification's pipeline software implementation, manuscript's NIRS section writing.
***Andres Jaramillo-Gonzalez*:** EEG pipeline's software implementation, manuscript's EEG section writing.
Shihze Wu: EEG pipeline's software improvement/testing, software debugging/validation.
Giovanni Zanella: Software testing/validation, NIRS pipeline's software improving/testing.
Giulia Corniani: EEG pipeline's software contribution (features).
Alberto Montoya-Soderberg: Classification pipeline's software improvement (feature consistency, dimension reduction).
Niels Birbaumer: Initiation, project design/conceptualization, funding.
Ujwal Chaudhary: Initiated, project design/conceptualization, software's initial development, project supervision, funding, and manuscript writing.

1. Overview and objectives of the research program

Motor function impairment in motor neuron disease varies depending on disease type, progression, and individual symptomatology, ranging from partial to complete deficits.

This is the case of patients suffering from Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's Disease. ALS progresses in a patient-dependent way, with varying speed and differences in the symptomatology during its progression. Invariably, all individuals develop an almost complete loss of motor control, including debilitation and paralysis of vocal cords, debilitation and paralysis of the muscles used for swallowing and eating, and eventual paralysis of the muscles used to breathe. This state is clinically known as Locked-in Syndrome (LIS). One of the consequences is the loss of communication means, with the consequent reduction in social interaction and a dependency on caretakers for even the most routine activities. Because of this, the Quality of Life (QoL) of these individuals is assumed to be severely affected.

Regardless of the unstoppable progression of the disease, some patients decide to extend their lives beyond this point by using life-supporting methods, such as assisted mechanical ventilation; this conducts to the loss of any remnant muscular control with no possibility of establishing communication. This state of a functional brain isolated within a non-functional body is known as Complete Locked-in Syndrome (CLIS).

Several tools and technologies have been proposed to assist these individuals in achieving communication and contributing to increase their QoL. Within this group of technologies, those known as Brain-computer interfaces (BCI) are promising tools to establish a path for communication by directly using the electrophysiological activity of the Central Nervous System (CNS). Fortunately, although still very few, the reported cases of successful communication of ALS patients in LIS by BCIs are abundant and steadily increasing.

However successful these technologies have been in the LIS population, in the case of completely paralyzed individuals, there are only a couple of reports of successful limited communication that await longitudinal replication of the principle in larger samples. According to meta-analysis and longitudinal studies, completely disabled patients who have been in CLIS for years cannot manage to successfully use a BCI except for ‘yes/no’ communication, much less communicate verbally. It has been speculated if this lack of success is related to the inadequacy of the BCI systems, cognitive decay of the patients, or loss of the contingencies between goal-directed thoughts and intentions, among others.

The research program of our laboratory has succeeded in previous years at proposing BCI systems that successfully allow people in different stages of ALS progression to communicate. Different types of experimental paradigms have been successfully used for this end. However, attempts to establish successful, reliable, and meaningful verbal communication in patients with CLIS have not been successful. Consequently, the research program at Prof. Dr. Birbaumer’s laboratory proposed a different approach to validate BCI verbal communication in ALS-CLIS patients. This dissertation explains my contribution as part of the aforementioned research program, by:

- Participating in the development and validation of software for analysis that would allow more flexible, adequate and reliable BCI-communication for ALS patients in LIS and CLIS.
- Continuing the investigation of different cognitive and neurophysiological aspects (e.g., electrophysiological activity, sleep patterns, QoL) in patients at different stages of the disease.
- Following the progression of ALS in selected patients until advanced stages of the disease, to record and describe the neurophysiological changes over time, until the patient enters the state of CLIS.
- Use the collected data and conclusions to help develop a BCI system that allows patients in CLIS to establish communication continuously and reliably.

In this dissertation I expose the results obtained from the systematic follow-up of ALS patients in LIS, the development and testing of BCI systems that allow exploration of the capabilities of LIS patients on the verge of CLIS to communicate, and the case of a single ALS patient taking part in an invasive clinical study to validate communication in the CLIS state.

The ultimate goal of these studies aims for the development of non-invasive and affordable BCIs that transcend the current limitation of 'yes/no' communication, enhancing reliability and reducing the error rate, particularly in the challenging context of completely paralyzed patients. By achieving these objectives, this approach empowers patients in CLIS by establishing meaningful and continuous communication, thus improving their Quality of Life (QoL) and overall well-being.

2. Background

2.1. Locked-in Syndrome and Amyotrophic Lateral Sclerosis

Locked-in Syndrome (LIS) is a pathological condition that can be characterized by a set of clinical criteria: 1) sustained eye-opening, 2) preserved oculomotor control or blinking, 3) aphonia or severe hypophonia, 4) quadriplegia or quadriparesis, and 5) preserved cognitive abilities (Brown & Al-Chalabi, 2017; Kotchoubey & Lotze, 2013; Vaughan, 2020). In addition to these traits, some patients preserve the ability to control some facial muscles and the external sphincter (Chaudhary, Mrachacz-Kersting, et al., 2021; Ramos-Murguialday et al., 2011).

LIS exhibits a highly variable aetiology. Is provoked by causes affecting the main descending tracts that conduct motor impulses from the cortex to the brain stem and spinal cord, leading thus to the loss of motor neuron function (Chaudhary et al., 2016; Vansteensel et al., 2023). The causes can be abrupt, such as stroke or trauma. However, some neurological diseases, such as Guillain-Barré syndrome or ventral pontine syndrome, provoke a gradual loss of normal motor function. That is also the case with ALS, which is characterized by the gradual dysfunction and eventual death of motor neurons in the brain and spinal cord that innervate skeletal muscles, including symptoms of increased fatigue, progressive muscle weakness and atrophy, leading to problems with swallowing and respiratory failure, and eventual death (Brown & Al-Chalabi, 2017; Chiò et al., 2013; Kotchoubey & Lotze, 2013; J. Mitchell & Borasio, 2007; Mitsumoto et al., 1998).

The progressive degeneration of the motor neuron system provoked by ALS comprises a combination of upper (UMN) and lower motor neuron (LMN) symptoms that affect four regions of the central nervous system: brainstem, cervical, thoracic, and lumbosacral (Brown & Al-Chalabi, 2017; Ferguson & Elman, 2007; J. Mitchell & Borasio, 2007). This deterioration manifests as a combination of symptoms with varying degrees, resulting in a complex clinical syndrome that is difficult to diagnose timely and correctly (Al-Chalabi et al., 2016; Hulisz, 2018). Unfortunately, there is not yet a standardized set of biomarkers fit for the evaluation and diagnosis applicable to all patients, and consequently, diagnosis is strongly dependent on clinical assessment (Al-Chalabi et al., 2016; Ferguson & Elman, 2007; Hulisz, 2018; J. Mitchell & Borasio, 2007). As a result of these complexities, the time of symptom onset to ALS diagnosis is reported to be about 9 to 12 months (Brown & Al-Chalabi, 2017; Vaughan, 2020).

The symptoms of ALS do not progress linearly. During the initial stages of the disease, in a period from weeks to months, there is little to no motor function loss, with the patient fully retaining higher cognitive functions, such as problem-solving, reasoning, understanding, or memory, even though they might be unable to produce intelligible speech and therefore unable to communicate verbally (Hulisz, 2018; Mitsumoto et al., 1998). Nevertheless, the progress of ALS is inexorable, leading to the destruction of the peripheral and central motor neuron system, and sometimes, to the death of the patient (Al-Chalabi et al., 2016; Hulisz, 2018; J. Mitchell & Borasio, 2007; Mitsumoto et al., 1998).

The rate of disease progression varies drastically; in some cases, the patients die within months after the onset (Robberecht & Philips, 2013), but the reported survival rate is two to three years after disease onset, being the main causes of death respiratory failure, pneumonia, or cardiac arrhythmias (Chiò et al., 2013; Ferguson & Elman, 2007; Westeneng et al., 2018). Only 5-10% of patients survive beyond 10 years (Chiò et al., 2013), but considering some means to extend the lifespan by using supportive technologies, some patients have survived for more than two decades (Chaudhary, Chander, et al., 2021; Robberecht & Philips, 2013).

2.2. Metrics to evaluate the impact of ALS

While the numbers may vary significantly based on geographical locations, and the majority of epidemiological studies rely on data from developed countries (Brown & Al-Chalabi, 2017; Hulisz, 2018; Xu et al., 2020), the estimated worldwide incidence of ALS stands at 1.59 (95% CI 1.39–1.81) per 100,000 person-years. Simultaneously, the estimated worldwide prevalence is approximately 4.42 (95% CI 3.92–4.96) per 100,000 person-years (Xu et al., 2020). The International Alliance of Amyotrophic Lateral Sclerosis/Motor Neuron Disease Associations reports that there are roughly 140,000 new cases diagnosed globally each year, equating to around 384 new cases daily (source: https://www.als-mnd.org/what-is-alsmnd/, Retrieved in October 2023). It's important to note that this number is projected to increase in the coming decades (Arthur et al., 2016).

To assist in better diagnosis and classification of ALS, different clinical diagnostic criteria have been proposed. The most used is the ‘El Escorial’ diagnostic criteria, developed in the late 1980s and successively revised over the decades. This is an algorithm established by the World Federation of Neurology to provide internationally accepted diagnostics (Brooks et al., 2000). Based on this, clinical observations during the evaluation of a patient for ALS can be further improved by incorporating laboratory, electrodiagnostic, radiological, and even pathological examinations to elevate diagnostic confidence (Brown & Al-Chalabi, 2017; Ferguson & Elman, 2007). The increasing international use of these criteria – field-tested in several North American and European clinical trials – has somehow improved the consistency of ALS diagnosis and contributed to the better setting of clinical and epidemiologic studies (Al-Chalabi et al., 2016; Ferguson & Elman, 2007).

In addition to diagnostics criteria, some metrics have been proposed to evaluate the patient’s degree of functional impairment. The ALS Functional Rating Scale (ALSFRS) was developed in 1996 to assess activities of daily living in patients with ALS in an easily administered format; it was revised in 1999 and renamed Revised ALS Functional Rating Scale (ALSFRS-R). This is a 12-item scale with each item scored from 0 (unable) to 4 (normal ability) according to the patients’ possibilities, with a possible total score range of 0 to 48 (Gordon et al., 2004; Hulisz, 2018).

Although diagnostic guidelines such as ‘El Escorial’ have proven useful, they omit variables important for clinical management, for example, the extent of motor neuron involvement, progression of the disease, age of onset, pattern of symptom distribution, and extent of pure-motor versus other (e.g., cognitive) involvements (Al-Chalabi et al., 2016). As expected, the lack of observation of these complex variables and the subject-dependent progression of the disease results in the current diagnostic tools overlapping, leading to confusion in diagnosing the correct phenotype and consequently, an imprecise prognosis (Al-Chalabi et al., 2016).

Hopefully, a comprehensive grasp of genetics and the identification of dependable biomarkers can pave the way for more rigorous and dependable criteria to expedite ALS diagnosis. This, in turn, could lead to improved treatment strategies, more accurate prognosis assessments, and a personalized therapeutic approach. Enhanced prognostic accuracy, along with a deeper understanding of the patient's functional decline, could contribute to elevate their subjective well-being and overall QoL, fostering a sense of inclusion and belonging within the patient community (Al-Chalabi et al., 2016; Bruno et al., 2011; Chaudhary, Chander, et al., 2021). Under such circumstances, any tool that allows the patients to retain their intentionality and communication will be considered with high regard by them and their caretakers.

2.3. Progression of Locked-in Syndrome to Complete Locked-in Syndrome

Subject-dependent variability in the progression of ALS makes it impossible to predict the landmarks in the process of neurodegeneration or to estimate how long muscular control will be retained (Ramos-Murguialday et al., 2011). Since no treatment is available, the progression of the disease is unstoppable. As a consequence of complete motor neuron degeneration, patients have to decide whether to accept respiratory support by tracheostomy and thus invasive ventilation after the disease destroys respiratory and bulbar functions, or to die of respiratory failure (Birbaumer, 2006; Vaughan, 2020). However, advances in diagnostics and life-support technologies in the past decades, have allowed people in advanced states of ALS to live beyond the point of respiratory failure, with a satisfactory QoL (Bourke et al., 2006; N. Hayashi et al., 2020). Expectedly, ALS progresses until the patient fully loses all muscular response, due to the destruction of all motoneuron paths. All voluntary residual movements cease, leading to complete lack of communication. This condition is known as Complete Locked-in State (CLIS) (Bauer et al., 1979; Birbaumer, 2006; Chaudhary et al., 2016).

Similarly to LIS due to ALS, patient-dependent progression of the neurodegeneration, comorbidities, or increased clinical risks make it impossible to predict the survival span. In the case of advanced-state ALS patients in CLIS, lifespans have been reported to last for decades (Chaudhary, Chander, et al., 2021; Chiò et al., 2013; Robberecht & Philips, 2013).

Common descriptions to determine when a patient is in CLIS state are mostly based on clinical/observational criteria with emphasis on eye movement and remnant muscle control. No accepted quantitative and reliable method is available to clinically discriminate sharply LIS from CLIS (Chaudhary, Chander, et al., 2021). Considering the observational scale ALSFRS-R, this is not specific enough to differentiate advanced LIS due to ALS, from CLIS.

A criterion can be established according to empirical findings. Extensive long-term measurement to verify the absence of oculomotor activity with EOG can be a valid indicator of CLIS (Bauer et al., 1979; Kübler & Birbaumer, 2008; Ramos-Murguialday et al., 2011; Tonin et al., 2020), nevertheless, the transition process to CLIS is patient-specific and no generally valid rule exists.

Additional measurements of facial EMG or the external anal sphincter may be required to validate the state of total paralysis (Ramos-Murguialday et al., 2011).

Although clinical descriptions of ALS emphasize that oculomotor functions might be resilient and even be spared by the disease, this description only applies to the LIS state (Leveille et al., 1982; Sharma et al., 2011). Once the patients reach CLIS, the control over oculomotor muscles in charge of gaze-fixation is lost, and due to the inability to blink and proper eye hydration, corneas dry out, leading to compromised vision and eventual blindness (Ramos-Murguialday et al., 2011). This makes it impossible for the patients to use any eye-based communication strategies (Tonin et al., 2020).

However, individuals in CLIS remain conscious, retaining some sensory functions with cognitive functions predominately intact during the initial stages of CLIS (Bauer et al., 1979; Kübler & Birbaumer, 2008; Ramos-Murguialday et al., 2011). Due to the “isolation” of a mind inside a completely paralyzed body, understanding the implications of CLIS is of special interest not only theoretically, but also for ethical and humanitarian reasons.

2.4. Brain-Computer Interfaces for Communication in LIS and CLIS

2.4.1. Augmentative and Alternative Communication Technologies

Patients in LIS due to ALS can use different means and technologies to communicate beyond the point of motor disability. During this phase of the disease, the implementation of augmentative and alternative communication (AAC) strategies proves to be a valuable and effective alternative (Ball et al., 2012; Vaughan, 2020). AAC refers to any mode of communication that supplements or replaces normal communication in a person with a disability. According to the disease and the degree of affectation the person can use different available AAC technologies based on a wide range of strategies, such as eye gaze tracking, head movement tracking, gesture tracking or speech recognition (Ball et al., 2012; Kent-Walsh & Binger, 2018; Vaughan, 2020).

Research evaluating the impact of AAC in patients with motor neuron degenerative diseases is scarce, nevertheless, a few studies in LIS patients due to ALS suggest that the use of an AAC is generally well accepted and improves their QoL (Chaudhary, Chander, et al., 2021; Vaughan, 2020). However, considering all the aforementioned factors, at a certain juncture in the transition from LIS to CLIS, AAC technologies cease to be effective for these patients. These systems struggle to keep pace with the disease's progression and the evolving challenges this poses for the patient, thus forming a significant obstacle to the patient's essential communication needs.

2.4.2. Brain-Computer Interfaces

Consequently, a more adequate and flexible type of technology is necessary to allow patients with advanced ALS in CLIS to communicate, and Brain-computer Interfaces (BCI) represent an adequate alternative. BCIs have successfully allowed severely disabled patients in LIS to communicate for over two decades (Birbaumer, 2006; Chaudhary, Mrachacz-Kersting, et al., 2021; McFarland, 2020; Vaughan, 2020) beyond the restrictions of traditional AAC technologies.

BCIs harness brain activity directly by bypassing the peripheral motor system. This allows individuals to exert control over computers and external devices, predominantly those of a prosthetic nature. The general principles ruling the functioning of all BCI systems are similar, including BCI-based communication systems. Neurophysiological signals are recorded from the user's CNS, amplified, filtered and classified. The classification looks for relevant features contained in the recorded neurophysiological modality (see Fig. 1) that are correlated with the type of task that the user should perform to control the computer or external device. This link between the performed type of task and the changes in neurophysiological activity defines the working paradigm of the BCI. Lastly, desired changes in the brain activity are feedback to the user for him/her to learn to control the BCI, and consequently, to control the movement of a prosthesis, orthosis, wheelchair, robot, cursor, letters, or to directly electrically stimulate muscles or the brain. The feedback can be either visual, auditory or haptic stimuli; this is decided according to the type of paradigm and purpose of the BCI (Chaudhary et al., 2016; Chaudhary, Mrachacz-Kersting, et al., 2021). Needless to say, a BCI system sending commands to a computer is of particular relevance for the maintenance or restoration of communication in patients with severe motor paralysis in LIS and CLIS. The different types of BCIs can be seen in Fig. 1 (Chaudhary et al., 2016).

Regardless of the recorded neurophysiological modality or the type of application, the brain response is not consciously perceived by the user of the BCI. Therefore, learning to produce and control a particular type of brain activity is similar to learning and controlling a new motor skill, where most elements and components are learned implicitly and do not require a conscious experience or memory access for their operant instrumental control (Birbaumer, 2006; Chaudhary et al., 2016; Chaudhary, Mrachacz-Kersting, et al., 2021).

The neurophysiological activity of the brain can be controlled through different modalities, using either invasive or non-invasive techniques (see Fig. 1). Invasive BCI systems record directly from neurons of the CNS, particularly from the cortex, acquiring different types of electric signals: tips of electrodes penetrating within the cortex to record Single-Unit Activity (SUA), Multi-Unit Activity (MUA), Local Field Potentials (LFPs); Electrocorticography (ECoG) can record with subdural grids of electrodes (Jin et al., 2019).

Trials of invasive BCIs are generally conducted in patients with severe motor paralysis. The rationale behind this is that, due to the high clinical risks derived from surgical implantation, only patients with extreme impairments might obtain a favourable balance of risks and potential benefits (Vansteensel et al., 2023). Accordingly, implantation accesses directly the cortical tissue, taking advantage of unique features of the recorded signals, specifically, high spatial and temporal resolution, high signal-to-noise ratio, and arguably, long-term, stable and reliable recordings (Jin et al., 2019; Salahuddin & Gao, 2021).

The total number of invasive clinical BCI trials remains relatively low; however, even from this limited pool of studies, valuable insights have emerged. These studies have contributed significantly to our understanding of neural coding in the human motor cortex and the biocompatibility of electrodes.

For an updated overview on invasive BCIs, we advise to consult specialized reviews (Jin et al., 2019; Salahuddin & Gao, 2021).

On the other hand, most of the experimental and clinical trials conducted in the field of BCIs have been performed using non-invasive technology. With it, there is no need for implantation and consequently, the recordings are restricted to the physiological brain activity that can be reached at the scalp level. Expectedly, these physical restrictions limit the quality of the spatial and temporal resolution of the recordings, as well as the signal-to-noise ratio (Engel et al., 2005; Waldert, 2016).

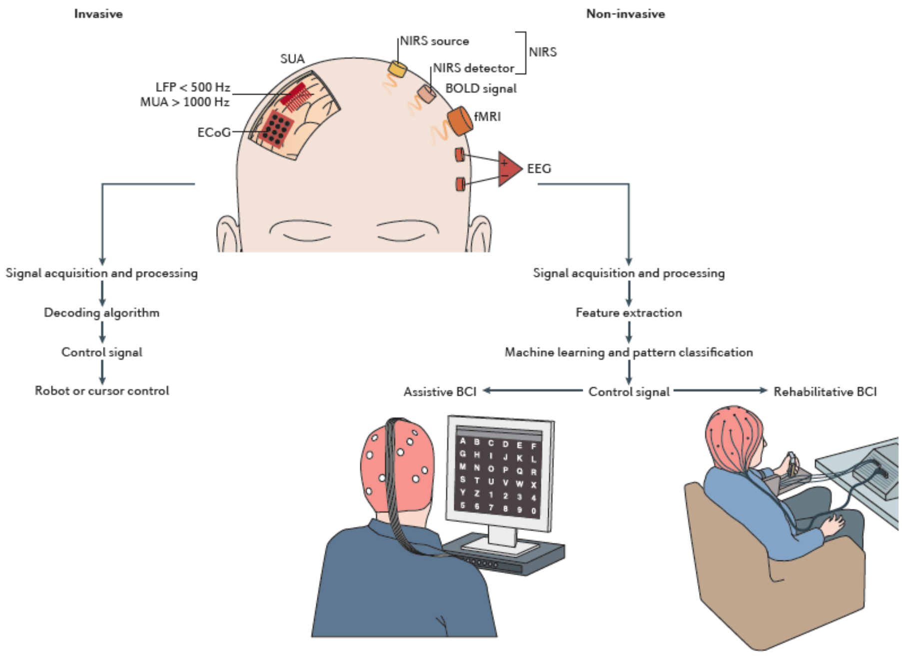

Fig. 1. **The overarching framework of Brain-Computer Interface (BCI) systems**. It encompasses both invasive (top left) and noninvasive (top right) approaches. Invasive BCI methodologies involve the measurement of Local Field Potentials (LFPs), Single-Unit Activity (SUA), Multi-Unit Activity (MUA), and Electrocorticography (ECoG). The non-invasive BCIs utilize Electroencephalography (EEG), Blood Oxygenation Level-Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI), and Near-Infrared Spectroscopy (NIRS). The black arrows show idealized pipelines for the different types of brain signals. The recorded signals undergo signal processing to extract features pertinent to the BCI's specific objective, such as communication. Subsequently, translational algorithms are employed to classify these features and create a control signal to operate the BCI, e.g., for a speller device. Adapted with permission from Chaudhary et al. (2016, p. 3).

Non-invasive BCIs are developed with consideration for various forms of neurophysiological activity in the CNS, each associated with a specific paradigm. The most widely used is the neuroelectrical modality recorded with Electroencephalography (EEG), from which different types of features can be extracted, e.g.: Slow Cortical Potential (SCP), Sensorimotor Rhythms (SMR), Event-Related Potentials (ERPs), Evoked Potentials (EPs) as the Steady-State Visual Evoked Potentials (SSVEP), among others. Likewise, the magnetic fields of brain activity can be measured using Magnetoencephalography (MEG). Furthermore, BCIs can be also based on the blood-oxygenation dynamics of the cerebral cortex, taking advantage of the Blood Oxygen Level-dependent (BOLD) effect. With this principle, two different techniques, functional Magnetic Resonance Imaging (fMRI) and functional Near-Infrared Spectroscopy (fNIRS) have been used as foundations for BCIs. Both non-invasive EEG and fNIRS-based BCIs comprise the most common recordig methods and the most used paradigms in the field. For a thorough overview of all the aforementioned modalities and paradigms, we suggest consulting updated introductory reviews (Salahuddin & Gao, 2021).

Despite the inherent limitations of non-invasive BCIs, they have facilitated remarkable experimental and clinical advancements since the 1970s (Vidal, 1973). Of particular interest for this dissertation are the successful clinical trials in patients suffering from diseases of a severely disabling nature, and specifically, milestones studies that allowed patients with advanced ALS in LIS to reliably communicate (Birbaumer, 2006).

2.4.3. Brain-computer Interfaces for ALS patients in LIS

There is an important amount of literature confirming that ALS patients in the early stages of the disease can successfully use AAC solutions to achieve communication, taking advantage of the oculomotor activity or another source of remnant muscular control (McNaughton et al., 2018). Nevertheless, as ALS progresses to advanced stages of the disease, the patients lose the ability to use any type of AAC and ultimately lose verbal communication (Ramos-Murguialday et al., 2011; Tonin et al., 2020). To address this critical issue, efforts have been made to develop both invasive and non-invasive BCIs for patients in LIS and CLIS due to ALS (Chaudhary, Mrachacz-Kersting, et al., 2021; McFarland, 2020; Rezvani et al., 2023; Vaughan, 2020).

Due to their accessibility and relatively low cost, non-invasive technologies have been consistently used for allowing BCI communication in ALS individuals since the beginning of the XXI century. The first successful clinical trial of a non-invasive EEG-based BCI was reported in 1999, with two patients in LIS due to ALS (Birbaumer et al., 1999). Since then, different EEG-derived paradigms have been validated to allow communication in ALS patients in LIS, for example, SCP (Kübler et al., 2001), SMR (Wolpaw et al., 2003), or P300 ERPs (Sellers & Donchin, 2006). Throughout the span of the last two decades, EEG-based BCIs have facilitated successful communication and interaction for these individuals, even in an at-home setting (Kübler & Birbaumer, 2008; Marchetti & Priftis, 2015; Rezvani et al., 2023; Wolpaw et al., 2018).

To a relatively lower extent, the BOLD effect has also been employed to establish communication using non-invasive BCIs among individuals suffering from ALS. Although fMRI-based attempts have been reported (Monti et al., 2010), most of the effort centers around the fNIRS technique, due to the portability and flexibility of the systems (Borgheai et al., 2020; Hosni et al., 2020). Nevertheless, the user's comfort and speed of the systems are a constraint for the generalization of such systems (Vansteensel & Jarosiewicz, 2020). The significance of functional fNIRS-based BCIs is particularly prominent in the context of individuals experiencing CLIS, as elucidated in the subsequent section.

Regarding invasive BCI trials, to date, the larger share of validations of the proof of principle has been performed either in epileptic patients – during presurgical evaluation – or participants with quadriplegia by spinal cord injury. A smaller proportion of these trials have been clinical implementations performed in ALS in LIS (Rezvani et al., 2023; Vansteensel et al., 2023). The first reported successful trial date of an ALS patient communicating with an invasive BCI, dates to 1998 (Kennedy & Bakay, 1998). Nevertheless, improvements in implantation techniques, biocompatible materials and electrodes, and signal-processing techniques, have made possible in the past decade several successful studies with clinical relevance, based in different invasive techniques to allow BCI-based communication: SUA or MUA acquisition by intracortical microelectrode arrays (Bacher et al., 2015), LFP (Milekovic et al., 2018), ECoG (Ramos-Murguialday et al., 2011; Vansteensel et al., 2016), and more recently, stentrode technology (P. Mitchell et al., 2023; Oxley et al., 2021). In the most favourable scenario, the BCI offers the participant successful home use of reliable long-term communication, which has been reported to last for more than 5 years in one case (Vansteensel et al., 2023). A comprehensive description of the success of BCIs in ALS patients is beyond the scope of this dissertation, but thorough specialized reviews are available (McFarland, 2020; Rezvani et al., 2023; Vansteensel et al., 2023; Vaughan, 2020).

Regardless of the type of technology, whether invasive or non-invasive, every positive result in these clinical trials is a significant achievement. It benefits not only the fields of medical science and BCI but, most importantly, the patients, enabling them to reestablish and maintain a fundamental connection with their social environment through communication, despite their critical impairments (Brady et al., 2016).

Nevertheless, an important distinction should be brought to attention. Many patients in initial or even advanced stages of ALS, although mechanically ventilated and artificially fed, retain some residual oculomotor or motor control; this has been the case of all the successful BCI trials reported on ALS patients, in most of the cases, with an ALSFRS-R above zero (Wolpaw et al., 2018). As mentioned earlier, in ALS oculomotor control is not spared and the patients extending their lives by assisted ventilation, sometimes even after five years, can lose this remnant muscular control too (H. Hayashi & Oppenheimer, 2003; Ramos-Murguialday et al., 2011). This particular subpopulation of ALS patients, those in CLIS, with an ALSFRS-R of zero, cannot benefit from AAC solutions. Regrettably, this group has received limited attention as a target for the development and validation of BCIs.

2.4.4. Brain-computer Interfaces for advanced ALS patients in CLIS

According to the results, there is a pronounced disparity in the performance between patients in LIS and those in CLIS state (Chaudhary, Mrachacz-Kersting, et al., 2021; Kübler & Birbaumer, 2008). A metanalysis meant to evaluate the use of BCI in ALS patients (Kübler & Birbaumer, 2008) concluded that successful use of the device for communication was possible for individuals in LIS, even for those in advanced stages of the disease; but individuals in CLIS were unable to successfully use a binary ‘yes/no’ BCI. A more recent metanalysis concluded that BCI performance in CLIS was not different from chance (Marchetti & Priftis, 2015), and a longitudinal study in advanced ALS concluded that the progression of the disease – as opposed to “stable health” – was a preventing factor to achieve communication through BCI. A similar observation can be made based on various studies involving participants from both LIS and CLIS categories, being a recurring finding that individuals in CLIS do not experience significant benefits from BCIs (Rezvani et al., 2023).

To the best of our knowledge, and in alignment with recent reviews (Rezvani et al., 2023; Vansteensel et al., 2023), the count of studies documenting successful communication in patients with CLIS remains limited, with a total of three instances limited only to binary ‘yes/no’ communication, employing alternatives to visual stimuli for providing feedback to the participants. First, we will mention key aspects these investigations and their results, followed by a critical comment of them.

The first study is based on commercially available EEG-based BCI (Guger et al., 2017), using two different paradigms: vibrotactile stimulators used to elicit a P300 response, and right- or left-hand Motor Imagery (MI); different sets of frontocentral electrodes were used for each paradigm. Feedback on the user’s answer was given after each trial. Classification and communication stages were performed for each participant, with only 5 communication trials for most of the participants. According to the authors, 9 out of 12 LIS patients (including 2 out of 3 CLIS patients) could successfully communicate using the vibrotactile P300 paradigm, while 3 out of 12 LIS patients achieved communication through the MI paradigm.

The other two studies report successful communication in CLIS with an fNIRS-based BCI. In the first one (Naito et al., 2007), changes in blood oxygenation were recorded with a single NIRS channel in the frontal lobe, looking for changes in brain activity associated with ‘yes’ (elicited by calculating mentally or by fast singing in the participant’s head), or ‘no’ (elicited by less demanding and more “stable” mental tasks). A set with 5/5 (‘yes/no’) training questions – with semantically known ‘yes/no’ answers – was used to build a classifier using the maximum amplitude and phase changes of the NIRS signal as features. Later, the model was tested using a set of 5/5 questions for all the patients. The analysis was performed offline, and no feedback on her/his performance was given to the patient. Reportedly, out of 40 ALS participants, 17 were in CLIS, from which, 7 were capable of replying to the test questions with an accuracy above 75%.

The second fNIRS-based BCI is a case report of a patient in CLIS (Gallegos-Ayala et al., 2014) using a similar paradigm, with 52 NIRS channels to cover the sensorimotor cortex and temporal areas. Questions were presented to the participant using an auditory paradigm, and she was instructed to think of ‘yes’ or ‘no’, after being presented with 10 to 20 semantically paired ‘yes/no’ training questions of known answers. Online feedback on the response was given to the participants immediately after the answer. The study took place in 3 different periods comprising several days each, scattered over 2012 and 2013 for a total of 67 sessions. A binary classifier was built session-wise (i.e., day-wise). Using reliable classifiers, during 7 sessions – interspersed among the rest – “open questions” were presented to the participant, following criteria suggested by family members and long-term reliability of the same answer. Reportedly, the average predictive value for the training sessions was 80.9% for ‘yes’ and 72.9% for ‘no’, with 100% correct classification for the open questions. The authors made clear that a definition of a correct answer for the open questions is not possible. An extension to this study, by Chaudhary et al. (2017) with four CLIS patients, communicating ‘yes/no’ no over long time periods, was later retracted for unknown reasons. Thus leaving the question open until a replication appears.

In all of the previously mentioned instances where successful communication was reported among CLIS users, the achieved success was primarily based on a 'yes/no' classification system for pre-defined semantic responses, with only a limited portion involving open-ended questions in only two of the publications. Nonetheless, it is crucial to acknowledge that, for individuals in both LIS and CLIS, even a binary method of responding to queries, holds immense value in restoring fundamental communication capabilities. The significance of these publications lies in their validation of the proof of principle, underscoring the need for the next logical phase in research: the development and evaluation of a spelling system that would empower CLIS users to engage in more expressive and comprehensive communication.

Regardless of the results, it is feasible to offer constructive comments and critiques to these studies. In the case of the EEG-based system by (Guger et al., 2017), although the same vibrotactile paradigm has been validated in healthy and severely paralyzed patients (Lugo et al., 2014; Ortner et al., 2013), the documentation and the description of patients in the study do not allow to conclude CLIS. The statistics of the study are questionable. The data used for validating the BCI for CLIS users was scarce, acquired in a single session with a total of 10 questions to classify for both classes. The number of sessions and trials was too small to confidently exclude accidental results, which not only makes it vulnerable to potential underfitting but also compromises the results in the classification (Scherer, 2019; Spüler, 2019).

A comparable observation is pertinent to fNIRS-based systems (Gallegos-Ayala et al., 2014; Naito et al., 2007), in which very few training questions, ranging from 5 to 10 for each class, were used for building the model. It is notable that in these instances, solely qualitative statistics are presented, with an absence of replicable, in-depth descriptions of the number of sessions conducted, a factor pivotal in the mitigation of accidental results.

In clinical trials like in the aforementioned studies, where the critical conditions of the patient and other unexpected constraints of the environment can limit the amount of empirical data collected, careful choice of classification method and model complexity is highly recommended (Scherer, 2019).

It's crucial to take into account that, due to the critical clinical condition of the CLIS patients, convincing replication of the results over a larger length of time would lead to more convincing results and validation. In the case of Gallegos-Ayala et al. (2014), after a thorough clinical and neuropsychological evaluation of the CLIS state of the patient, the trials were performed over several days and dispersed over a span of more than a year. Similarly to this publication, a long-term longitudinal study fits better to understand the case of advanced state ALS patients in LIS and in CLIS since, due to the patient-specific progression of the disease, no general rule applies (Kiernan et al., 2011) and only a longitudinal observation will allow to validate reliable and stable use of the BCI.

It is clear that, although the mentioned studies show promising results, neither a larger population of participants nor a longitudinal study on its own, are enough. Unfortunately, testing the proof-of-principle in a single session does not imply a successful clinical application, and in the same way, a well-documented longitudinal case study is just a step further. A thoroughly validated clinical application for BCI-based communication with CLIS users would imply a larger population, long-term study and sufficient amount of data; and even fulfilling these requirements, the testing is still exposed to intrinsic challenges of *in situ* research with people who cannot communicate.

Considering the results presented in this section, is possible to set of questions: Can individuals in CLIS effectively utilize BCIs for communication and verbal communication? Why are there only a couple of publications and a case report demonstrating the proof of principle? Why do long-term clinical trials for communication in CLIS remain elusive? Can this lack of success in communication be intrinsic to the CLIS state, or is it due to methodological flaws in current research?

2.5. Quality of Life in LIS and CLIS patients

It is possible to imagine the scenario in which the QoL of ALS patients understandably declines, especially following the diagnosis of a life-threatening illness, being overwhelmed by the onset of respiratory symptoms and the subsequent deliberation on the use of artificial ventilation. Nevertheless, after the advanced symptoms settle, this scenario changes. As an important amount of epidemiological and empirical studies show, ALS patients are capable of finding a sufficient, and even good QoL (Lulé et al., 2009, 2013), with positive mood and emotions during the different stages of the disease. Before entering the LIS, reliable muscle responses such as finger twitches and eye movements are still possible and might allow for reliable communication. Under these conditions, ALS patients in LIS report good QoL when assisted with an eye-based AAC system for communication (Linse et al., 2017).

For the general population, it is a common assumption that such a devastating neurological condition forces ALS patients to a poor QoL, arguing that being trapped in one's own body is an unbearable condition, and therefore, the only path is euthanasia. But it is a well-researched fact with abundant evidence that the QoL in LIS patients is often significantly underestimated by the patient's kin and primary caregivers, compared with what the patients claim about their own condition (Bromberg, 2007; Kuzma-Kozakiewicz et al., 2019; Lulé et al., 2009; Rousseau et al., 2013). Surprisingly, as long as they maintain cognitive function and a fully functional brain, the majority of ALS patients desire a meaningful life, as much as a healthy person does (Bruno et al., 2011; Lulé et al., 2009; Rousseau et al., 2015). This phenomenon is known as the disability paradox (Albrecht & Devlieger, 1999). Contrary to expectations, there is no significant difference in the perception of their overall personal health and mental well-being reported by LIS patients when compared to matched control individuals (Lulé et al., 2008), and it has even been reported as higher (Gauthier et al., 2007). Another surprising discovery is that, despite patients confirming the presence of suicidal thoughts (Anderson et al., 1993), they aim for the eventual use of life-sustaining means, with a very low number of requests for euthanasia among them (Doble et al., 2003). Nevertheless, is important to consider that differences in opinions about the end-of-life in LIS, might be affected by availability of family care at home and sociopolitics.

While the overall degree of physical impairment may not exhibit a correlation with the overall QoL (Lulé et al., 2008), it's important to note that the loss of speech significantly impacts the QoL in individuals with ALS (Felgoise et al., 2016). Preserving social interaction, especially through retained communication abilities, plays a pivotal role in determining the QoL among ALS patients in LIS (Lulé et al., 2009). In Corallo et al. (2017) the impact of AAC solutions on the QoL of 15 LIS patients was evaluated, concluding that AAC could decrease depression and anxiety symptoms both in the patients as well as primary caregivers, improving their QoL significantly. In particular, the use of AAC technologies for ALS individuals allows them to engage in communication with their caretakers, participate in family life, and maintain some autonomy, which has been demonstrated to enhance their QoL (Brady et al., 2016; Caligari et al., 2013).

Although enough has been researched regarding the QoL of ALS patients, very few studies can report on the effects of BCI communication in the QoL of severely paralyzed patients. The requirement is that there must be reliable, stable, and long-term BCI communication for use in a home environment. This accessibility is vital not only for users to become proficient with the system but also to allow them to assess the influence of the BCI on their daily lives comprehensively. According to these criteria, only a few available studies can claim that BCIs help to keep (Wolpaw et al., 2018) or improve (Holz et al., 2015) the users' QoL. Much more research is needed in this area once the clinical or at-home stage of BCIs has become the norm.

To summarize, considering the circumstances of patients diagnosed with LIS, and particularly the devastating and isolating condition of those in CLIS – incapable of using either AAC or BCI for communication, it becomes both a scientific and ethical imperative not to lose hope in these patients and actively contribute to better their QoL.

2.6. Cognition in CLIS patients and BCI performance

It is essential to keep in mind that the distinctions between LIS and CLIS mentioned before may appear to be superficial, meaning that they are merely external observations and do not provide insights into the underlying physiological or cognitive changes occurring in patients concerning the disease. To date, there are no quantitative reliable criteria to differentiate LIS from CLIS; no biomarker is available yet. The criteria established by Bauer more than 40 years ago (Bauer et al., 1979) is still the standard clinical-observational criteria: the absence of voluntary eye movements or any other somatic-motor muscle under voluntary control. Nevertheless, such criteria are subjective, depending on the expertise of the clinician, making it not entirely reliable. A more quantitative approach will consider continuous EOG and surface EMG measuring from several face muscles (especially the ones surrounding the eye sockets), as well as the external sphincter (Chaudhary, Mrachacz-Kersting, et al., 2021; Ramos-Murguialday et al., 2011). And even in such cases, is possible that due to the highly patient-specific progress of the disease, some somatic-motor control might reappear, making obsolete the diagnosis of CLIS (Chaudhary, Mrachacz-Kersting, et al., 2021).

For ALS patients in advanced stages of the disease, it will always be better to preserve at least a single remnant muscle to control volitionally to use as a channel for communication; but once the remnant muscular control disappears, some cognitive or physiological changes might take place. These changes might be among the reasons for the little evidence of patients in CLIS communicating.

Convincing validation of BCI communication in ALS-CLIS patients has not been achieved before 2022 (Chaudhary et al., 2022). In a metaanalysis, Kübler and Birbaumer (2008) concluded that, although ALS patients in different stages of physical impairment learned and achieved successful BCI communication, this was not possible for the seven patients in CLIS considered in the study. The authors concluded that there was no relationship between the severity of the disease, physical decline, and BCI performance for the ALS sample. Rather, there seems to be a sharp separation between the CLIS sample and the rest of the patients. Considering this impossibility, Birbaumer (2006) had already hypothesized that the patients in CLIS might undergo an "extinction of goal-directed thinking". Individuals who have been for a long time in CLIS may lose the bonding between the required physiological behaviour and its consequences, and as a result, the extinction starts due to the lack of reinforcement in the learning process. In this scenario, thoughts and intentions are never followed by consequences from one's own behaviour, or responses from the environment; basically, for these completely paralyzed individuals the stream "thought-action-consequence" cannot be interpreted as a conscious unit, but separate cognitive elements incapable of acquiring any contextual meaning. As the ultimate consequence, any thoughts, imagery and goal-directed intentions become extinguished (Birbaumer, 2006), and this extinction might happen even if auditory afferent input and cognitive processing remain intact (Birbaumer & Cohen, 2007).

A similar conclusion can be drawn from aforementioned reviews. In the metaanalysis of Marchetti and Priftis (2015) it was found that out of 27 eligible BCI studies with ALS patients who retained at least some muscle control, pooled classification accuracy was above 70%, but in 8 single cases of ALS-CLIS, the classification accuracy was not different from zero. In the longitudinal study by Wolpaw et al. (2018), they evaluated the result of their at-home EEG-based BCI with visual stimuli, for up to 18 months; out of 42 patients with different degrees of progression of ALS, 64% were able to use the BCI at home and from those, 14 patients (33%) in stable health learned how to use the BCI mainly for communication, nevertheless, from the beginning and along the study, the progression of the disease (correlated with the decrease of the ALSFRS-R) resulted in the inability to use the BCI, being also the most important factor for attrition from the study.

From all the BCI literature reviewed here is clear that patients with LIS due to ALS can communicate using invasive or non-invasive BCIs, and use speller systems based on this technology; whereas the patients who were already in CLIS were unable to learn how to use a BCI, even if it is adapted to their condition of CLIS (i.e., auditory feedback, binary system of answers).

Other ideas have been proposed to explain the impossibility of communication in CLIS patients through BCIs. It has been hypothesized that the progression of neuropathology in ALS results in BCI illiteracy (Cipresso et al., 2012; McFarland, 2020). The hypothesis of BCI illiteracy claims that not all users can successfully use BCI technology, derived from the fact that a proportion of apparently healthy individuals are unable to learn the use of BCI (Allison & Neuper, 2010). In the case of ALS patients, the associated neuropathology may lead to Cognitive Impairment (CI) by compromising the neural systems and/or the cognitive processes that are the basis for the signals used by the paradigms of BCIs.

The development of CI is a well-documented fact in a proportion of ALS patients (Ringholz et al., 2005; Wheaton et al., 2007). Different metaanalysis claims incidence of CI in 36% (Massman et al., 1996), or as much as 50% (Phukan et al., 2012) of ALS patients, with evidence of impairment in fluency, language, social cognition, executive function, and verbal memory (Beeldman et al., 2016). In 5% of the cases, CI in ALS overlaps with Frontotemporal Dementia (FTD) (Lomen-Hoerth et al., 2003; Phukan et al., 2007). Nevertheless, is difficult to reject the argument of CI empirically, since neuropsychological testing for cognitive function is impossible in a severely paralyzed person with very limited or no communication abilities (Kübler & Birbaumer, 2008). All the clinical evidence of cognitive evaluation is obtained through standard neuropsychological batteries which are performed using tests and self-reports, bringing the dilemma of how effective can verbal-motor measures be to perform the cognitive evaluation of ALS patients in LIS and CLIS (Cipresso et al., 2012; Neumann & Kotchoubey, 2004). In the condition of complete paralysis “the only available information channel about cognitive processing is the brain itself” (Kübler & Birbaumer, 2008) and therefore, for LIS and CLIS patients more adequate tests for cognitive assessment are necessary (Kotchoubey et al., 2003, 2005). This battery test is based on ERPs with a series of cognitive paradigms, from simple oddball P300 tasks to highly complex semantic mismatch N400, and patient-custom memory tasks. According to the obtained results, most of the CLIS patients had ERP responses to one or more of the complex cognitive tasks, indicating at least partially intact cognitive processing in CLIS. Nevertheless, the results of ERPs cannot prove or disprove normal information processing in CLIS; they only suggest some intact “processing modules” in most ALS patients with CLIS, despite a reduced general arousal (Kübler & Birbaumer, 2008).

Clearly, symptoms of CI could be a significant hindrance to both learning and using a BCI for communication, especially in advanced cases of ALS that have progressed to CLIS. Having reviewed all the aforementioned evidence is important to consider that CI and FTD cannot be generalized to the whole ALS population, and the methods used in the clinic for cognitive assessment in LIS and CLIS are not adequate. More adequate methods based on ERP responses show the possibility of intact cognitive processing in these patients. Moreover, the substantial body of successful cases of invasive and non-invasive BCI in advanced states of ALS, and the very few attempts of BCI communication in CLIS, demonstrate that CI is not a factor that has categorically kept the scientific community from achieving success in these attempts.

2.7. Methodological approach for BCI communication in CLIS patients

The initial setbacks to establishing a successful validated BCI communication in individuals in CLIS could also be attributed to the employment of an inadequate methodological approach. Consequently, in the pursuit of this objective, the present research program explored diverse methodological strategies aimed at addressing the challenge.

The aforementioned “extinction of goal-directed thinking” presumably relates to the lack of perceived relationships between intent and effects on the environment in CLIS patients. Under this rationale, any effort that helps to maintain to some degree the relationship between intent and effects in LIS patients on the verge of CLIS (e.g., through BCI-based technologies) might prevent the user from experiencing this extinction (Kübler & Birbaumer, 2008; Marchetti & Priftis, 2015; McFarland, 2020). In the studies mentioned in previous sections, the introduction and training in BCI control to CLIS patients typically occur after several years of being in the CLIS state, with them relying already on assisted respiration for survival. Given this context, it can be hypothesized that a longitudinal approach may be more suitable by commencing BCI training in the early stages of ALS, to allow the users to master the communication system under the logic that they will acquire and retain these skills well before reaching the CLIS stage, enabling them to proficiently utilize the BCI for communication and thereby preventing "extinction" during the CLIS phase.

It is a common opinion in clinical research that CI might occur over the progression of ALS in a considerable percentage of patients but, with the available evidence, it cannot be claimed categorically that cognitive decline has a neuropathological origin derived from the progression of ALS. As elaborated in this dissertation, an inverted approach is equally worth considering: the extinction of contingency-dependent thinking and intention "… might be responsible for the cessation of voluntary cognitive activity, goal-directed thinking and imagery" (Kübler & Birbaumer, 2008). Certainly, more research is necessary to inquire into the matter.

Clinical studies demonstrate that the progression of cognitive symptoms in ALS is slower compared to motor decline, with the cognitive deficits manifesting, if ever, early in the course of the disease (Abrahams et al., 2005; Robinson et al., 2006). Additionally, it has been found that patients with bulbar-onset ALS exhibit a progression of cognitive deficits across various domains over time, while limb-onset ALS patients show no decline within the same study period (Strong et al., 1999). Taking this evidence into account, along with the recognition that cognitive decline and impairment may not be universally applied to all ALS individuals, enables a more precise patient profiling approach for identifying potential successful users of a BCI in the CLIS stage, thereby addressing the pertinent research objectives.

As has been claimed earlier (Birbaumer, 2006) and validated in this research program (Maruyama et al., 2021; Secco et al., 2021), the spectral EEG patterns of ALS patients change during the progression of the disease. Regardless of the nature of these changes, they may impede patients from becoming proficient users of BCIs, potentially leading to BCI illiteracy. These changes could, for instance, alter signals that are crucial for some BCI paradigms. There is a possibility that these physiological changes render these signals not only challenging for researchers to decode and exploit but also for patients to produce and control. Therefore, it is worth considering alternative neural signals as a source for CLIS patients.

Clinical tests of BCIs reliant on implanted microelectrodes in the motor cortex of patients in advanced stages of ALS have shown that is possible for them to interact with a computer, offering advantages such as increased stability in the signal and a significantly improved signal-to-noise ratio. In these tests, the users are capable of selecting letters from a speller scheme to elaborate long and meaningful sentences. For these patients in LIS with preserved oculomotor control and vision, the BCIs compare in efficiency to eye-tracking speller.

Even in the challenging state of severe paralysis, there is no reason to assume that, at least in the initial stages of CLIS, invasive approaches could not enable flexible spelling through cellular activity in CLIS patients (Chaudhary, Mrachacz-Kersting, et al., 2021). However, as ALS progresses to CLIS and results in the loss of oculomotor control and subsequent blindness, the use of visual paradigms and the eyes to provide feedback in a BCI prototype becomes impractical. For CLIS individuals, auditory or tactile paradigms emerge as the only viable options.

All of these methodological considerations underscore the notion that validating CLIS communication is not a task predetermined to fail. The successful operation of a BCI by one ALS-CLIS patient has the potential to demonstrate the preservation of cognitive functions despite complete paralysis, thereby questioning the “extinction of goal-directed thinking” and prompting to reconsider the assumptions regarding the cognitive status of patients in advanced stages of ALS (Birbaumer, 2006; Kübler & Birbaumer, 2008). Additionally to all this, there is a profoundly positive ethical dimension in "giving a voice" to this patients.

3. Results of the considered publications

3.1. EEG features of LIS and CLIS patients: oscillations and sleep patterns

To design more adequate BCI systems is fundamental a better understanding of the physiology of advanced ALS, and a better description of how the progression of the disease changes some neurophysiological features. Since EEG activity is the most accessible correlate of the brain, it can be used to record and analyze its activity during behavioural and cognitive processes of interest. For this particular research program, is fundamental to understand how different EEG features change longitudinally during the progression of ALS, particularly during the transition from LIS to CLIS.

In the study by Maruyama et al. (2021) (see Appendix 5), EEG recordings of 10 patients in CLIS during resting state were compared with healthy controls, analyzing the differences in brain regions. The findings revealed significant power reduction in the high alpha, beta, and gamma EEG frequency bands in frontocentral and/or central areas, indicating the dominance of slower EEG frequencies in brain activity of CLIS patients. This overall slowing may indicate a different state of vigilance and attention and may not allow the application of comparable cognitive tasks as in healthy subjects for which most BCI paradigms were developed. The results reveal that further investigation with longitudinal recordings is necessary to clarify the effect of BCI as a communication method and to explore if the power decrease correlates with loss of motor control, cognitive changes, reduced vigilance, and/or emergency treatment effects such as artificial respiration and feeding.

To this end, in the study by Secco et al. (2021) (see Appendix 4) the investigation was focused on the longitudinal changes in the EEG's Power Spectral Density (PSD) of patients with ALS in transition from a LIS to CLIS. The study analyzed the EEG recordings of three ALS patients acquired over more than a year, recording resting-state during each visit. The paper highlights significant differences in PSD between two CLIS patients without any communication means and a patient transitioning from LIS to CLIS with communication means. The patients already in CLIS showed stable EEG frequency spectra dominated by delta and theta bands. In contrast, the patient transitioning from LIS to CLIS (a.k.a. patient 11), showed different EEG characteristics with activity in the alpha band but a decrease in EEG power as paralysis progressed. This patient retained communication abilities longer due to eye movement control, provided by our group (Tonin et al., 2020). In the paper, it is hypothesized that these differences in the spectra of patients might be due to the persistence of communication. It is also proposed that the absence of alpha and higher frequency bands in CLIS patients might be one of the reasons for their impossibility of using current EEG-based BCI methodologies.

To continue characterizing the electrical correlates of ALS patients in CLIS, in the study by Malekshahi et al. (2019) (Appendix 1), we studied the sleep patterns of individuals with ALS in CLIS. The study conducted polysomnographic recordings on eight CLIS patients. The analysis surprisingly revealed that despite their condition, all CLIS patients exhibited a discernible circadian sleep-wake pattern with periods of Slow-Wave Sleep (SWS) – activity most prominent after midnight – indicating the presence of deep sleep phases; an unusual alpha-like theta/delta oscillation was also found, which might be linked to a lack of sensory stimulation or overuse of alpha-generating circuitry, although no classification of rapid eye movement (REM) was possible due to the absence of eye movements and oculomotor activity. The findings suggest that providing undisturbed nighttime sleep is crucial for their mental well-being and maintaining a reasonable QoL despite their severe physical limitations.

3.2. Development and Validation of a BCI for LIS and CLIS Users

Taking into account the laboratory's previous achievements in using different EEG paradigms for enabling clinical applications for BCI technology, we aimed to create and validate a versatile software platform for this end. This ‘general-purpose framework’ was envisioned to facilitate BCI-based communication with ALS patients in both LIS and CLIS states. Considering the promising findings presented by Gallegos-Ayala et al. (2014), we considered that fNIRS, alongside EEG and EOG, will be incorporated into this software platform.

To bring this concept to fruition, a comprehensive framework for a ‘HybridBCI’ was meticulously designed and developed, as shown in Khalili-Ardali et al. (2023) (see Appendix 9). The primary aim of this software was to allow individuals with advanced stages of paralysis due to ALS, to explore diverse signal sources for BCI communication control. The framework is Matlab© based, developed modularly, with a clear and straightforward pipeline for data acquisition, signal analysis and classification, with a modular implementation for each part. It allowed to customize the channels to be acquired, the features for EEG, fNIRS and EOG to be used, and the use of different types of classifiers for offline and online classification during the ongoing trials. For individuals with complete paralysis, the system operates using an auditory-based paradigm, although it can accommodate various modalities within its framework. In each session, it facilitates the presentation of customized questions or sentences for classifying physiological responses as 'yes' or 'no,' thus constructing a prediction model. This model can subsequently be employed to classify responses to questions or sentences, or it can be utilized within the speller module as done in Tonin et al. (2020) and Jaramillo-Gonzalez at al. (2021).

Additionally, considering the relevance of remnant muscular activity for ALS patients on the verge from LIS to CLIS, control of the BCI by EOG was also part of the ‘HybridBCI’. Considering this, the same principles for EOG control were validated in a dedicated publication as part of an AAC open-source platform (Martínez-Cerveró et al., 2020) (see Appendix 2).

3.3. Spelling performance in the transition from LIS to CLIS

A primary objective of this research program was to follow up patients during their transition from LIS to CLIS, with a specific focus on the verge of CLIS. To achieve this, we proposed a study with a sample of 4 patients with advanced ALS in LIS with ALSFRS-R score of 0, transitioning to CLIS, in which they can learn how to use a BCI system (Tonin et al., 2020) (see Appendix 3). First, a ‘yes/no’ training session was performed to build a model, and once a reliable prediction model was obtained, copy-spelling and spelling sessions took place. The spelling scheme was customized for each patient, based on their previously available AAC solutions. The software framework ‘HybridBCI’ (Khalili-Ardali et al., 2023) was used to this end. During each session, the patients were provided with the opportunity to use either EEG or EOG to control the BCI. Nevertheless, at the beginning of the study, all the participants still retained some oculomotor control, and preferred EOG over EEG to control the BCI, since it was easier for them to find an oculomotor strategy, compared to the concentration effort required to control the EEG signals.

Although the participants retained some remnant oculomotor control, they were unable to use eye tracking systems due to the dryness of the cornea and loss of gaze fixation, being only capable of performing eye movements with a very small amplitude range. With the 'HybridBCI' system, the patients were asked to move their eyes when the answer was 'yes' and to do nothing when the answer was 'no'. EOG features were harnessed to train a binary classification model, subsequently applied during spelling sessions to predict oculomotor activity. Auditory feedback was integrated into the system to facilitate letter selection and sentence formation for the users. These individuals demonstrated remarkable proficiency, independently composing complete sentences and engaging in unrestricted communication, all while maintaining EOG movement within an amplitude range of ±200μV and ±40μV throughout the follow-up period.

While our initial expectations revolved around patients adopting thought-based strategies to govern the EEG-based BCI, alongside the decline in oculomotor control, this outcome did not materialize. Nevertheless, throughout the study's duration, all four patients consistently demonstrated their ability to generate meaningful responses and construct sentences using the speller interface. This observation holds particular significance in the case of patient 11, whose progression into CLIS was marked by clinical developments and the gradual loss of residual muscular control.

The conclusions learned from this study were determinant for the next part of the research program. Naturally, the information gathered during these sessions proved to be highly valuable, not only for enhancing our comprehension of ALS progression and its associated EEG-EOG correlates, which can contribute to refining the clinical assessments of CLIS, but also for subjecting this data and the resultant conclusions to the scrutiny of our peers and collaborators as we advance in the subsequent and determinant phases of our research program. With this objective, in Jaramillo-Gonzalez at al. (2021) (see Appendix 6) we undertook a curation of the data to render it more comprehensible and readily accessible to a broader scientific community. The curated dataset comprises EEG and EOG recordings from numerous visits, varying between 2 and 10 visits for each patient. Each visit encompasses an average duration of 3.22 ± 1.21 days and includes approximately 5.57 ± 2.61 recording sessions per day. The dataset contains the different types of sessions, i.e., training, feedback, copy spelling and free spelling, the stimuli audio files used in the paradigm, as well as the classification models that allowed online communication (Jaramillo-Gonzalez et al., 2021). Furthermore, the dataset comprises recorded evidence of ALS patients transitioning from LIS to CLIS, effectively conveying meaningful phrases expressing their desires and intentions.

3.4. BCI-based communication in a CLIS patient

To this date, invasive BCI solutions employing neuro-electrical signals from the brain through implanted electrodes, have proven to be reliable and successful means to grant communication to patients in LIS, even in at-home settings. Taking previous methodological considerations into account, it cannot be assumed beforehand that a patient in the initial stages of CLIS should not adapt to produce meaningful spelling (Chaudhary, Mrachacz-Kersting, et al., 2021). Moreover, considering that patient has been proficiently using a speller scheme to communicate, up to the time of his entry into CLIS. That is the case of patient 11, whose participation in our studies has already been described in previous sections.

Until now, invasive BCI solutions employing implanted electrodes have demonstrated reliability and success in facilitating communication for patients in LIS, even in at-home environments. When considering more adequate methodologies, there is no reason to assume that a patient in the early stages of CLIS, who had previously demonstrated proficiency with a spelling system, cannot adapt to meaningful spelling through an invasive BCI. These criteria applies specifically to patient 11, whose involvement and advancements within our research have been detailed in the preceding sections.

Using the available dataset, extensive EOG recordings were analyzed to confirm that no muscle-based communication signals were possible, confirming thus that patient 11 had truly transitioned from LIS to CLIS state. Taking this into account, in Chaudhary et al. (2022) (see Appendix 8), a groundbreaking case study was conducted featuring patient 11. The study aimed to prove that neural-based verbal communication remains possible in the state of complete paralysis. For this, the patient underwent implantation of two intracortical microelectrode arrays in the dominant left motor cortex and Supplementary Motor Cortex (SMA). The patient used auditory neurofeedback to modulate neural firing rates voluntarily, selecting letters one at a time to form words and sentences to verbally communicate. Despite being unable to voluntarily open his eyes and experiencing a total loss of visual input, the patient effectively communicated using the auditory-guided neurofeedback system. While communication rates were slower than some other intracortical interface studies, they were faster than non-invasive alternatives for ALS patients.

These findings provide optimism for enhancing both the QoL and communication prospects for individuals grappling with severe neurological conditions. Nonetheless, it's crucial to acknowledge that, at this point, these outcomes apply to a patient within the first year of the CLIS stage. The idiosyncratic progression of ALS complicates extrapolating these findings broadly, requiring further investigation to refine and broaden this promising outcome.

3.5. Quality of Life in CLIS patients

Our laboratory possesses significant expertise in conducting clinical trials with BCI-based communication systems for patients in both LIS and CLIS; notably, the previously mentioned case study (Chaudhary et al., 2022) exemplifies this track record. Throughout these endeavours, there has always been a particular concern about the QoL of severely paralyzed ALS patients, and how the use of a BCI impacts their lives (Birbaumer et al., 2014; Nijboer et al., 2010). The same emphasis in assessing QoL has been placed on the case of patient 11. Once he mastered communication with the spelling BCI some months after implantation, he was questioned about his QoL (data available, not yet published) and at least until the time of the publication of Chaudhary et al. (2022), his QoL assessment was overall positive.

Considering all the previous evidence of positive assessments of QoL in ALS in LIS patients (Albrecht & Devlieger, 1999; Lulé et al., 2013; Rousseau et al., 2013) in addition to the recent evidence involving a CLIS patient (Chaudhary et al., 2022), these collective results affirm the existence of the so-called 'disability paradox' within severe paralysis (Albrecht & Devlieger, 1999). These results lead us to propose in Chaudhary et al. (2021) (see Appendix 7) that the extinction of contingency-dependent thinking and intention, in addition to the muscular relaxation, might induce a meditative state in CLIS, paradoxically contributing to the reported high QoL. We also propose that features found in LIS and CLIS patients, such as compensatory cognitive or neuroplastic changes, reduced negative emotions, and increased positive emotional tone, are correlated to this positive self-assessment of QoL. Some neurological aspects of the patients in CLIS are also discussed, proposing that the predominance of slow oscillations in the EEG (Maruyama et al., 2021; Secco et al., 2021) might be an indicator of reduced cognitive processing or compromised vigilance states, possibly linked to reduced cortical arousal and sleep-like patterns, all these aspects, with a potential link to BCI illiteracy in CLIS patients.

Within the same publication, we delve into the social determinants impacting the QoL of severely paralyzed individuals. This examination reviews evidence showcasing a notable disparity in perception between patients and their relatives, as well as society at large, with patients consistently assigning more favourable QoL ratings to themselves. We also explore the ramifications of BCI utilization for communication in the lives of severely paralyzed patients in both LIS and CLIS. For these individuals, BCIs might represent the only method of communication, affording us insights into their emotional states and QoL.

4. Summary of findings

Building upon previous work conducted in this laboratory, the current research program focused on ALS patients in the LIS and CLIS states. We aimed to gain a deeper understanding of the neurophysiological changes that accompany advanced stages of the disease, with a particular emphasis on the transitional phase from LIS to CLIS.

We obtained EEG recordings during resting states from CLIS patients, confirming a notable slowing of brain activity, especially in the high alpha, beta, and gamma frequency bands within frontocentral areas. This slowing suggests alterations in vigilance and attention states, raising questions about the suitability of the BCI paradigms used so far for CLIS. Additionally, longitudinal investigations of ALS patients transitioning from LIS to CLIS showed differences in the PSD of EEG, between patients with and without communication means, emphasizing the need for further research to elucidate the impact of BCI use on communication abilities in CLIS. Polysomnographic recordings in CLIS patients revealed normal sleep cycles of nighttime sleep. Considering the previous findings, providing these patients with reliable means of communication can contribute to their well-being and positive QoL, despite severe physical limitations.

To this end, we improved previous software versions to implement a versatile software platform for BCIs intended to allow communication in both LIS and CLIS patients. The validated software, known as 'HybridBCI,' incorporates, fNIRS, EEG and EOG modalities, allowing the user to train using auditory paradigms, so it can predict a given answer based on the neurophysiological activity related to it.

In a longitudinal study, we worked with ALS patients transitioning from LIS to CLIS, teaching them to use the BCI system for verbally communicating. The users had the choice of using either EEG or EOG, but most preferred EOG due to its simplicity compared to the cognitive demand for EEG control. The four users manage to efficiently control the system using EOG micro-movements. This study's findings were instrumental in understanding ALS progression and its correlates with EEG and EOG signals. One of the patients entered CLIS after having used the speller system for over a year, and took part in a clinical trial for receiving implanted microelectrode arrays, becoming the first person in CLIS to use a BCI to achieve verbal communication. He was able to use the BCI through auditory neurofeedback to sequentially select letters, allowing him to construct meaningful words and coherent sentences for unrestricted effective communication.

Transferring the ability to operate a BCI for spelling (considered as a contingency between an intention and its instrumental outcome), learned in LIS before the onset of CLIS, effectively prevented the extinction of goal-directed voluntary thinking in the early stages of CLIS for this patient. These positive and encouraging results offer hope for improving the QoL and communication possibilities during the CLIS stages. It's worth noting that BCIs are currently the sole means of gaining insight into the thoughts of CLIS patients, underscoring the need for further research to generalize these findings to a non-invasive and more affordable approach.

5. Conclusion and Discussion

In this research program, different cognitive and neurophysiological aspects of ALS patients in LIS and CLIS were investigated; a software platform was developed to allow more flexible, and reliable BCI systems for users with severe paralysis. This platform was employed to monitor the progression of ALS in a patient sample, enabling the recording and characterization of neurophysiological changes over time. One of the patients who entered CLIS participated in the clinical evaluation of an invasive BCI system that successfully enabled reliable communication, thereby enhancing his QoL and preventing the decline of goal-directed voluntary thinking.

The developed 'HybridBCI' was reliable enough to try, *in situ* and online, different physiological signals. Nevertheless, as mentioned earlier, ALS patients in LIS held on to EOG during the visits, for as long as this signal was useful for them to manipulate the speller. During the longitudinal approach, the classification model built from EEG features reached very low accuracy regardless of our request for the patients to perform either MI or motor attempt (analysis not reported, but data available in Jaramillo-Gonzalez et al. (2021)). It can be criticized that an EOG speller system is a type of AAC and not a BCI, and we point out that the purpose of the longitudinal study was not to force the participants towards mastering control of a certain physiological signal but to grant them communication. Forcing them to achieve success only by using EEG under continuous cognitive fatigue and failure, might have only led to frustration and eventual withdrawal from the study. On the other hand, keeping the participants communicating successfully, contributed to their QoL and motivated them to participate in further stages of the study. With this longitudinal study, we managed to capture the transition from LIS to CLIS in only one out of four of the participants. While this may initially seem insufficient for drawing meaningful conclusions, it is important to acknowledge the patient-dependent nature of ALS progression. Predicting the exact timing of the total loss of remnant muscular activity is impossible. Therefore, successfully capturing a single transition represents a significant achievement, especially in light of the clinical determinants involved. This outcome holds particular relevance for informing the subsequent stages of the research program, for the development of the micro-electrode-based BCI.

We made significant findings concerning the physiological changes associated with the progression of ALS, with a specific emphasis on EEG patterns. Our findings underscore how the advancement of the disease results in a prevalence of slow oscillations in the brain activity of CLIS patients. These results align with previous findings in the literature, where severely paralyzed patients (with a diagnosis other than ALS) exhibit no alpha or beta rhythms and very atypical EEG signatures (Höhne et al., 2014) and the hypothesis that the aetiology of ALS-LIS may affect the spectral activity in sensorimotor cortex leading to different baseline spectral characteristics (Bensch et al., 2014), this, under the consideration that certain EEG-BCI paradigms that worked well on healthy subjects do not necessarily indicate successful performance with completely paralyzed patients (Hill et al., 2006).

The spectral changes observed in these patients may not necessarily be linked to CI or physiological deterioration, as it is a well-established fact that ALS patients in LIS can effectively utilize EEG-based paradigms in a BCI. Different electrophysiological signals other than sensorimotor rhythms have proven that LIS and CLIS users are capable of successful performance (Chaudhary et al., 2022; Nijboer et al., 2008; Vansteensel et al., 2016). Rather, this ‘displacement’ towards slower bands might be part of adjustments and adaptations taking place in severe paralysis, as proposed in (Chaudhary, Chander, et al., 2021), whose underlying mechanisms are still unknown. This observation can be reinforced by what we learned from patient 11. He transitioned from LIS to CLIS while participating in our study and mastering the speller system, in which, although using oculomotor activity, he retained a channel of communication, During the time of the study, it was not possible to identify consistently the production of MI. Nevertheless, once implanted, he quickly developed a strategy to control the firing rate in the left motor cortex, using a different mental/cognitive strategy to control the same speller system, that lasted for the time of publication. However, it is crucial to note that this evidence does not necessarily exclude the potential for further cognitive and neurophysiological changes that may become evident as external indicators of cognitive decline as the disease progresses.

Several neurophysiological features characterize the CLIS state. In this research program, we found that a patient on the verge of transitioning from LIS to CLIS retained activity in the alpha wave, albeit with a significant decrease in the power of this band as the disease progressed. There might be several explanations for this phenomenon. It is possible that alpha waves might be among the features that ALS spares until the late stages of the disease, disappearing once CLIS is reached, as the evidence shows. Another possibility is that the retention of this still 'active' alpha band might be related to the patient's ability to learn to spell proficiently with the BCI, and its disappearance could coincide with BCI illiteracy. Under this logic, it remains to be determined how long the user can continue using the BCI and whether this correlates with the PSD of the EEG.

Different theories of embodied cognition have been proposed over time. Enactivism, as suggested by Varela et al. (1991), proposes that cognitive processes are rooted in the sensorimotor interactions of an organism with its surroundings. However, as early as the end of the 19th century, James (1890) proposed that the cessation of voluntary cognitive activity could be a consequence of the absence of movement. Given the impossibility of establishing validated and long-term communication by BCI in CLIS patients, it was hypothesized by Kübler and Birbaumer (2008) that "the complete lack of motor control and feedback... might be responsible for the cessation of voluntary cognitive activity, goal-directed thinking, and imagery" in this population.

The milestone finding from this research program demonstrates that by providing a patient with the means – in this case, the BCI-speller – to maintain the relationship between intent and effects during the transition from LIS to CLIS, prevented the "extinction of goal-directed thinking." This, in contrast to individuals already in CLIS, who appear to have reached this state of extinction of intentions. The patient had successfully communicated for over a year prior to implantation using an oculomotor-controlled speller. After transitioning to the CLIS state and receiving a neuroimplant-based BCI, the patient continued to employ the same spelling system for over a year. Despite the shift to a different neurophysiological modality, mastering the BCI speller seemed to transfer as a contingency, and it appears to have played a role in maintaining the patient's ability to associate intentions with outcomes. Throughout the data collection period for this publication, the patient consistently produced coherent speech and engaged in conversations, albeit with certain limitations. Consequently, it can be asserted that the patient retained functional cognition, regardless of the specific features observed in the PSD of his EEG.

These findings align with principles of embodied cognition and enactivism, supporting hypotheses about the fundamental nature of the nervous system. They suggest that "motricity" is the biological impetus driving the development of a nervous system, primarily required by multicellular organisms capable of coordinating and executing active movements to respond to their environment (Llinás, 2002).

Nonetheless, the phenomenon often referred to as the “extinction of goal-directed thinking” should not be regarded in dichotomous ‘all-or-none’ terms. As empirically demonstrated, the onset of this extinction can be notably delayed, particularly within the initial year of CLIS in ALS patients. Nevertheless, the inexorable progression of ALS may precipitate further cognitive deterioration and neurophysiological alterations. It is imperative to underscore that, within the scope of this particular case study, verbal communication and interaction facilitated by the BCI were limited to a temporal window of a few hours daily. Inevitably, although this channel preserves the contingency of thought-action-consequence, constitutes a rather 'narrow' substitute for the comprehensive sensorimotor framework intrinsic to human functioning. To quote Kübler and Birbaumer (2008), “with a mere two hours of daily training and the remaining 22 hours devoid of such contingency, the potential for cognitive extinction remains significant”. Personal communications with N. Birbaumer in January 2023 suggest that the patient's proficiency in using the speller system, may face a decline.

In conclusion, to validate many of the hypotheses presented here, it is imperative to conduct longitudinal studies involving a larger cohort of individuals in the transition from LIS to CLIS or within the CLIS stage itself. However, it's crucial to recognize that, while invasive clinical trials hold promise, the substantial resources required for such an expanded research program are substantial. Therefore, the primary challenge ahead lies in the translation of this knowledge into non-invasive, validated, and affordable BCIs for CLIS patients.

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Appendices

Appendix 1.

A. Malekshahi & U. Chaudhary, **A. Jaramillo-Gonzalez**, A. Lucas Luna, A. Rana, A. Tonin, N. Birbaumer, S. Gais (2019). Sleep in the Completely Locked-in State in Amyotrophic Lateral Sclerosis, *Sleep*, 42, 12, zsz185.
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Sleep in the completely locked-in state (CLIS) in amyotrophic lateral sclerosis

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Abstract

Persons in the completely locked-in state (CLIS) suffering from amyotrophic lateral sclerosis (ALS) are deprived of many zeitgebers of the circadian rhythm: While cognitively intact, they are completely paralyzed, eyes mostly closed, with artificial ventilation and artificial nutrition, and social communication extremely restricted or absent. Polysomnographic recordings in eight patients in CLIS, however, revealed the presence of regular episodes of deep sleep during night time in all patients. It was also possible to distinguish an alpha-like state and a wake-like state. Classification of rapid eye movement (REM) sleep is difficult because of absent eye movements and absent muscular activity. Four out of eight patients did not show any sleep spindles. Those who have spindles also show K-complexes and thus regular phases of sleep stage 2. Thus, despite some irregularities, we found a surprisingly healthy sleep pattern in these patients.

Statement of Significance

The presence of circadian variation in EEG activity points to a conserved sleep-wake cycle in amyotrophic lateral sclerosis (ALS) patients in completely locked-in state (CLIS). There are marked differences between these patients and healthy participants, e.g. a complete loss of sleep spindles in some patients and the presence of sinusoid, high-amplitude theta activity instead of alpha activity. Slow-wave generation, on the other hand, seems intact in all patients. Rapid eye movement (REM) sleep is present in at least some patients, but it cannot be ascertained in all patients. The existence of intact sleep in patients in CLIS is another important sign that their wakefulness is likewise intact. It also indicates that providing undisturbed sleep opportunity will be important for the patients' mental well-being.

Key words: movement disorders; neurological disorders; sleep/wake physiology; circadian rhythms; completely locked-in state; polysomnography

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Introduction

The sleep-wake cycle is a crucial component of neural and bodily development and restitution involved in a plethora of homeostatic processes [1]. Different exogenous zeitgebers, such as daylight, social stimulation, motor activity or food intake, synchronize the various central and peripheral endogenous oscillators [2–7] In the locked-in condition and the completely locked-in state (CLIS) [8], most of these zeitgebers are absent or attenuated due to complete immobility and absence of muscular activity, artificial respiration, artificial feeding and artificial lighting [9–12] Patients in CLIS suffering from advanced motor neuron diseases such as amyotrophic lateral sclerosis (ALS), who have an inability to open or close their eyes voluntarily, have their eyes closed most of the day and during the night to avoid drying of the immobile eyeball and cornea. In some cases, the complete closure of the eyelids remains impossible, leading to corneal lesions due to extensive drying with little or no differentiated vision left. Artificial feeding and breathing through a tracheostoma impose an extreme regularity on the internal organ systems, impeding the differentiation between day and nighttime. Social stimulation is certainly more frequent during the day but 24-hour care entails multiple activities also during the night (suction of saliva, excrements, eye care, position changes to avoid decubitus, change of tubes and feeding devices, etc.). The reduction of active social interaction and the complete lack of (verbal or signing) communication further minimize the differences between daytime and nighttime stimulation. Muscular paralysis also dramatically reduces the amount of afferent proprioceptive inputs towards the spinal cord and brain. Patients are bedridden and completely motionless over months and years, except during short periods of passive position changes. Although effects of constant conditions on homeostatic and circadian processes and on sleep have been investigated in constant routine studies and forced desynchrony protocols [13], in CLIS patients who constantly live in a controlled environment, the effects on their circadian rhythm are largely unknown [14]. Although, the scientific literature is rich on circadian rhythm and sleep-wake cycle in healthy populations [15–19] and patients with other neurological disorders [14, 20–25], there exists virtually no information about circadian rhythm and sleep-wake cycle in patients in the CLIS.

For brain-computer interface (BCI) communication with these patients, it is necessary to discriminate periods of sleep and wakefulness in the individual EEG. It has been argued that the main reason for decreased or random performance in BCI communication might be the lack of attention and the presence of micro sleep during the presentation of the questions [11]. In a study of one CLIS and two LIS patients over a whole year it has been shown that a reduced P300 amplitude during the BCI task predicted lower performance, again suggesting reduced wakefulness and attention as a major limiting factor for BCI applications in these severely compromised patients [26].

To our knowledge, the sleep pattern of only one patient from our lab shortly after the transition from the locked-in state to the CLIS has been reported [27]. An irregular sleep pattern with daytime episodes of slow-wave sleep disrupted slow-wave sleep during the night and irregular appearance of different sleep stages during day and night was reported in this patient. The overall slow-wave sleep duration was normal for the age of the patient. It is of clinical and theoretical importance to study sleep in a larger sample of CLIS patients. The presence of distinguishable sleep and wake periods in these patients would constitute another piece of evidence for their cognitive functioning. Undisturbed sleep could also serve to prevent depression and maintain sufficiently high quality of life in these patients [28].

Hence, to elucidate their sleep-wake cycle, we recorded sleep in eight CLIS patients. We will outline criteria, which can be used to delineate the sleep stages, and describe and discuss the sleep cycles of the individual patients. Already at this point we need to mention the main limitations of this research, which are dictated by the clinical condition: the absence of eye movements and of changes in muscular tone due to the complete paralysis complicate scoring of rapid eye movement (REM) sleep. Mainly because of this limitation, it is impossible to label each 30-second epoch of the night with a sleep stage. We, therefore, refrain from presenting hypnograms and percentages of sleep stages, but only describe which sleep stages occur in a specific patient.

Materials and Methods

The Internal Review Board of the Medical Faculty of the University of Tubingen approved the experiment reported in this study and the patients' legal representatives gave written informed consent for the study with permission to publish the results. The study is in full compliance with the ethical practice of Medical Faculty of the University of Tubingen. The clinical trial registration number is ClinicalTrials.gov identifier: NCT02980380.

Patients

The details of patients 1, 3, and 4 are described in Ref. [11] as patients F, G, and W, respectively. The remaining patients are described below.

Patient 5 (male, 50 years old, CLIS) was diagnosed with bulbar sporadic ALS in May 2008, as locked-in in 2009, and as completely locked-in May 2010, based on the diagnosis of neurologists and on our recordings (see below and Ref. [11]). He has been artificially ventilated since September 2009, fed through a percutaneous endoscopic gastrostomy tube since October 2009, and is in home care. No communication with eye movements, other muscles, or assistive communication devices was possible since 2010.

Patient 6 (male, 38 years old, CLIS) was diagnosed with bulbar ALS in 2009. He lost speech and capability to move by 2010. He has been artificially ventilated since September 2010 and is in home care. No communication with eye movements, other muscles, or assistive communication devices was possible since 2012.

Patient 7 (female, 57 years old, CLIS) was diagnosed with Mills' syndrome of ALS with atypical progression at the beginning of 2010. She lost speech and capability to walk by 2011. She has been fed through a percutaneous endoscopic gastrostomy tube since June 2010, artificially ventilated since June 2010, and was in home care until she passed away in 2017. She started using assistive communication devices employing eye movement for communication in 2011. Eye-tracker-based communication failed at the beginning of 2015. The family and caretakers communicated with her since the middle of 2015 based on her thumb-movements, which after a year became unreliable.

Patient 9 (male, 23 years old, CLIS) was diagnosed with juvenile ALS with FUS mutation heterozygote on Exon 14: c.1504delG, gene mutation diagnosed in 2013. He has been artificially ventilated since August 2014 and is in home care. He started communication using MyTobii eye-tracking device in January 2015. He was able to communicate with MyTobii until December 2015 after which the family members attempted to communicate by training him to move his facial muscles near the nose to answer "yes" but the response was unreliable. No communication was possible since June 2016.

Patient 10 (male, 25 years old, locked-in state on the verge of CLIS) was diagnosed with familial juvenile ALS with ALS 6-FUS gene mutation in December 2012. He was completely paralyzed within a year after diagnosis, has been artificially ventilated since November 2013, and is in home care. He was able to communicate with eye-tracking from early 2014 to August 2016 but was unable to use the eye-tracking device after the loss of eye control in August 2016. No communication with eye movements, other muscles, or assistive communication devices was possible since 2016.

In none of these patients, voluntary eye movement responses to questions were recorded in any of the recording sessions. None of these patients showed any brain disease unrelated to ALS. CLIS onset was on average 38 months after initial diagnosis, which corresponds to expectations [29]. The proportion of juvenile-onset ALS was higher in our sample than in the general population of ALS patients [30].

Sleep recording

Sleep EEG was recorded consecutively for two nights from each patient, except patient 4 and 7 (one night only). The first recording was carried out in order to adapt the patients to the electrodes. The second night EEG, EMG, and EOG were recorded for later sleep scoring. As shown in Table 1, sleep EEG data was acquired for more than 12 hours for all the patients, except patient 4.

The sleep polysomnography was recorded with a multichannel EEG amplifier (Brain Amp DC, Brain Products, Germany) from 11 Ag/AgCl passive electrodes mounted on a head cap. Six electrodes (F3, F4, C3, C4, O1, and O2) were used to acquire EEG signals, four electrodes were used to acquire the vertical and horizontal EOGs, and one electrode was used to acquire chin-EMG. EEG-channels were referenced to an electrode on the right mastoid and grounded to the electrode placed at the Fz location of the scalp. Electrode impedances were kept below 10 kΩ and the EEG signal was sampled at 500 Hz.

Preprocessing

The recorded EEG and EOG signals were low-pass filtered using a finite impulse response low-pass filter of 30 Hz. For the EMG, the signal was filtered with a 50 Hz notch filter.

Sleep scoring

The EEG of patients in CLIS is dissimilar in large extents to that of healthy participants. These patients show, e.g. regular high-amplitude oscillatory activity in the theta (4–8 Hz) frequency range for longer periods of time, which cannot be found in healthy participants. Moreover, they have no detectable eye movements during wakefulness and no muscle tone, due to their condition. Thus, the standard sleep-scoring criteria, particularly for REM sleep, have to be adapted to score the sleep stages from patients in CLIS. Still, initial visual inspection of the whole night EEG shows already obvious variations of EEG patterns over time. It can, therefore, be hypothesized that the states of arousal and consciousness also fluctuate throughout the night. Based on time of day and on interaction with the patient (movement artifacts), we had a starting point for a rough assumption of sleep and wakefulness: during the night, longer quiet periods without movement would have a higher probability of representing sleep than morning recordings and periods directly after movement (suction of saliva, repositioning of the patient). We then applied the criteria of Rechtschaffen and Kales [31] to the recordings to determine whether some features of sleep could be found. This scoring was performed visually on 30-s epochs. It resulted in the detection of a number of EEG patterns that generalized over patients, some of which resembled the classical sleep stages. Scoring was done by an experienced sleep scorer (S.G.) and discussed in detail among all authors. We describe the criteria that had to be adjusted as well as the criteria that could be applied directly in the results section.

Signal analysis

Power spectra were computed using Welch's method with a resolution of 0.5 Hz for each 30-second epoch for all EEG channels. Channels containing obvious artifacts were excluded from further analysis. Whole-night spectrograms were calculated based on the median of all artifact-free channels. The median was used to further suppress artifacts and unusually high or low power values. Spectrograms were normalized by subtracting the median and dividing by the value of the 75th quantile of each frequency, analogous to Z-standardization, in order to have comparable ranges. The scale of the spectrograms is, therefore,

Table 1. Summary of findings for each patient

Patient	Start of recording	End of recording	W [active]	W [inactive]	α-like freq.	SWS	REM sleep	Sleep spindles
1	10:34 pm	11:14 am	+	+	4–6 Hz	+	(+)	-
3	10:00 pm	10:17 am	(+)	+	4–7 Hz	+	+	(few)
4	10:14 pm	07:33 am	+	+	2–4 Hz	+	(+)	+
5	08:32 pm	05:11 pm	+	+	3–6 Hz	+	+	-
6	08:38 pm	03:45 pm	+	+	2–4 Hz	+	(uncertain)	-
7	09:10 pm	08:50 am	(+)	+	1–3 Hz	+	(+)	+
9	02:04 pm	09:04 am	+	+	3–5 Hz	+	(+)	+
10	06:49 pm	09:53 am	(+)	+	2–4 Hz	+	(uncertain)	-

+: clear signs of sleep stage present; (+): some signs of sleep stage present; (uncertain): possible signs of sleep stage present; -: no sign of sleep stage present.

dimensionless. Additionally, for all patients, the power spectra of a period of quiet wakefulness is presented to show peaks in EEG power.

As the heartbeat was clearly reflected in the EMG trace of two patients (Pat. 1 and Pat. 5), we used these recordings to calculate the continuous heart rate. The 50 Hz notch-filtered EMG channel was band-pass filtered between 5 and 70 Hz using an IIR filter. Individual heart beats were detected as spikes in the signal. Spikes that were too large or too small were removed as outliers. Then, heart rate was calculated from the distance between spikes. Finally, outliers in heart rate were removed and the whole time series filtered with a 30-point moving average filter.

Results

Three main observations could be made during visual sleep scoring: (1) All patients had cyclic changes in their brain activity throughout the recording in the sense that we found alternating periods with and without slow-wave activity. (2) The discrepancy to healthy sleep EEG differed between patients. (3) Some commonalities in EEG anomalies across patients could be found. Because we observed that each patient has his or her own idiosyncrasies in the sleep-wake cycle, the result of each patient will be described first in this section. Subsequently, we will describe common patterns between participants and suggest heuristics for the scoring of sleep in CLIS patients. Exemplary epochs for individual sleep stages and whole-night power spectrograms can be found for each patient in the Supplementary Material. Exemplary data for patient 9 is presented in Figure 1.

Patient 9

This patient shows clear high amplitude slow waves during the night, starting at around 1:30 am (Figure 1). These waves are in shape and in their clustered occurrence indistinguishable from slow waves of healthy patients. In the spectrogram, they are visible as a strong <2 Hz band. For longer periods of up to 45 minutes, the criteria for slow-wave sleep (SWS), sleep stages 3 (S3) or S4 are reached. For about 1 hour before the onset of S3, individual slow waves (K-complexes) and sleep spindles can be found (S2). In-between periods of S2, epochs dominated by bursts of regular, sinusoidal EEG activity of 3–5 Hz with medium to high amplitude can be found. These bursts have varying length, typically

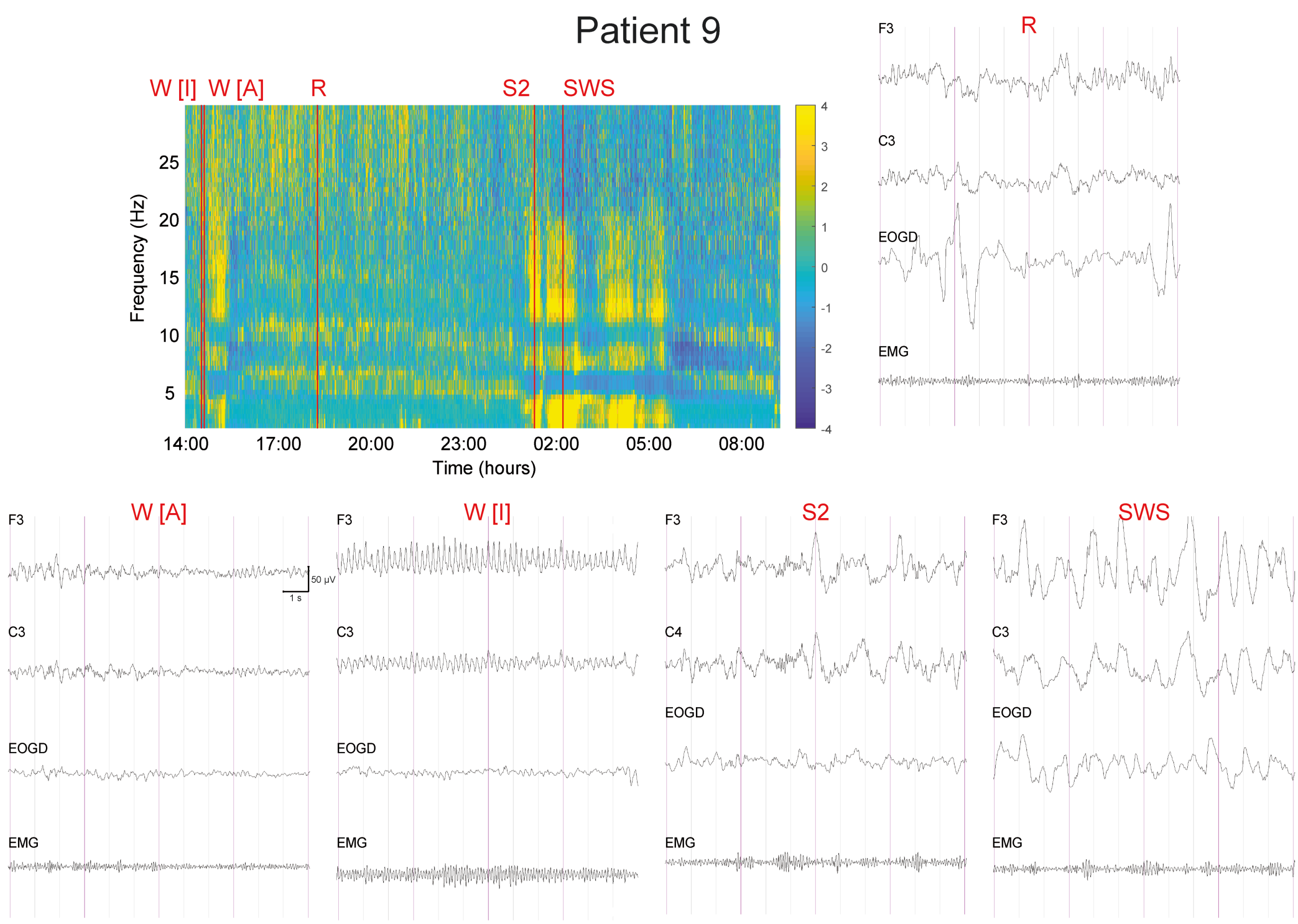

Figure 1. Normalized spectrogram (upper left) and segments of selected sleep epochs of patient 9. Yellow color in the spectrogram reflects higher than average activity in a frequency band; blue color signifies lower than average activity. Red lines on the spectrogram indicate epochs belonging to particular sleep stages. Twelve-second segments of these epochs are shown in the other panels. Here, vertical lines represent 1-s intervals. The EEG during active wakefulness (W[A]) is largely similar to that of healthy participants. EEG activity during inactive wakefulness (W[I]) is around 5 Hz, but resembles alpha activity rather than typical theta activity. Stage 2 sleep (S2) with spindles and K-complexes as well as slow-wave sleep (SWS) can be clearly discerned in this patient. Note the large eye movements during REM sleep (R), which the patient is unable to perform voluntarily during wakefulness. Recordings of the other patients are available in the Supplementary Material, following the same arrangement.

between 5 and 20 seconds. Because of its regularity and the duration of bursts, this activity is strongly reminiscent of alpha activity (see Figure 1, section W[I]). It also occurs for longer periods of several hours in the afternoon and in the evening before the first signs of S2. Although having theta band frequency, these waves have no similarity to the typical, irregular, sawtooth-shaped theta activity of healthy participants. Except for its frequency, this activity, therefore, in all other aspects seems to be equivalent to alpha activity in healthy patients. We, therefore, use this alpha-like activity to score periods of inactive, relaxed wakefulness (W[I]). Starting around 6:00 am, after signs of S2 have diminished, longer periods of low amplitude, high-frequency activity appear. Frequencies are dominated by beta-band activity, with a varying degree of intermixed irregular theta activity. Because of its similarity to typical wake activity and because of its strongest occurrence in the morning after sleep, we score this activity pattern as active wakefulness (W[A]). In the morning, this high-frequency activity is occasionally interrupted by 5- to 20-second periods of regular theta activity as described above (W[I]). In the afternoon, the pattern inverses and long periods of W[I] are interrupted by epochs of W[A].

Unrelated to S2 or SWS sleep phases, there are some epochs that show eye movements that resemble those typical for REM sleep. These occur mainly in the afternoon in the middle of longer periods of W[I], and are accompanied by a brief discontinuation of the alpha-like regular theta activity and appearance of irregular theta and beta waves. Although the timing of these periods is not typical for REM sleep, we suggest that these signs are indicative of REM sleep-like processes and score the corresponding epochs as REM sleep (R).

Patient 1

This patient shows clear high amplitude slow waves (SWS) during the night, starting at around 2:00 am (Supplementary Figure S1). These waves are co-occurring with sinusoidal 4–7 Hz activity in some epochs. There are two more periods of SWS around 5:30 am and 7:30 am. There are no signs of sleep spindles throughout the night. The EEG in the evening before occurrence of SWS is dominated by the same regular, alpha-like 4–7 Hz (theta) activity (W[I]) as in patient 9, although with a lower amplitude. It is intermixed with high-frequency, low-amplitude activity (W[A]) to varying degrees. Interspersed throughout the recording are periods of dominant irregular theta activity during which REMs are manifest. Although the timing of these periods is not typical for REM sleep, we again suggest that these signs are indicative of REM sleep-like processes and score the corresponding epochs as R. Heart rate tendentially increases or reaches maxima over periods during which we did not detect any SWS (e.g. 10:30 pm – 02:00 am and 08:30 am – 10:30 am). During periods of SWS (marked by strong < 1.5 Hz activity) heart rate tendentially decreases.

Patient 3

The EEG of this patient is dominated by regular, high-amplitude, alpha-like 4–7 Hz (theta) activity (W[I]), particularly in the evening and in some parts of the night (Supplementary Figure S2). Starting at 2:00 am, slow waves occur, first together with the alpha-like activity then replacing it more and more. There are several periods of SWS, alternating with periods of W[I]. In the morning, activity becomes more irregular (high-frequency beta and irregular theta activity), especially after intervals of (external) movement (W[A]); but still these periods contain amounts of alpha-like theta activity. After awakening and morning hygiene there is a 2-hour period of strong, continuous REM, accompanied mainly by irregular (sawtooth) theta activity and only little regular (sinusoidal) alpha-like theta activity. In this patient, the eye movement and EEG activity provide strong evidence for REM sleep. There is also evidence for a few sleep spindles in the morning after the period of morning hygiene and before REM sleep.

Patient 4

We find two >1-hour periods of extensive SWS, at 11:00 pm and at 2:00 am (Supplementary Figure S3). During SWS, strong sleep spindle activity (12–14 Hz) is present. Strong spindle activity is also found during a 1-hour period around 4:00 am, which also presents K-complexes (S2). In-between SWS periods, there are periods dominated by 5- to 20-second bursts of regular, sinusoidal 2–4 Hz activity, which resemble the 4–7 Hz activity described in the patients above. These also occur in the evening, intermixed with high-frequency, low-amplitude activity. Because it shows all properties of alpha activity except the frequency range, we score these periods as W[I]. In the evening before sleep, the EEG is dominated by irregular theta and low-amplitude beta activity W[A]. In the morning starting around 6:00 am, we see similar irregular theta and low-amplitude beta activity, but accompanied by (mainly small and a few larger) REMs. Although difficult to discriminate from W[A], the quieter EMG (no external disturbance), the REMs, and the absence of alpha-like activity lead us to score R.

Patient 5

This patient shows several periods of SWS between 10:00 pm and 5:00 am (Supplementary Figure S4). The slow waves are slower than usual and have a higher amplitude. In the evening before sleep and for 1 hour after the end of SWS in the morning, the EEG is dominated by 3–6 Hz alpha-like activity (W[I]). Starting at 6:00 am, the EEG becomes more mixed with irregular theta, beta, and only little alpha-like activity (W[A]). Throughout the day, periods of W[A] and W[I] alternate. In the afternoon at 05:00 pm, a period of clear REM sleep with strong REMs, irregular theta and low amplitude beta activity was found, which continued for >15 minutes until the end of the recording. No sleep spindles were found in this patient. Heart rate is minimal during the night period, during which strong <1.5 Hz activity is recorded (09:30 pm – 7:30 am). It increases in the morning during interaction with the patient.

Patient 6

In patient 6, there are two clear periods of SWS between 4:30 am and 7:00 am (Supplementary Figure S5). In between these two periods, we find several quiet epochs of low-amplitude, high-frequency activity that contain a certain degree of small eye movements. Because they do not resemble periods of wakefulness in this patient, we label these epochs tentatively as uncertain R. The rest of the day alternates between periods of

W[I] (mainly in the evening) and W[A] (more abundant in the morning), showing more or less alpha-like 2–4 Hz activity, respectively. Again, no sleep spindles were found.

Patient 7

This patient shows about 1 hour of SWS with very slow, high-amplitude EEG around midnight (Supplementary Figure S6). Before this period, a few minutes of S2 sleep containing sleep spindles was found. This period is also represented with a yellow spot in the 12–15 Hz band in the spectrogram of this patient. The rest of the recording contains mainly mixed frequency activity in the 1–3 Hz, theta, and beta bands. The amount of low-frequency activity varies throughout the recording, probably reflecting W[I] and W[A]. However, these variations are only gradual, so that a clear distinction between these two stages is difficult in this patient. Moreover, the 1–3 Hz low-frequency activity is less regular and sinusoidal than the alpha-like activity of the previous patients. Although it lies in the delta band and could be taken for slow-wave activity, it occurs also during periods where caretakers interact with the patients, and it much faster than the patients SWS activity, which can be clearly delineated in the patient's spectrogram. We, therefore, believe this activity corresponds to the alpha-like activity in the other patients. During an undisturbed period at the beginning of the night, we found irregular theta activity together with some REMs and an absence of 1–3 Hz activity. We score this as a brief period of R.

Patient 10

The spectrogram of this patient shows three periods of SWS between 3:00 am and 7:00 am (Supplementary Figure S7). During these periods, very slow (<1 Hz) activity can be seen in the sleep recording. These slow waves have the typical shape of sleep slow waves. In the evening before 3:00 am, the EEG is dominated by strong 2–4 Hz activity, which, as in patient 7, can be distinguished from SWS. Because of its regular sinusoidal shape, we score it as alpha-like activity and W[I]. In the morning, alpha-like activity alternates with slightly faster regular and irregular theta activity, which we score as W[A]. During a period with only a minimum of 2–4 Hz activity, we see a few small eye movements that could represent REMs. We, therefore, score some epochs as uncertain R. Sleep spindles were not found.

The power spectra of channel C3 of all eight patients can be found in Supplementary Figure S8. The figure shows a single peak in the spectrum in most patients. This peak is not found in the alpha band, but in a lower range between 2 and 7 Hz depending on the patient. The individual alpha-like frequency band for each patient is shown in Table 1. Comparing all six recorded channels, we did not observe any obvious topography (e.g. anterior-posterior) of alpha-like activity across the scalp.

Discussion

Polysomnographic recordings in CLIS patients show that these patients have a circadian sleep-wake pattern. All patients show <1 Hz slow-wave activity during one or several periods during the night. In most patients, the dominant activity outside of SWS was a regular, sinusoidal 4–6 Hz or 2–4 Hz activity, which resembles alpha activity in its distribution and burst-like behavior. This inactive wakefulness could be discriminated from active wakefulness in most patients, with active wakefulness showing irregular, higher frequency activity. Sleep spindles were absent in half of the patients. REM sleep was clearly present in two patients and probably present in most. Impaired REM sleep and lack of sleep spindles were independent, as the two patients showing the strongest REM sleep did not present any sleep spindles.

Slow activity dominates the EEG of CLIS patients during sleep and wakefulness. The slow waves of SWS have their typical frequency in some patients, in others they appear to be distinctly slower. However, all patients have slow waves in the range below 1 Hz, which can be easily detected by visual scoring or automatic analysis in the EEG. The timing of this activity, which occurs mainly after midnight and before 6:00 am in the morning, and which represents the slowest activity for each patient, leaves little doubt, that this activity actually represents SWS. All patients thus showed one or more periods of clear S3 or S4 sleep. Consistent with expectations, in both patients for which heart rate data was available, heart rate was decreasing or minimal during periods scored as SWS. During the 12-hour section of the circadian rhythm that we have recorded, we found longer stretches with slow-wave activity, which were mostly split into several consecutive periods. Night-time periods with and without slow-wave activity did not differ systematically with regard to light or other stimulation, except that sometimes a period of slow-wave activity ended with EMG activation (patient being moved). Our findings speak to an astonishingly well-conserved circadian rhythm, at least within our period of observation. It is, however, possible that there are additional periods of sleep during daytime that we did not record in the present study. Moreover, there might be periods of light S2 sleep, which we have not detected because of the lack of sleep spindles in most patients.

There is, however, another type of slow activity, which can be confounded with SWS in more than half of the patients. Most of the recordings are dominated by a regular oscillation in the upper delta/lower theta range (2–7 Hz). Several reasons speak against this activity being sleep-related. First, it appears at all times of day throughout the recordings: more strongly in the evenings, but also in the mornings. It often continues throughout periods of interaction with the patient. Second, it is distinct from the slower <1 Hz oscillations, which occur during the night, and mostly disappear during these periods. Third, this oscillation has a regular, sinusoidal shape, occurs in 5- to 20-second bursts, and has a waxing and waning amplitude during these bursts. Its shape clearly distinguishes it from theta and delta activity, which is usually more sawtooth or rectangular shaped. In most patients, it is also reflected by a single, pronounced peak in the power spectrum. Apart from the lower frequency, it is therefore strongly reminiscent of periods of alpha, which occur during resting wakefulness with eyes closed in healthy participants.

CLIS patients have their eyes closed most of the time to prevent drying of the eyeballs. It could, therefore, be expected to see strong alpha oscillations, but none are found in the 8–12 Hz range in any patient. Previous studies in locked-in ALS patients also showed a significant reduction in the alpha band over the central electrodes [32]. Moreover, our observations confirm the observations of Hohmann *et al.* [33], who showed in two CLIS patients that alpha frequency activity has completely disappeared and shifted towards lower frequencies. We, therefore, hypothesize that the continuous alpha activity is gradually slowing in frequency throughout the progression of the disease, may be due to lack of sensory stimulation or overuse of alpha-generating circuitry. This, however, remains open for further investigation.

In fact, there are reports of “alpha coma” and dominant alpha-theta activity in locked-in patients that are not completely locked-in [34, 35]. The alpha-like theta/delta oscillation might, therefore, serve as an indicator of absence of slow-wave sleep. In healthy participants, alpha activity serves, together with rolling eye movements, as an indicator of falling asleep (S1). No CLIS patient showed rolling eye movements. Because of the persistence of alpha-like activity, the impossibility to describe consistent and distinct features of wake EEG in these patients, and the lack of light S2 sleep in most patients, it was impossible to distinguish a transitory S1 sleep stage in CLIS patients. We have therefore described the state of continuous (>50% of an epoch) alpha-like activity as inactive wakefulness (W[I]). During most parts of the day, this stage alternates with periods of active wakefulness, which has faster more irregular activity with lower amplitudes.

Sleep spindles (11–17 Hz), are the hallmark of light S2 sleep. These were completely absent in four out of eight patients. The lack of sleep spindles mirrors the findings by Pavlov *et al.* [36], who also found few or no spindles in most of their non-responsive (vegetative state) patients. It is yet unclear when and why sleep spindles cease to occur in these patients. As spindles have been linked to the reprocessing of new memories during sleep [37], one might speculate that the daily routine of the patients with lack of change or new information renders sleep spindles superfluous. It is conceivable that the frequency of spindle oscillations also slows with the progression of the disease, but we have not found any indication of such a slowing. In fact, in those patients with spindles, these had all typical characteristics of sleep spindles in healthy participants. K-complexes, which often have a higher frequency than full slow-waves, were difficult to delineate. The presence of high-amplitude delta and theta band activity during wakefulness prevents the clear definition of individual K-complexes. However, no periods resembling S2 sleep (low-amplitude activity with a few, clearly delineated high-amplitude waves) were found in patients that did not also show sleep spindles.

Scoring of REM sleep according to standard rules relies largely on eye movements and muscle tone changes. Although patients in CLIS cannot produce any voluntary eye movements or muscle contractions, we found strong REMs during sleep in two patients and rudimentary eye movements during sleep in another four patients. This finding indicates that voluntary and autonomous eye movement control can be independent in CLIS patients. REM sleep-like irregular theta activity with medium amplitude was present during these REM periods. Scoring of REM sleep by EEG alone, which is feasible by experienced scorers in healthy patients, was impossible in our patients. The EEG could only be used in conjunction with the eye movement signal, and confident judgments of REM sleep were only possible in a few patients. Heart rate, which was unfortunately available only in patients 1 and 5, might be an additional helpful parameter for scoring REM sleep. In both patients, heart rate during periods scored as REM sleep or potential REM sleep was higher than during periods scored as sleep, and variability of the heart rate was greater. Further studies should consider placing explicit ECG electrodes.

Although we did not find any increase in spectral power during REM sleep, we noticed a distinctive decline in 2–3 Hz activity in the spectrograms of those patients with strong REMs. We found similar periods of distinctly decreased power in this frequency band in most patients. Visual inspection of the EEG during these periods visually confirmed REM sleep-like theta activity with small deflections in the EOG trace that could not be accounted for other than by eye movements (e.g. no corresponding activity in the EEG traces, no movement artifacts). These eye movements are much smaller and fewer than those habitually seen in healthy participants, but still, as there are no other sources of artifacts in CLIS patients, they can be taken as signs of autonomous eye movement activity. We can thus confirm the presence of REM sleep in some CLIS patients and the presence of possible REM sleep in most. However, new rules for scoring REM sleep, perhaps based on spectral EEG power, should be developed to increase sleep scoring accuracy in these patients. The present data indicates that REM sleep seems to be uncoupled from the typical NREM-REM cycle and to occur at different times of the day. This pattern might be related to the lack of movement and structure in the daily routine of the patients or to an uncoupling of circadian and ultradian cycles. Comparison with other bed-ridden patients might illuminate this aspect of CLIS sleep.

The analysis of the nighttime EEG demonstrates that patients in CLIS with ALS show slow-wave sleep episodes comparable to the healthy aged population. The two younger patients (9 and 10), suffering from a genetically determined ALS, do not substantially differ from the older ALS patients. Overall, sleep is fragmented, as already noticed [27], in these completely inactive patients, which spend most of their time, some of them since more than 5 years, in a completely paralyzed state in their bed, with only some transfer to the wheelchair during daytime. This constant, mostly bedridden routine and closed eyes, weakening the influence of light as the most potent zeitgeber, might be one reason for the disruption of the NREM-REM cycle and the absence of some of the typical sleep signs. Further studies should include neuroimaging to allow a more mechanistic investigation of the relation between pathologic changes in the brain and in sleep. Still, the maintenance of SWS in all patients might be an important factor contributing to preserve the quality of life in patients in an advanced locked-in state. Undisturbed nighttime sleep should, therefore, be aimed at in CLIS patient care.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Appendix 2.

J. Martínez-Cerveró, M. Khalili-Ardali, **A. Jaramillo-Gonzalez**, S. Wu, A. Tonin, A. Tonin, N. Birbaumer, U. Chaudhary (2020). Open Software/Hardware Platform for Human-Computer Interface Based on Electrooculography (EOG) Signal Classification, *Sensors*, 20(9), 2443. https://doi.org/10.3390/s20092443

sensors

MDPI

Article

Open Software/Hardware Platform for Human-Computer Interface Based on Electrooculography (EOG) Signal Classification

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Abstract: Electrooculography (EOG) signals have been widely used in Human-Computer Interfaces (HCI). The HCI systems proposed in the literature make use of self-designed or closed environments, which restrict the number of potential users and applications. Here, we present a system for classifying four directions of eye movements employing EOG signals. The system is based on open source ecosystems, the Raspberry Pi single-board computer, the OpenBCI biosignal acquisition device, and an open-source python library. The designed system provides a cheap, compact, and easy to carry system that can be replicated or modified. We used Maximum, Minimum, and Median trial values as features to create a Support Vector Machine (SVM) classifier. A mean of 90% accuracy was obtained from 7 out of 10 subjects for online classification of Up, Down, Left, and Right movements. This classification system can be used as an input for an HCI, i.e., for assisted communication in paralyzed people.

Keywords: electrooculography (EOG); Human-Computer Interface (HCI); Support Vector Machine (SVM)

1. Introduction

In the past few years, we have seen an exponential growth in the development of Human-Computer Interface (HCI) systems. These systems have been applied for a wide range of purposes like controlling a computer cursor [1], a virtual keyboard [2], a prosthesis [3], or a wheelchair [4–7]. They could also be used for patient rehabilitation and communication [8–11]. HCI systems can make use of different input signals such as voice [7], electromyography (EMG) [12], electroencephalography (EEG) [13], near-infrared spectroscopy (NIRS) [14–16] or electrooculography (EOG) [5].

In this paper, we describe an EOG classification system capable of accurately and consistently classifying Up, Down, Left, and Right eye movements. The system is small, easy to carry, with considerable autonomy, and economical. It was developed using open hardware and software, not only because of economic reasons, but also to ensure that the system could reach as many people as possible and could be improved and adapted in the future by anyone with the required skills.

The end goal of this work is to build a system that could be easily connected to a communication or movement assistance device like a wheelchair, any kind of speller application, or merely a computer mouse and a virtual keyboard.

To achieve these objectives, we have developed and integrated the code needed for:

- Acquiring the Electrooculography (EOG) signals.

- Processing these signals.
- Extracting the signal features.
- Classifying the features previously extracted.

EOG measures the dipole direction changes of the eyeball, with the positive pole in the front [17]. The technique of recording these potentials was introduced for diagnostic purposes in the 1930s by R. Jung [18]. The presence of electrically active nerves in the posterior part of the eyeball, where the retina is placed, and the front part, mainly the cornea, creates the difference in potential on which EOG is based [19]. This creates an electrical dipole between the cornea and the retina, and its movements generates the potential differences that we can record in an EOG.

There are several EOG HCI solutions present in the literature. One of the issues with current HCI systems is their size and lack of autonomy, the use of proprietary software, or being based on self-designed acquisition and processing devices. Regarding the acquisition system, the most common approach is to use a self-designed acquisition device [1,4,20–22]. In our view, this solution dramatically restricts the number of users who can adopt this system. Other proposed systems make use of commercial amplifiers [23,24], which in turn make use of proprietary software and require robust processing systems, mainly laptops. This also reduces the number of potential users of the system and its applications since it increases the cost of the system and reduces its flexibility, portability, and autonomy. As far as signal processing is concerned, most systems choose to use a laptop to carry out these calculations [1,20–22,24,25], but we can also find the use of self-designed boards [6,26]. Table 1 shows the characteristics of some solutions present in literature as a representation of the current state of the art. The goal of our work is to achieve results equivalent to the present state of the art using an open paradigm, demonstrating that it is possible to arrive at a solution using cheaper components that could be modified to build a tailored solution. As far as we know, this is the first time that an open system is presented in this scope.

Table 1. Comparison of results between different studies.

Study	Movements	Acquisition	Processing	Method	Accuracy
Qi et al. [27]	Up, Down, Left, Right	Commercial	-	Offline	70%
Guo et al. [28]	Up, Down, Blink	Commercial	Laptop	Online	84%
Kherlopian et al. [24]	Left, Right, Center	Commercial	Laptop	Online	80%
Wu et al. [20]	Up, Down, Left, Right, Up-Right, Up-Left, Down-Right, Down-Left	Self-designed	Laptop	Online	88.59%
Heo et al. [26]	Up, Down, Left, Right, Blink	Self-designed	Self-designed + Laptop	Online	91.25%
Heo et al. [26]	Double Blink	Self-designed	Self-designed + Laptop	Online	95.12%
Erkaymaz et al. [29]	Up, Down, Left, Right, Blink, Tic	Commercial	Laptop	Offline	93.82%
Merino et al. [27]	Up, Down, Left, Right	Commercial	Laptop	Online	94.11%
Huang et al. [21]	Blink	Self-designed	Laptop	Online	96.7%
Lv et al. [19]	Up, Down, Left, Right	Commercial	Laptop	Offline	99%
Yathunanthan et al. [6]	Up, Down, Left, Right	Self-designed	Self-designed	Online	99%

In our system, the signal is acquired using the OpenBCI Cyton Board (Raspberry Pi 3B+ official website), a low-cost open software/hardware biosensing device, resulting in an open hardware/software-based system that is portable, with considerable autonomy and flexibility.

Once we have the EOG signal, this is processed using a Raspberry Pi (OpenBCI Cyton official website), a single board computer that allows installing a Linux-based distribution, which is small, cheap, and gives us the option to use non-proprietary software.

Features are then extracted from the acquired signal and classified employing a machine learning algorithm. The feature extraction process aims to reduce the dimensionality of the input data without losing relevant information for classification [28] and maximizing the separation between elements of different classes by minimizing it between elements of the same class [27]. To achieve this, several models have been proposed on EOG feature extraction [29–32]. We employed Support Vector Machine (SVM) to classify the data [33,34], which creates a boundary to split the given data points into two different groups.

The result of this process, in the context of signal (EOG) mentioned in this article, is the classification of the subject's eye movement to be used as input commands for further systems. This process and the tools used for it are explained in detail in Section 2. The Section 3 shows the performance achieved by the system. Finally, in the Section 4, we discuss the designed system and compare our system with existing related work along with the limitations of our system and future work.

2. Materials and Methods

2.1. Hardware-Software Integration

In the present study, OpenBCI Cyton board was used for the signal acquisition. This board contains a PIC32MX250F128B microcontroller, a Texas Instruments ADS1299 analog/digital converter, a signal amplifier and an eight-channel neural interface. This device is distributed by OpenBCI (USA). Figure 1 depicts the layout of the system.

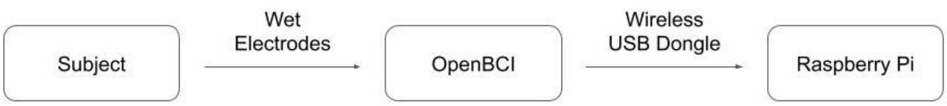

Figure 1. Block diagram with system connection.

This device gives us enough precision and sampling rate (250 Hz) for our needs, it has an open-source environment (including a Python library to work with the boards (OpenBCI Python repository)), it has an active and large community, and it can be powered with a power bank, which is a light and mobile solution. Attached to the board, we have 4 wet electrodes connected to two channels on the board in a differential mode. Differential mode computes the voltage difference between the two electrodes connected to the channel and doesn't need a reference electrode. The two channels correspond to the horizontal and vertical components of the signal.

The acquisition board is connected to a Raspberry Pi, a single-board computer developed by the Raspberry Pi company based in the United Kingdom. Although its firmware is not open source, it allows installing a Linux-based distribution keeping the open paradigm in our system. In this case, we chose to install Raspbian, a Debian-based distribution. The hardware connection between the OpenBCI board and the Raspberry Pi is made using a wireless RFDuino USB dongle. On the software side, we used an open Python library released by OpenBCI. To run this library over the Raspberry Pi, the source code of the mentioned library has been partially modified. It has also been necessary to recompile some third-party libraries so that they could run on the Raspberry Pi. We decided to power both the OpenBCI board and the Raspberry Pi via a USB connection to a power bank (20,000 mAh) to maximize the system autonomy and mobility.

This hardware configuration offers us all the characteristics that we were looking for: it has enough computational power to carry our calculations, it's small and light, it allows us to use free and open-source software, and is economical. It should be noted that although we have used the OpenBCI board as acquisition system there are some other solutions that fit our needs like the BITalino biosignal acquisition board. This board offers an EOG acquisition module and an open environment which includes a Python-based API for connection and signal acquisition over Raspberry Pi.

It should be mentioned that the data presented in this article have been processed using a conventional laptop instead of the Raspberry Pi, just for the convenience of the experimenters. During the development of the research, several tests were carried out that did not show any difference in the data or the results depending on the platform used.

We decided to use EOG over other eye movement detection techniques like Infrared Reflection Oculography (IROG) [35] or video-based systems [25], as the EOG technique does not require the placement of any device that could obstruct the subjects' visual field. Four electrodes were placed in contact with the skin close to the eyes to record both the horizontal and the vertical components of the eye movements [36,37].

2.2. Experimental Paradigm

Ten healthy subjects between 24 and 35 years old participated in the study and gave their informed consent for inclusion. The signal acquisition was performed in two stages: training and online prediction. For both stages, we asked the subjects to perform four different movements: Up, Down, Left, and Right. Each movement should start with the subject looking forward and then look at one of these four points already mentioned and look again at the center. For the training stage, we acquired two blocks of 20 trials, 5 trials per movement. In these blocks, five "beep" tones were presented to the subject at the beginning of each block in 3 s intervals to indicate the subject the interval that they had to perform the requested action. After these initial tones, the desired action was presented via audio, and a "beep" tone was presented as a cue to perform the action. The system recorded during the 3 s after this tone was presented, and the system presented again another action to be performed. For some of the subjects, these two training blocks were appended in a single data file. The schematic of the training paradigm (offline acquisition) is shown in Figure 2a.

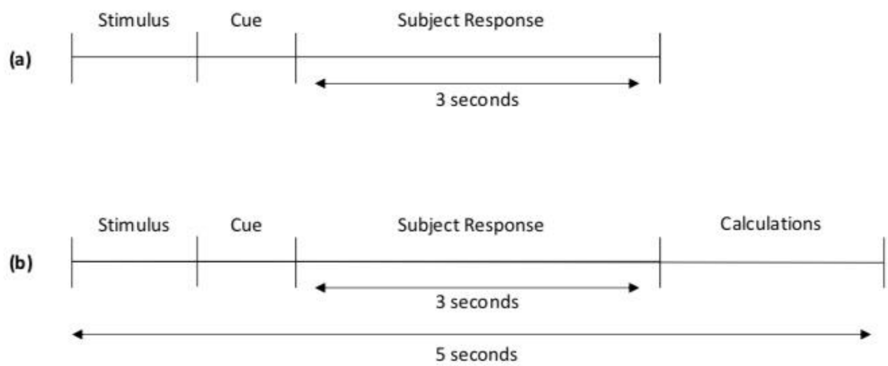

Figure 2. Acquisition paradigm. (**a**) Offline acquisition. (**b**) Online acquisition.

The online classification was performed with a block of 40 trials, 10 per movement, on Subject 1. After this experiment, we decided to reduce the number of trials per block to 20, 5 per movement, for the convenience of the subject. This online block had the same characteristics as the classification blocks except that the five initial tones were not presented, and the actions to be performed were separated by 5 s interval to have enough time for the prediction tasks. Furthermore, in these blocks, the system recorded only during the 3 s after the cue tone was presented. During this stage, we generate two auxiliary files: one with the acquired data and the other containing the action that the user should perform and the action predicted. We only considered predicted actions with a prediction probability higher than a certain threshold. For the first subject, we set this threshold as 0.7, but after that experiment, we changed the threshold to 0.5. In this case, the auxiliary file corresponding to subject 1 contains the predictions made using 0.7 as a prediction probability threshold. Figure 2b depicts the schematic of the online prediction paradigm.

2.3. Signal Processing

A second-order 20 Hz lowpass Butterworth filer [37] was used to remove the artifacts arising from electrodes or head movements and illumination changes [19,27,38]. A 20 Hz lowpass filter was used because the artifacts, as mentioned earlier, appear in the high frequencies [17], and the EOG signal information is contained mainly in low frequencies [30]. The irregularities in the signal after the lowpass filter were removed using a smoothing filter [30]. For applying these filters, we used the SciPy library. This library is commonly used and has a big community supporting it.

The last step in pre-processing was to standardize the data. This is done to remove the baseline of EOG signals [27]. The standardization was done using the following formula:

$$X_t = \frac{x_t - \mu_i}{\sigma_i}, \tag{1}$$

where i is the sample that we are processing, t corresponds to a single datapoint inside a sample, X_t is the resulting datapoint, x_t is the data point value before standardization, μ_i is the mean value of the whole sample and σ_i is the standard deviation of the whole sample. An example of the processed signal can be seen in Figure 3, which shows a single Down trial extracted from a classification block of Subject 5.

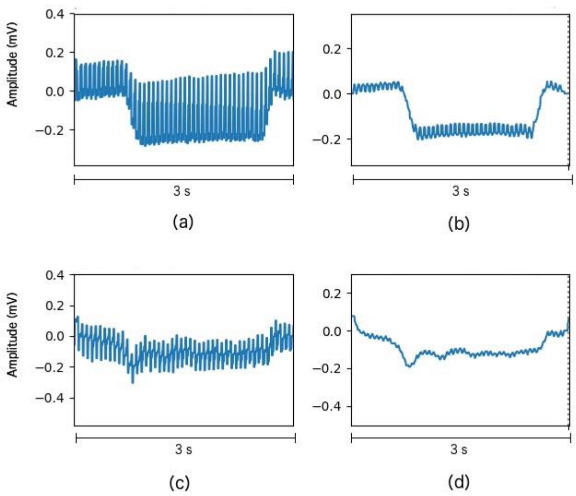

Figure 3. Down movement example taken from Subject 5. The x-axis depicts time (in seconds), and Y-axis represents the signal amplitude (in millivolts). (**a**) Unfiltered vertical component. (**b**) Filtered vertical component. (**c**) Unfiltered horizontal component. (**d**) Filtered horizontal component.

Figure 4 depicts the vertical and horizontal component for four different eye movement tasks performed by subject 5.

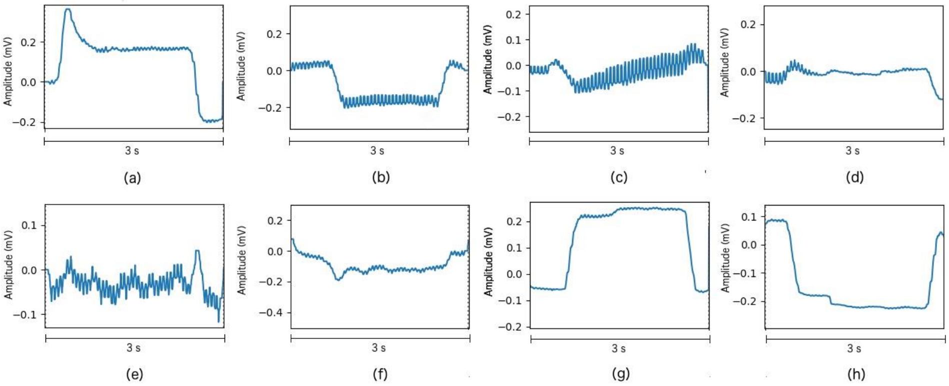

Figure 4. Processed signals examples taken from Subject 5. The x-axis depicts time (in seconds), and Y-axis represents the signal amplitude (in millivolts). (**a**) Vertical component for Up movement. (**b**) Vertical component for Down Movement. (**c**) Vertical component for Left movement. (**d**) Vertical component for the Right movement. (**e**) Horizontal component for Up movement. (**f**) Horizontal component for Down movement. (**g**) Horizontal component for Left movement. (**h**) Horizontal component for Right movement.

2.4. Feature Extraction

An essential step in our system's signal processing pipeline is feature extraction, which for each sample, calculates specific characteristics that will allow us to maximize the distance between elements in different classes and the similarity between those that belong to the same category. We use a model based on the calculation of 3 features for the horizontal and vertical components of our signal, i.e., 6 total features per sample. The features are the following:

- Min: The minimum amplitude value during the eye movement.
- Max: The maximum amplitude value during the eye movement.
- Median: The amplitude value during the eye movement that has 50% values above as below.

2.5. Classification

Once we have calculated the features of each sample, we create a model using that feature values and its class labels. Even though some biosignal-based HCI use other machine learning techniques, such as artificial neural networks [29,36] or other statistical techniques [19], most of the HCI present in the literature use the machine learning technique called Support Vector Machine. We have decided to use SVM because of its simplicity over other techniques, which results in a lower computational cost and excellent performance.

In this study, we have used the implementation of the SVM of Scikit-Learn, a free and open-source Machine Learning Python library. This library has a high reputation in Machine Learning, and it has been widely used. The selected parameters for creating the model are a Radial Basis Function (RBF) as kernel [39], which allows us to create a model using data points that are not linearly separable [40], and a One vs. One strategy [41], i.e., creating a classifier for each pair of movement classes. Finally, we have performed 5-fold cross-validation [42], splitting the training dataset into 5 mutually exclusive subsets and also creating 5 models, each one using one of these subsets to test the model and the other four to create it. Our model accuracy is calculated as the mean of these 5 models.

3. Results

The acquired signal is processed to remove those signal components that contain no information, resulting in a clearer signal. The data were acquired from 10 healthy subjects between 24 and 35 years old. The result of signal processing can be seen in Figures 3 and 4, which shows the single trials of a training block performed by Subject 5. As Figures 3 and 4 show, the result of this step is the one expected. For Subject 8, we found flat or poor-quality signals in the vertical and horizontal component, so we decided to stop the acquisition and discard these data. Some trials extracted from this discarded block can be seen in Figure 5 which shows no clear steps or any other patterns for the four movements. This situation is probably due to an electrode movement, detachment, or misplacement that could not be solved during the experiment.

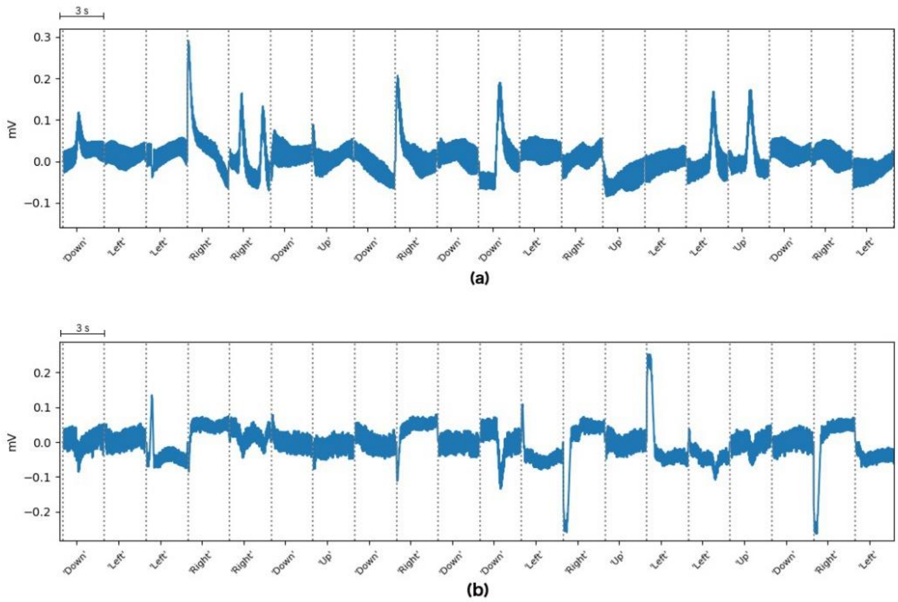

Figure 5. Example trials taken from Subject 8. The x-axis depicts time (each trial is 3 s), and Y-axis represents the signal amplitude (in millivolts). (**a**) Vertical component. (**b**) Horizontal component.

After artifact removal, feature extraction is performed to reduce the dimensionality in input, leading to characteristics that define the signal without information loss. As mentioned above, the features used were Maximum, Minimum, and Median. It should be noticed that Up and Down movements have relevant information only for the vertical channel of our signal as well as Left and Right movements have this relevant information in the horizontal component. Figures 6 and 7 present an example of this feature extraction process over two blocks of 20 trials, each corresponding to the training data of Subject 5, who ended up with 100% accuracy. Figures 8 and 9 present an example of the same feature extraction process over two blocks of 20 trials performed by Subject 6, who ended up with 78.7% accuracy. In these figures, we can appreciate that Subject 5, with 100% accuracy, shows a more evident difference in the data values than Subject 6, with 78.7% accuracy. Figures 8 and 9 show some overlapping in the data values, which explains the lower classification accuracy achieved.

The last step in our pipeline is to build a model and perform an online classification of the subject's eye movements. As we mentioned before, we build our model using 5-fold cross-validation. Table 2 shows the model accuracy, the accuracy-related on how good the model has been classifying the training data, as the mean of these five models for each subject. For the prediction accuracy—the accuracy related to the prediction of unseen data—we have asked the subject to perform 20 movements per block (five of each movement), as is explained in Section 2.2. We predicted those movements using the pre-built model and, finally, validated how accurate that prediction was.

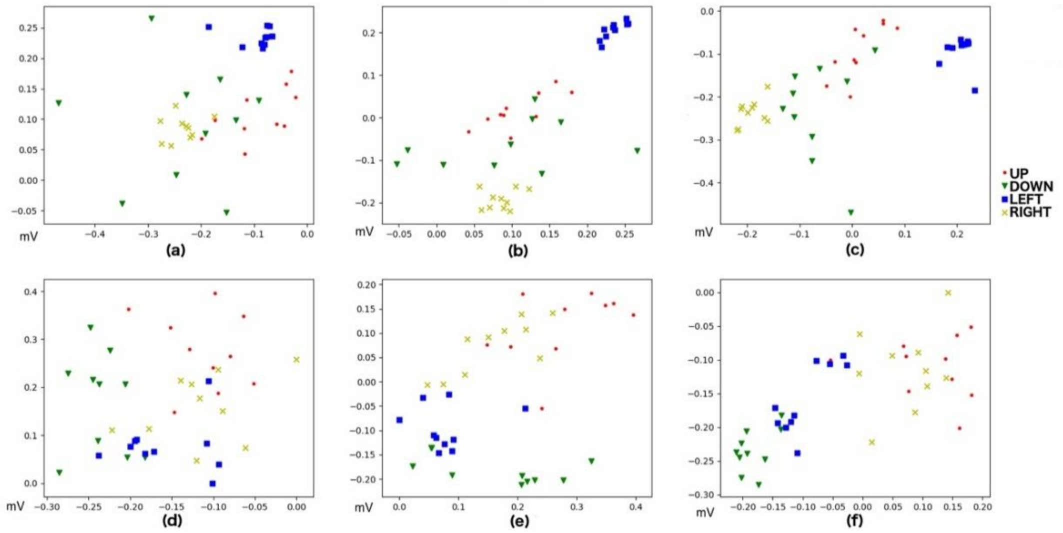

Figure 6. Values after Feature Extraction for Up, Down, Left, and Right movements performed by Subject 5 (100% model accuracy). Both *X*-axis and *Y*-axis depict signal values (in millivolts). (**a**) Horizontal Min vs. Max. (**b**) Horizontal Max vs. Median. (**c**) Horizontal Median vs. Min. (**d**) Vertical Min vs. Max. (**e**) Vertical Max vs. Median. (**f**) Median vs. Min.

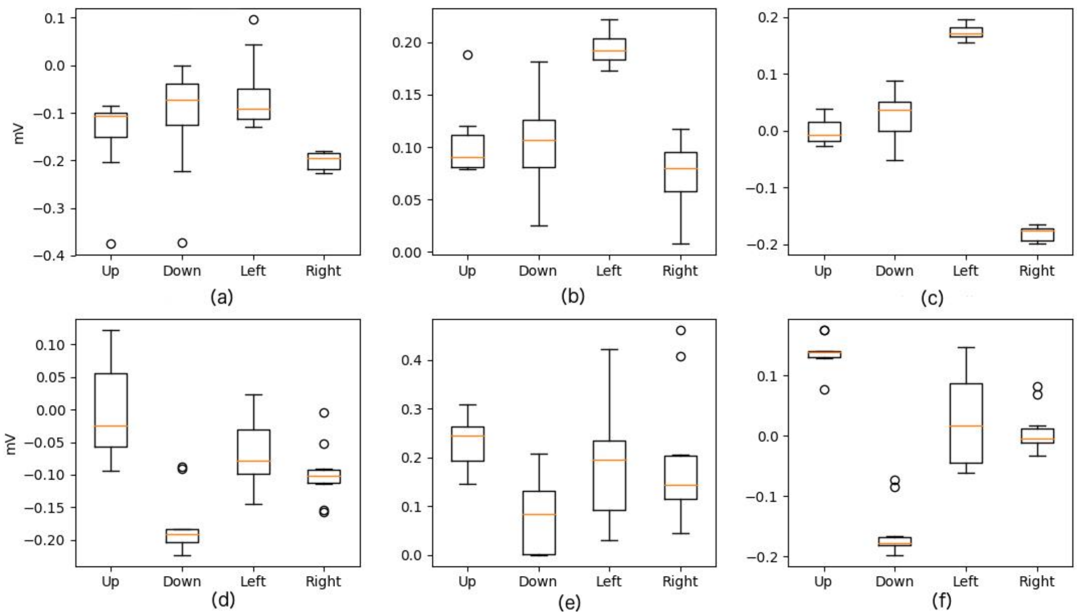

Figure 7. Values after Feature Extraction for Up, Down, Left, and Right Movements performed by Subject 5 (100% model accuracy). The *x*-axis depicts movement class, and *Y*-axis depicts signal amplitude (in millivolts). (**a**) Horizontal Min. (**b**) Horizontal Max. (**c**) Horizontal Median. (**d**) Vertical Min. (**e**) Vertical Max. (**f**) Vertical Median.

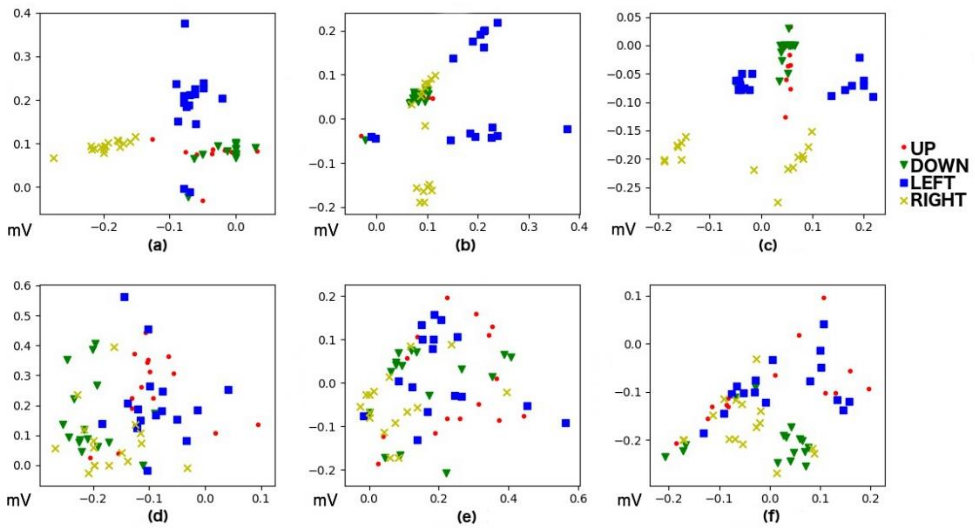

Figure 8. Values after Feature Extraction for Up, Down, Left, and Right movements performed by Subject 6 (78.7% model accuracy). Both *X*-axis and *Y*-axis depict signal values (in millivolts). (**a**) Horizontal Min vs. Max. (**b**) Horizontal Max vs. Median. (**c**) Horizontal Median vs. Min. (**d**) Vertical Min vs. Max. (**e**) Vertical Max vs. Median. (**f**) Median vs. Min.

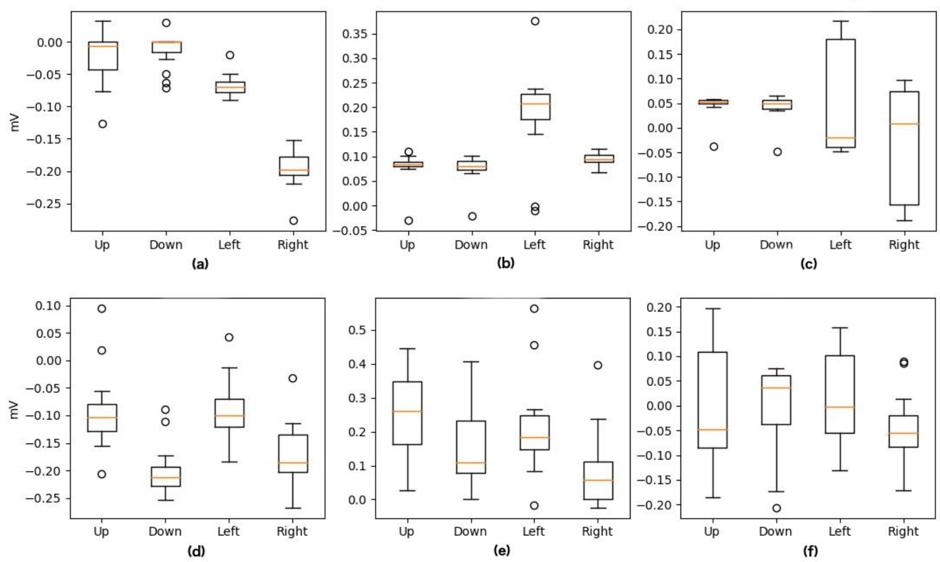

Figure 9. Values after Feature Extraction for Up, Down, Left, and Right Movements performed by Subject 6 (78.7% model accuracy). The *x*-axis depicts movement class, and *Y*-axis depicts signal amplitude (in millivolts). (**a**) Horizontal Min. (**b**) Horizontal Max. (**c**) Horizontal Median. (**d**) Vertical Min. (**e**) Vertical Max. (**f**) Vertical Median.

Table 2. Model and Prediction Accuracies.

Subject	Model Mean Accuracy	Online Accuracy
Subject 1	100%	90%
Subject 2	100%	95%
Subject 3	92.5%	85%
Subject 5	100%	100%
Subject 6	78.7%	85%
Subject 7	97.5%	95%
Subject 10	90.8%	80%
MEAN	94.21%	90%

As mentioned in Section 2.2., we only consider those predicted actions with a prediction probability higher than 0.5. For subject 1, the prediction probability threshold was set to 0.7 during the online acquisition, so the auxiliary file with the predictions corresponds to this threshold, and after experimenting, we re-analyzed the online data using a 0.5 threshold.

We acquired one single online block for subjects 1, 2, 5 and 7. For subject 3, we acquired three online blocks with 50%, 80%, and 85% accuracy. For subject 6, we acquired two online blocks with 80% and 85% accuracy. For subject 10, we acquired three online blocks with 55%, 70%, and 80% accuracy. It can be seen that for all subjects, the online accuracy increases with each block acquisition. The accuracy shown in Table 1 corresponds to those online blocks with the highest accuracy for each subject. For subject 4, the training and online data have poor quality (66.7% accuracy for the model and 20% accuracy for the online prediction). Subject 9 had a good model accuracy (95%) but poor-quality signals during online acquisition (50% and 20% accuracy). Post-experimental analysis of the data revealed noisy and flat signals, showing no clear pattern in the signal acquired from subjects 4 and 9, similar to the signal acquired from Subject 8 (Please see Figure 5 for the signal from patient 8). These distortions may have arisen due to the probable electrode movement, detachment, or misplacement. Thus, we decided to discard the data from Subjects 4, 8 and 9.

4. Discussion

It must be clear that in order to make a completely fair comparison between our system and the state-of-the-art systems, some extensive testing would be required. These tests should process the data acquired in this study with other processing pipelines, run our pipeline over the data acquired in other studies, and adapt our acquisition and processing modules to be connected to further systems found in the literature. The results obtained after this process would give us a full picture of the differences between our system and those already in place. Unfortunately, due to lack of time and materials, these tests could not be carried out.

Concentration loss and tiredness are two of the biggest challenges when it comes to EOG-based HCI. As reported in Barea et al. [43], the number of failures using this kind of system increases over time after a specific period of use. This has been seen during the development of this study, where long periods of system use have led to the appearance of irritation and watery eyes. This could be a problem for subjects who use the system for a long time. In the paper above mentioned [43], the researchers deal with this problem by retraining the system.

Another challenge related to our system is the presence of unintentional eye blinks. Eye blinks create artifacts in the EOG signal and, also, during the eye blinks, there is a slight eye movement [37]. The trials containing eye blinks can lead to a reduced model accuracy if it occurs in the training stage or to a trial misclassification if it is in the online acquisition stage. Pander et al. [44], and Merino et al. [30] have proposed methods to detect spontaneous blinks so these trials can be rejected. Yathunanthan et al. [6] proposed a system where eye blinks are automatically discarded.

Our system, like most of the available systems in the literature [19–21,29,30,38,43], uses a discrete approach, i.e., the user is not free to perform an action when desired, but the action must be performed at a specific time. This affects the agility of the system by increasing the time needed to perform an action. Barea et al. [38,43] and Arai et al. [25] have proposed systems with a continuous approach where the subject has no time restrictions to perform an action.

There are different ways to improve our system in future work. First, we could put in place a mechanism to detect and remove unintentional blinks. This would prevent us discarding training blocks, or could improve the training accuracy in the cases in which these unintentional blinks occur. In some cases, a continuous online classification means a considerable advantage. Therefore, it would be interesting to add the necessary strategies to perform this type of classification. Finally, by combining our system with further communication or movement assistance systems, we could check its performance in a complete HCI loop.

5. Conclusions

We have presented an EOG signal classification system that can achieve a 90% mean accuracy in online classifications. These results are equivalent to other state-of-the-art systems. Our system is built using only open components, showing that it is possible to avoid the usage of expensive and proprietary tools in this scope. As intended, the system is small, easy to carry, and has complete autonomy. This is achieved using OpenBCI and Raspberry Pi as hardware, connected to a power bank as a power source.

Because of the use of open hardware and software technologies, the system is also open, easy to replicate, and can be improved or modified by someone with the required skills to build a tailored solution. The use of open technologies also helps us to obtain a cheap platform.

Finally, the resulting system is easy to connect to subsequent communication or movement assistance systems.

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Sample Availability: Corresponding code and data are available at https://github.com/JayroMartinez/EOG-Classification.

Appendix 3.

A. Tonin & **A. Jaramillo-Gonzalez**, A. Rana, M. Khalili-Ardali, N. Birbaumer, U. Chaudhary (2020). Auditory Electrooculogram-based Communication System for ALS Patients in Transition from Locked-in to Complete Locked-in State, *Nature Scientific Reports,* 10, 8452. https://doi.org/10.1038/s41598-020-65333-1

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Auditory Electrooculogram-based Communication System for ALS Patients in Transition from Locked-in to Complete Locked-in State

Alessandro Tonin[1,3], Andres Jaramillo-Gonzalez[1,3], Aygul Rana[1], Majid Khalili-Ardali[1], Niels Birbaumer[1] & Ujwal Chaudhary[1,2]✉

Patients in the transition from locked-in (i.e., a state of almost complete paralysis with voluntary eye movement control, eye blinks or twitches of face muscles, and preserved consciousness) to complete locked-in state (i.e., total paralysis including paralysis of eye-muscles and loss of gaze-fixation, combined with preserved consciousness) are left without any means of communication. An auditory communication system based on electrooculogram (EOG) was developed to enable such patients to communicate. Four amyotrophic lateral sclerosis patients in transition from locked-in state to completely locked-in state, with ALSFRS-R score of 0, unable to use eye trackers for communication, learned to use an auditory EOG-based communication system. The patients, with eye-movement amplitude between the range of ±200µV and ±40µV, were able to form complete sentences and communicate independently and freely, selecting letters from an auditory speller system. A follow-up of one year with one patient shows the feasibility of the proposed system in long-term use and the correlation between speller performance and eye-movement decay. The results of the auditory speller system have the potential to provide a means of communication to patient populations without gaze fixation ability and with low eye-movement amplitude range.

Swiss philosopher Ludwig Hohl stated that "The Human being lives according to its capacity to communicate, losing communication means losing life"[1]. Our ability to communicate ideas, thoughts, desires, and emotions shapes and ensures our existence in a social environment. There are several neuronal disorders, such as amyotrophic lateral sclerosis (ALS), or brain stem stroke, among others, which paralyzes the affected individuals severely impairing their communication capacity[2–5]. The affected paralyzed individuals with intact consciousness, voluntary eye movement control, eye blinks, or twitches of other muscles are said to be in locked-in state (LIS)[6–11].

Early and modern descriptions of ALS disease emphasize that oculomotor functions are either spared or resistant to the progression of the disease[9], and consequently, eye-tracking devices can be used to enable patients in the advanced state of ALS to communicate[12,13]. Besides, longitudinal studies evaluating eye-tracking as a tool for cognitive assessment report that the progression of the disease does not affect eye-tracking performance[9]. Nevertheless, a subset of the literature reports a wide range of oculomotor dysfunctions in these patients[14–17] that might prevent the use of eye-tracking devices[18]. The most used metric to evaluate the patient's degree of functional impairment is the revised ALS functional rating scale (ALSFRS-R)[19], which is not a precise measure of the ability to communicate. A patient with an ALSFRS-R score of zero can still have eye-movement capability or control over some other muscles of the body, which can be used for communication[8].

CLIS is an extreme type of LIS, which leads to complete body paralysis, including paralysis of eye-muscles combined with preserved consciousness[6,20]; therefore, even if the individuals are incapable of voluntary control of any muscular channels of the body, they might remain cognitively intact[9]. Several systemic or traumatic

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neurological diseases may result in a LIS with the potential to progress towards CLIS, such as ALS, Guillain-Barré, pontine stroke, end-stage Parkinson disease, multiple sclerosis, traumatic brain injury and others with different etiological and neuropathological features[4,7,10]. In the case of ALS patients in LIS who survive longer attached to life-support systems, the disease progression might ultimately destroy the oculomotor control in many patients, leading to the loss of gaze-fixation[17]. Thus, patients become unable to use eye-tracker-based communication technologies and are therefore left without any means of communication. This raises the question, what happens with those ALS patients in transition from LIS to CLIS with highly compromised oculomotor skills unable to retain gaze-fixation, and therefore unable to use eye-tracking systems to communicate?

There is a considerable amount of research related to patients in the early stages of ALS who can successfully achieve communication by using gaze-fixation-based assistive and augmentative communication (AAC) technologies or brain-computer interfaces (BCIs). These patients have intact cognitive skills, residual voluntary movements, intact or partial vision with complete gaze-fixation capabilities. Several examples of communication technologies for ALS patients in LIS can be found in the literature. Concerning BCI-based communication, different types of systems have been developed to provide a means of communication to LIS patients[4,10,11], among the most recognized are the ones based in features of the EEG, as the slow cortical potential[21], or evoked potentials, mainly the P300[22–26] or SSVEP[27]; or the BCIs based in metabolic features, as NIRS[28–31]. Concerning the use of eye-tracking systems, as long as the patients have intact vision and control gaze fixation, commercial systems are an accessible and reliable option to allow them limited communication[32]. Other types of eye-tracking technologies as the scleral search soils, infrared reflection oculography, or video-oculography (or video-based eye-tracking)[33], have not yet been tested on LIS patients to our knowledge. Except for two studies[28,29], all the developed BCIs for ALS patients describe patients with remnant muscular activity, remnant eye movement control, or even without assisted ventilation, and in general with ALSFSR-R score above 15.

The progress of ALS often, if not always, diminishes the general capabilities of the patients making BCI-based communication impossible[7,24]. On the other hand, even though eye movement might be the last remnant voluntary movement before CLIS[34], during this transitional state from LIS to CLIS, patients become unable to maintain gaze-fixation and, unable to use eye-tracking AAC technologies.

Some electrooculogram (EOG) -based systems have been presented to overcome the limitations of other AAC technologies. However, most of the studies were performed on healthy participants or tested in LIS patients in the early stages of ALS, reporting results of single sessions or sessions performed closely in time, allowing the patients in advanced LIS to reply yes/no questions, but without the feasibility of freely communicate spelling sentences[35,36]. To our knowledge, no studies report on the long-term use of EOG or eye-tracking for patients on the transition from LIS to CLIS, and how this progression affects communication capabilities using these AAC technologies. Either in clinical descriptions or technical applications, very little is known about how this LIS to CLIS progression affects the oculomotor capabilities precluding the patient's communication.

Considering ALS patients in an advanced state, a first meta-analysis has shown that there is a correlation between the progression of physical impairment and BCI performance[7], and a recent one has suggested that the performance of CLIS patients using BCI cannot be differentiated from chance[37]. The only available long-term studies are either single cases for patients able to perform with a P300-based BCI[38,39] or a thoroughly home-based BCI longitudinal study[40] that shows favorable results. However, these studies do not provide details on how the progression affected the performance, particularly for the patients with the lowest ALSFSR-R score.

It has been shown in a single case report[34], that during the transition from LIS to CLIS, despite compromised vision due to the dryness and necrosis of the cornea and inability to fixate, some remaining controllable muscles of the eyes continue to function. Hence, there is an opportunity to develop a technology to provide a means of communication in this critical transition. Such a technology would extend these patients' communication capacities until the point the disease progression destroys any volitional motor control. Pursuing that goal, an EOG-based auditory communication system was developed, which enabled patients to communicate independent of their gaze fixation ability and independent of intact vision. This study was performed with four ALS patients in transition from the locked-in state to the completely locked-in state, with ALSFRS-R score of 0, and unable to use eye-trackers effectively for communication, i.e., without any other means of communication. The patients, with eye-movement amplitude between the range of $\pm 200\,\mu$V and $\pm 40\,\mu$V, were able to form complete sentences and communicate independently and freely, selecting letters from an auditory speller system. Moreover, the study shows the possibility of using the proposed system for a long-term period, and, for one patient, it shows the decay in the oculomotor control, as reflected in EOG signals, until the complete loss of eye control. Such a communication device will have a significant positive effect on the quality of life of completely paralyzed patients and improve mandatory 24-hours-care.

Results

Four advanced ALS patients (P11, P13, P15, and P16) in the transition from LIS to CLIS, all native German speakers (Table 1), used the developed auditory communication system to select letters to form words and hence sentences. All the patients attended to four different types of auditory sessions: training, feedback, copy spelling, and free spelling session. Each training and feedback sessions consisted of 20 questions with known answers (10 questions with "yes" answer and 10 questions with "no" answer, presented in random order), for example, "Berlin is the capital of Germany" vs. "Paris is the capital of Germany". All the questions were presented auditorily. While in the copy and free spelling sessions, the patients were presented the group of characters and each character auditorily (see "Methods" section for the details). Patients were instructed to move the eyes ("eye-movement") to say "yes" and not to move the eyes ("no eye-movement") to say "no". Features of the EOG signal corresponding to "eye-movement" and "no eye-movement" or "yes" and "no" were extracted to train a binary support vector machine (SVM) to identify "yes" and "no" response. This "yes" and "no" response was then used by the patient to auditorily select letters to form words and hence sentences during the feedback and spelling sessions. Due

Patient	Gender/ Age	ALS type	Medical history	Visits
P11	M/33	Non-bulbar	Aug 2015: Diagnosis Aug 2017: Last use of AAC	10 visits over 13 months from March 2018 onwards
P13	M/58	Bulbar	Jan 2011: Diagnosis Jan 2018: Last use of AAC	4 visits over 12 months from Jun 2018 onwards
P15	F/63	Lower motor neuron predominant (ICD-10: G12.2)	Feb 2017: Diagnosis Nov 2018: Last use of AAC	2 visits over 5 months from Feb 2019 onwards
P16	M/56	Lower motor neuron	Dec 2012: Diagnosis Jun 2018: Last use of AAC	2 visits over 3 months from March 2019 onwards

Table 1. List of participants. The table lists the patient's number, the gender and the age at the time of the first visit, the type of diagnosed ALS, year of diagnosis, and the last use of assistive and augmentative communication (AAC) technologies, and the number of performed visits and their time range.

to the degradation of vision in ALS patients[14,16,17], the system was designed to work only in the auditory mode without any video support. We frequently traveled to the patient's home to perform the communication sessions. Each visit (V) lasted for a few days (D), during which the patient performed different session (S) as listed in Supplementary Tables S1–S4.

Eye movement. According to the literature, in healthy subjects, the amplitude of the EOG signal varies from 50 to 3500 μV, and its behavior is practically linear for gaze angles of ±30 degrees and changes approximately 20 μV for each degree of eye movement[41,42]. Nevertheless, like any other biopotential, EOG is rarely deterministic; its behavior might vary due to physiological and instrumental factors[32]. For LIS patients in the transition to CLIS, the range and angle of movement are affected by the progress of the ALS disease, affecting the range of voltage amplitude as well. Figure 1 depicts the horizontal eye movement of P11, P13, P15, and P16 during one of the feedback sessions of their first visit (V01). In each plot, for a particular feedback session, all the questions' responses classified as "yes" or "no" by the SVM models were grouped and averaged. Figure 1 elucidates the differences in the dynamics of the signals corresponding to the "yes" and "no" responses, and it can be observed that each patient used different dynamics to control the auditory communication system.

Figure 2 depicts a decrease in horizontal eye-movement amplitude of P11 over 13 months. During the 12 months period, from March 2018 (V01) to February 2019 (V09), P11 performed feedback sessions with a prediction accuracy above chance level, in which small eye-movements recorded with EOG allow classification of "yes" and "no" signals. Employing the same eye-movement dynamics with an approximate amplitude range smaller than ±40 μV over 4 months, from V06 (November 2018) to V09 (February 2019), P11 was able to select letters, words and form sentences using the speller. The eye-movement amplitude range decreased to ±30 μV during V10, i.e., 12 months after the first BCI sessions, because of the progressive paralysis typical of ALS. During V10, model-building for prediction during feedback and spelling sessions was unsuccessful. Thus, V10 was the last visit for a communication attempt by P11 using this paradigm. During this visit, even if this training session allowed to build a model of 80% of cross-validation accuracy (Supplementary Table S1), it proved unsuccessful for predicting any classes from the data (50% accuracy).

In the case of P13, the progression of the disorder has been slower, which can be ascertained by the relatively high and constant amplitude of EOG, in an approximate range of ±300 μV, but still, he was unable to communicate with the commercial eye-tracker technology. Employing the eye-movement strategy, as shown in Fig. 1B, P13 was able to maintain a constant dynamic to control the auditory communication system for feedback and spelling sessions (see Supplementary Table S2). Similar observations can be drawn for P15 and P16 EOG plots in Fig. 1C,D. During two visits each, they achieved successful performance for feedback and spelling sessions (see Supplementary Tables S3 and S4), with stable eye-movement dynamics.

Speller results. The performance of the SVM during all the feedback sessions by each patient is reported in Fig. 3 as a Receiver-Operating Characteristic (ROC) space. The ROC space of P11, who was followed for one year from March 2018 to March 2019, shows a trend in the performance of the feedback sessions. As shown in Fig. 3A, during the initial visits P11 exhibited a successful feedback performance (markers located in the upper-left corner in the ROC space), while during the later visits, particularly V08 and V09, P11 exhibited a decrease in feedback performance and ultimately by V10, it was impossible to perform a successful feedback session. This negative trend is due to the progressive neurodegeneration associated with ALS[8], which leads to the complete paralysis of all muscles, including eyes muscles. For each of the three patients P13, P15, and P16, the feedback sessions' performances are located mostly in the upper-left region of the ROC space, which means successful feedback performance. Nevertheless, for each of these three patients, a few feedback sessions also fall in the lower-right region of the ROC space. This might be due to a learning process of the patients in which they improved or adjusted their eye-movement strategy or due to the suboptimal performance of the SVM classifier during the first few feedback sessions.

The patients were asked to attempt a spelling session when a model was validated with a successful feedback session, i.e., results above random[43]. After the feedback session, patients performed two different types of spelling sessions: copy spelling and free spelling, i.e., sessions in which the patient was asked to spell a predetermined phrase, and sessions in which the patient spelled the sentence she/he desired.

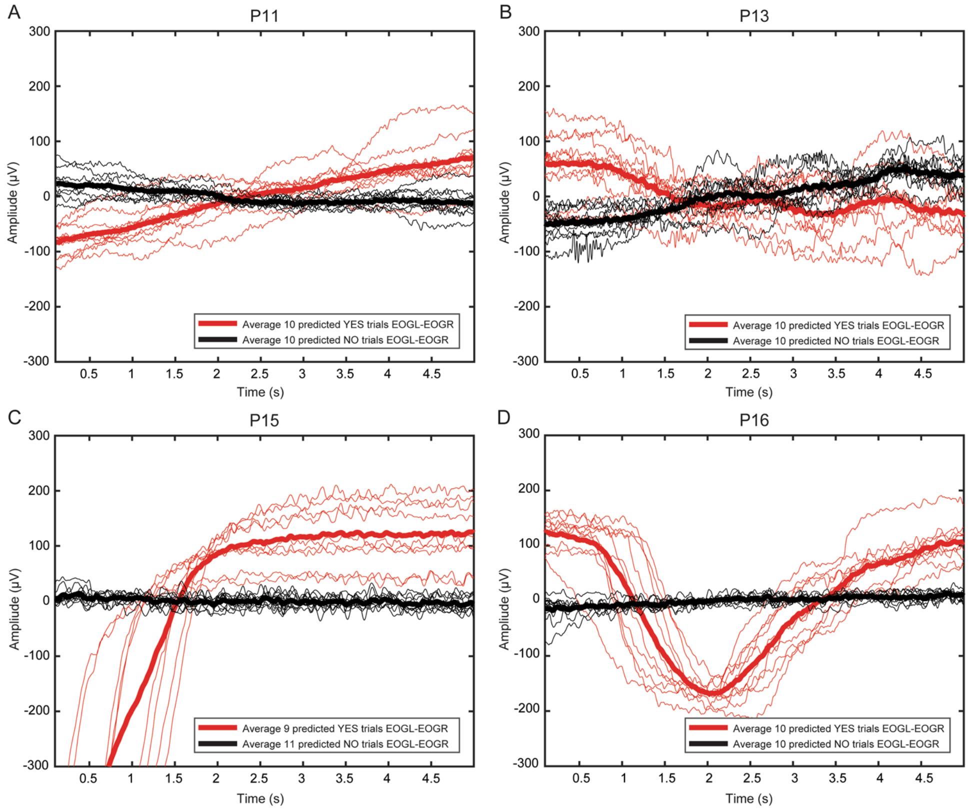

Figure 1. Horizontal eye movement during feedback sessions for all patients. Differential channel EOGL-EOGR for a particular feedback session performed by (**A**) P11, (**B**) P13, (**C**) P15, and (**D**) P16 during the first visit. In each subfigure, the x-axis is the response time in seconds, and the y-axis is the amplitude of the eye-movement in microvolts (μV). The thin and thick red trace corresponds to a single "yes" response and average of all the "yes" responses, respectively. The black thin and thick trace corresponds to a single "no" response and average of all the "no" response. The box at the bottom right of each subfigure lists the number of trials classified as "yes" and "no" by the SVM classifier for that particular session.

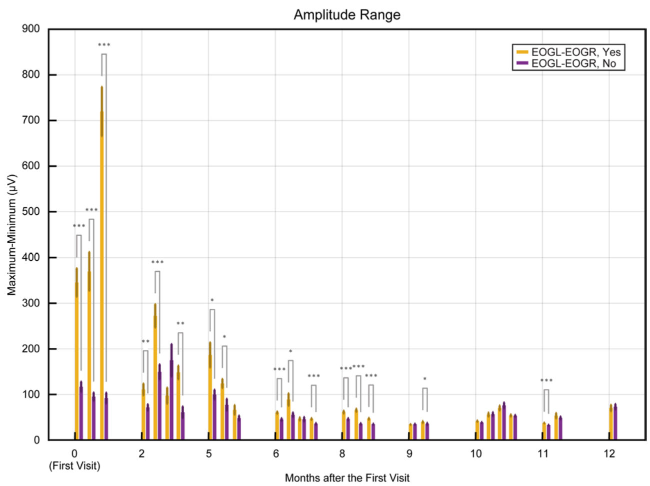

Figure 2. Progressive decline of the eye-movement amplitude along the visits for P11. Depicts the trend of decline in the range of the amplitude of the EOG signal for yes/no questions answered by the patient during the period March 2018 to March 2019. The figure shows the mean and the standard error of the mean of the extracted range of the amplitude of the horizontal EOG signal across each day for yes and no trials. The x-axis represents the month of the sessions, and the y-axis represents the amplitude in microvolts. The asterisk (* - p-value less than 0.05; ** - p-value less than 0.01; *** - p-value less than 0.001) in the figure represents the results of the significance test performed between yes and no for horizontal EOG employing the Mann-Whitney U-test.

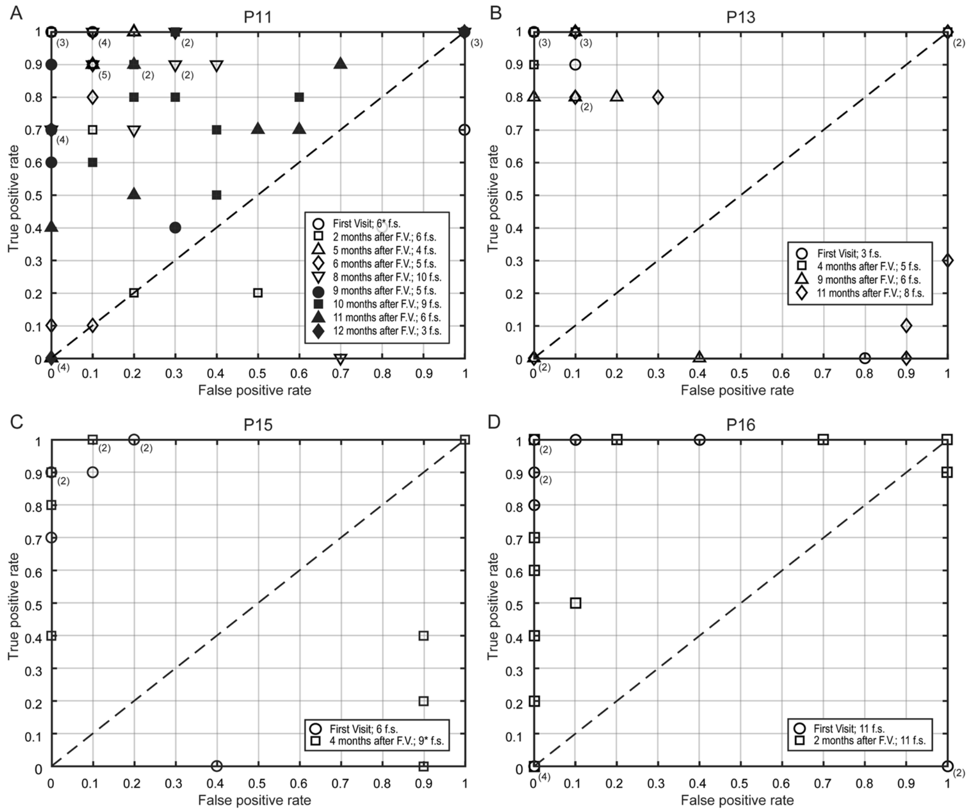

Figure 3. ROC space of feedback sessions for the four patients. Receiver operating characteristic (ROC) space for the performance of the binary support vector machine (SVM) classifier during the total number of feedback sessions performed by (A) P11, (B) P13, (C) P15, and (D) P16. In the figures, the x-axis is the false positive rate (FPR), and the y-axis is the true positive rate (TPR). The diagonal line dividing the ROC space represents a 50% level. Points above the diagonal represent good classification results (accuracy better than 50%), points below the line represent poor classification results (accuracy worse than 50%). In each subfigure, FPR vs. TPR for the feedback sessions are indicated by different arbitrary symbols according to the visit (V) they belong and the date, as defined in the legend at the bottom right side of each subfigure. The rectangular box at the bottom right of each subfigure lists the visit's month and the number of feedback sessions performed during each visit. Some feedback sessions have the same coordinate values in the ROC space, and their symbols overlapped; in these cases, the number of overlapped symbols is specified in parenthesis close to the symbols.

In the developed auditory communication system, the letters have been grouped in different sectors in a layout that was personalized for each patient to match the paper-based layout developed independently by each family (Supplementary Fig. S1). To select one letter, every sector was sequentially presented to the patient and the patient auditorily selected or skipped a sector, once a sector was selected the letters inside the sector were presented auditorily. This select/skip paradigm (i.e., yes/no answer to auditory stimuli) allows the system to work using just a binary yes/no response. The patient could form words by selecting every single letter, but the speed of the system was improved by a word predictor, which, based on the previous selections, suggested the completion of a word whenever it was probable. The speller algorithm is described in detail in the section Speller algorithm.

The results of the copy spelling sessions performed by all the patients are reported in Supplementary Table S5. As shown in Table 2, P11 performed 14 copy-spelling sessions out of which 7 times he correctly copy-spelled the target phrase. Moreover, in one of the other cases, he just miss-selected one letter, and in another one, he selected only one of the two requested words. P13 over 8 sessions copy spelled correctly the target word 6 times. P15 selected correctly the target phrase 3 times out of 5 sessions. Finally, P16 was able to correctly copy spell a target phrase 3 out of 5 sessions. The typing speed achieved by each patient is shown in Table 2.

The system can present one question every 9 seconds, which implies an information transfer rate of 6.7 bits/min. The optimal speed of the speller, along with the user accuracy, depends on the two factors mentioned: first, the speller design for the letter selection (Supplementary Fig. S1); second, the collection of stored sentences (i.e., corpus) needed for the word prediction. In order to describe and evaluate the performance, the sentence "Ich bin" (German for "I am") followed by the name of the patient was considered as a standard example for P11 and P13, while the name of the spouse was considered for P15 and P16. These standard example sentences are composed of 13, 11, 5, and 6 characters for P11, P13, P15, and P16, respectively. Therefore, considering no errors in the answers' classification, the average typing speed for the sentence mentioned above is 1.14 char/min for P11, 1.19 char/min for P13, 1.08 char/min for P15, and 0.87 char/min for P16. These theoretical results show that, due

Type	Patient	Number of sessions	Characters selected	Speed (char/min)
Copy	P11	7/14	5,28 ± 3,59	0,54 ± 0,30
	P13	6/8	4,00 ± 1,67	0,50 ± 0,35
	P15	3/5	5,00 ± 0,00	0,49 ± 0,30
	P16	3/5	5,00 ± 1,73	0,69 ± 0,14
Free	P11	5/9	11,60 ± 8,79	0,57 ± 0,29
	P13	10/11	13,00 ± 10,34	0,48 ± 0,24
	P15	4/5	26,67 ± 19,14	0,68 ± 0,13
	P16	3/3	14,00 ± 4,36	0,64 ± 0,13

Table 2. Results of the spelling sessions performed by the four patients. The columns indicate the type of sessions, the patient, the number of considered sessions over the total number of sessions, the number of characters selected (mean ± standard deviation), and the typing speed in characters per minute (mean ± standard deviation). For the copy and free spelling sessions, only the sessions in which the target was spelled correctly, and the spelled sentence was meaningful, respectively, have been considered. Sessions have been excluded a priori if an error in the code occurred, if the signal was noisy, if they terminated before 15 trials, if the patient did not select any letter, or if all the answers have been classified only as "yes" or only as "no": in total 6 sessions from P11, 2 sessions from P13, 10 sessions from P15, and 3 sessions from P16 were excluded.

to the word prediction, the performance of the speller improves when the patient auditorily spells a complete sentence rather than a single word. The difference between the theoretical and the real typing speed is due to the nature of the speller that requires many inputs to correct a mistake, e.g., if a sector is wrongly skipped, to select that sector again the patient must first skip all the other sectors.

After successful copy spelling sessions, the patients were free to form words and sentences of their choice. The results of these free spelling sessions performed by all the patients are reported in Supplementary Table S6. The typing speed in these sessions is similar to the speed achieved by each patient during the copy spelling; one exception is P13 who due to the low number of errors and to better words' prediction reached the speed of 1.02 char/min during one of the sessions shown in Supplementary Table S6. In most of the sessions, the patients were able to form complete sentences communicating their feelings and their needs. Nonetheless, some of the performed sessions were not successful. Videos of selected spelling sessions are available in Supplementary Videos S1–S3.

Discussion

The auditory communication system enabled four ALS patients, with ALSFRS-R score of 0, on the verge to CLIS to select letters and words to form sentences. Three out of the four patients (P13, P15, and P16) showed, during all the sessions, a preserved eye movement. One patient (P11), followed over one year from March 2018 to March 2019, demonstrated an effective eye-movement control until the penultimate visit (V09 in February 2019), despite August 2017 being the last successful communication with a commercial AAC device. However, the progression of the disease varies from patient to patient.

Nonetheless, P11's successful results of V09, even if not perfect, are very encouraging since they show the possibility of communicating even with an eye-movement amplitude range of ±30 μV. Even if the developed auditory communication system was used only from V06, the evolution of eye movements of P11 (Fig. 2) indicates that the eye signal was clear enough to be used for communication purposes since the first visit in March 2018. The results of the feedback sessions confirm this during the initial five visits (Fig. 3A). Speed is the main limitation of the developed system since the spelling of one single word could take up to 10 minutes. In the literature, other spelling systems have been successfully tested with ALS patients, and they achieved an information transfer rate of 16.2 bits/min[44] and 19.95 bits/min[45]. However, since all of them are based on visual paradigms, except a single study where the patients communicated just "yes" or "no" using an auditory system[46], comparison with the here proposed system is difficult. The slow speed of our system is an intrinsic characteristic of its auditory nature, even though the spelling time can be reduced by optimizing the speller schema and improving the word prediction with the creation of a corpus of words personalized for each patient. Even though the user experience was not assessed with a questionnaire, it is vital to notice that the patients showed no frustration for this slow speed, which they indicated by moving their eyes when questioned, "Would you like to continue?". The patient formed sentences like, "I am Happy", "I am happy to see my grandchildren growing up", and "I look forward to a vacation" indicating their willingness to communicate. From these, we infer speculatively that the slow speed did not frustrate the patients, probably because even this slow communication is preferred and valued in comparison to the isolation experienced without a functioning eye-tracker. It is essential to employ such a paradigm and follow these patients regularly to elucidate their eye-movement dynamics further and provide them a means of communication.

In conclusion, the long-term viability of an EOG based auditory speller system in ALS patients on the verge of CLIS (with ALSFSR-R score of 0) unable to use eye-tracking based AAC technologies were explored. For one of the patients, it was possible to perform a long-term recording, capturing the changes in the EOG signal, evidencing a correlation between speller performance and progressive degeneration of the oculomotor control. After a follow-up of one year, the patient was unable to take advantage of the spelling system proposed because of the complete loss of oculomotor control. Although the reported system cannot be considered as the ultimate communication solution for these patients according to the best of the authors' knowledge, this is the only system that, during the period of transition from LIS to CLIS, might offer a means of communication that otherwise is not possible. Nevertheless, whether this can be generalized to other patient populations or not is an empirical question.

Methods

The Internal Review Board of the Medical Faculty of the University of Tubingen approved the experiment reported in this study. The study was performed per the guideline established by the Medical Faculty of the University of Tubingen. The patient or the patients' legal representative gave informed consent with permission to publish the results and to publish videos and pictures of patients. The clinical trial registration number is ClinicalTrials.gov Identifier: NCT02980380.

Instrumentation. During all the sessions, EOG channels were recorded with a 16 channel EEG amplifier (V-Amp DC, Brain Products, Germany) with Ag/AgCl active electrodes. A total of four EOG electrodes were recorded (positions SO1 and IO1 for vertical eye movement, and LO1 and LO2 for horizontal eye movement). During some sessions, a minimum of seven EEG channels were recorded for analysis, not directly related to the purpose of this paper. All the channels were referenced to an electrode on the right mastoid and grounded to the electrode placed at the FPz location on the scalp. For the montage, electrode impedances were kept below 10 kΩ. The sampling frequency was 500 Hz.

Patients. Four ALS patients with ALSFRS-R score of 0 participated in this study. Table 1 summarizes the clinical history of each patient and lists the number of visits (V). After the last successful use of AAC, all the four patients were still communicating with the relatives saying "yes" and "no" by moving and not moving the eyes. Using this technique, patients P11, P13, and P15 were forming words by selecting letters from a paper-based layout (Supplementary Fig. S1A–C) developed, independently, by each family. These same layouts were integrated into our developed system to provide each patient with a personalized schema for selecting letters. For patient P16, based on the feedback and suggestions of the family members, we proposed and tested the spelling schema shown in Supplementary Fig. S1D.

Paradigm. The developed paradigm is based on a binary system, in which a patient is asked to reply to an auditorily presented question by moving the eyes to say "yes" and by not moving the eyes to say "no". The paradigm includes four different types of sessions: training, feedback, copy spelling, and free spelling session. Each training and feedback session consists of 10 questions with a "yes" answer and 10 questions with a "no" answer well known by the patient. Each question represents a trial. Copy and free spelling sessions consist of yes/no questions (i.e., trial) in which a patient is asked whether he wants to select a particular letter or group of letters (see the below paragraph Speller algorithm). Each of these trials consists of the baseline (i.e., no sound presented), the stimulus (i.e., auditory presentation of the question and the speller options), the response time (i.e., time for the patient to move or not move the eyes), and feedback (i.e., auditory feedback to the patient to indicate the end of the response time). The training sessions differ from the feedback sessions in terms of the feedback that is provided to the patient. During the training sessions, the feedback is a neutral stimulus ("Danke" – "Thank you" in English) to indicate the end of the response time, while during the feedback sessions, the feedback is the answer that the program classifies (see Online analysis for details). Copy and free spelling sessions differ in terms of the instruction given to the patient. During the copy spelling sessions, the patient was asked to spell a specific sentence, while during the free spelling sessions, the patient was asked to spell whatever he desired.

The length of the response time-window was determined according to the progress and performance of the patient as described in the Supplementary Tables S1–S4 and varies between 3 and 10 seconds. The duration of each trial varies accordingly between 9 and 20 seconds. Therefore, each training and feedback session lasted for 3–7 minutes. The spelling sessions were usually longer (up to 57 minutes), but no fixed time can be indicated since the number of trials is different from session to session; on average, the copy and free spelling sessions lasted respectively for 10 and 27 minutes.

Speller algorithm. After the patients were unable to communicate with the commercial eye-tracker based AACs devices, the primary caretakers developed a speller design/layout. The auditory speller layouts used here were developed by optimizing and automatizing the schematics already used by the primary caretakers. The spellers used by the patients are shown in Supplementary Fig. S1. The spellers consist of letters grouped in different sectors, plus one sector with some special characters ("space", "backspace" for P11 and P15, and for P13 and P16 along with these the additional option, "delete the word"). Despite the different layouts, the same algorithm, as described below, drives all the spellers. The spellers enable the patients to auditorily select letters and compose words. To increase the speed of the sentence completion, the speller predicts and proposes words based on the letters previously chosen. The auditory speller developed to enable patients without any means of communication to spell letters, words freely, and form sentences auditorily have two main components called "Letter selection" and "Word prediction", which are described below.

Letter selection. The patient, in order to select a letter, first must select the corresponding sector, and only once he is inside the sector, he can select the letter. The selection is made, answering "yes" or "no" to the auditory presentation of a sector or a letter. As schematized in the diagram in Supplementary Fig. S2, to avoid false positives, the speller uses a single-no/double-yes strategy. If the recognized answer is "no" the sector is not selected, and the following sector will be asked, if the answer is "yes" the same sector is asked a second time as a confirmation: the sector is selected if the patient replies "yes" also the second time. If the last sector is not selected, the program asks the patient whether he wants to quit the program. If he replies "yes", and confirms the answer, the program is quit.

Otherwise, the algorithm restarts from the first sector. Once a sector is selected, the paradigm for selecting a letter (or a special character) uses the same single-no/double-yes strategy as described above. If none of the letters in a sector is selected, the patient is asked to exit the sector. If he replies a confirmed "yes" the speller goes back asking the sectors starting from the one after the current, otherwise, if he replies "no", the algorithm asks the letters of the current sector again starting from the first one. Whenever a letter or a special character is selected, the speller updates the current string and gives auditory feedback reading the words already completed (i.e., followed by a space) and spelling the last one if it is not complete. After every selected letter, the speller searches for probable words based on the current string (the details are explained in the paragraph below). If a word is probable, the program presents that word auditorily. Otherwise, it starts the letter selection algorithm from the first sector again.

Word prediction. To speed up the formulation of sentences, the speller is provided with a word predictor that compares the current string with a language corpus to find if there is any word that has a high probability of being the desired one. To have a complete and reliable vocabulary, the German general corpus of 10000 sentences compiled by the Leipzig University[47] was used. Since the developed speller contains only English letters, firstly the corpus is normalized converting the special German graphemes (ä, ö, ü, ß) with their usual substitutions (ae, oe, ue, ss). Thus, a conditional frequency distribution (CFD) is created based on the n-gram analysis of the normalized corpus; for word prediction, we considered the frequencies of the single words (i.e., unigrams), of two consecutive words (i.e., bigrams), and three consecutive words (i.e., trigrams). Whenever a letter is added to the current string, the program returns the CFD of all the words starting with the current non-completed word (if the last word is complete, it considers all the possible words). For these words first, the frequency value is considered concerning the two previous words, i.e., trigram frequency. Then, if for the current string, there is any stored trigram in the corpus, the program considers only the last complete word and checks the bigram frequency. Finally, if it is not possible to find any bigram, it considers the overall frequency value of the single word, i.e., unigram frequency. Once all the frequency values of the words are stored, considered as trigrams, bigrams, or unigrams, the program establishes if any of these words are highly probable comparing their values to a predefined threshold. To predict words, we considered a word as probable if its frequency value is more significant than half of the sum of all the frequency values of the possible words. If a word is detected as probable, the speller, after a letter is selected, instead of restarting the algorithm from the first sector, proposes that word to the patient, and if a confirmed "yes" is answered it adds the word followed by a space to the current string.

Online analysis. The EOG data were acquired online in real-time throughout all the sessions. During all the trials belonging to a session (except for the training sessions), the signal of the response time was processed in real-time to extract features to be fed to a classification algorithm for classifying the "yes" and "no" answers. Features computed from the trials of the training sessions were used to train an SVM classifier that was validated through 5-fold cross-validation. The obtained SVM classifier was used to classify feedback and speller sessions only if its accuracy was higher than the upper threshold of chance-level[43].

To extract the features from the signal during the response time, the time-series were first preprocessed with a digital finite impulse response (FIR) filter in the passband of 0.1 to 35 Hz and with a notch filter at 50 Hz. The first 50 data points were removed to eliminate filtering-related transitory border effects at the beginning of the signal. Then all the channels were standardized to have a mean of zero and a standard deviation of one. Subsequently, features were extracted from all the data series from the "yes" and "no" answer for all the channels.

Different features were extracted for the different patients: for P11 and P13 the maximum and minimum amplitude and their respective value of time occurrence feature were used; while for P15 and P16 the range of the amplitude (i.e., the difference between the values of maximum and minimum amplitude) feature was used.

The code was developed and run in Matlab_R2017a. For the SVM classification, the library LibSVM[48] was used. The detailed list of sessions used for building the model and, therefore, perform feedback and spelling sessions are described in the Supplementary Tables S1–S4.

Receiver-operating characteristic space. For binary classifiers in which the result is only positive or negative, there are four possible outcomes. When the outcome of the prediction of the answer is yes (positive), and the actual value is positive, it is called True Positive (TP); however, if the actual answer to a positive question response is negative, then it is a False Negative (FN). Complementarily, when the predicted answer is negative, and the actual answer is also negative, this is a True Negative (TN), and if the prediction outcome is negative and the actual answer is positive, it is a False Negative (FN). With these values, it is possible to formulate a confusion or contingency matrix, which is useful to describe the performance of the classifier employing its tradeoffs between sensitivity and specificity. The contingency matrix can be used to derive several evaluation metrics, but it is particularly useful for describing and visualizing the performance of classifiers via the Receiver-Operating Characteristic (ROC) space[49]. A ROC space depicts the relationship between the True Positive Rate (TPR) and the False Positive Rate (FPR). TPR and FPR were calculated for each feedback session, and they were then used to draw ROC space, as shown in Fig. 3.

Data availability

The data and the scripts are available without any restrictions. The correspondence between sessions and the corresponding raw files are listed in Supplementary Table S7. Data link: https://doi.org/10.5281/zenodo.3605395.

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Alessandro Tonin – Performed 35% of the BCI sessions and data collection; Data analysis; Manuscript writing. Andres Jaramillo-Gonzalez – Performed 35% of the BCI sessions and data collection; Data analysis; Manuscript writing. Aygul Rana – Performed 35% of the BCI sessions and data collection. Majid Khalili Ardali – Data analysis. Niels Birbaumer – Study design and conceptualization; Manuscript correction. Ujwal Chaudhary – Study design and conceptualization; Performed 65% of the BCI sessions and data collection; Data analysis supervision; Manuscript writing.

Competing interests
The authors declare no competing interests.

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Appendix 4.

A. Secco, A. Tonin, A. Rana, **A. Jaramillo-Gonzalez**, M. Khalili-Ardali, N. Birbaumer, U. Chaudhary (2020). EEG power spectral density in locked-in and completely locked-in state patients: a longitudinal study, *Cognitive Neurodynamics*, 15, 473–480.
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RESEARCH ARTICLE

EEG power spectral density in locked-in and completely locked-in state patients: a longitudinal study

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Abstract

Persons with their eye closed and without any means of communication is said to be in a completely locked-in state (CLIS) while when they could still open their eyes actively or passively and have some means of communication are said to be in locked-in state (LIS). Two patients in CLIS without any means of communication, and one patient in the transition from LIS to CLIS with means of communication, who have Amyotrophic Lateral Sclerosis were followed at a regular interval for more than 1 year. During each visit, resting-state EEG was recorded before the brain–computer interface (BCI) based communication sessions. The resting-state EEG of the patients was analyzed to elucidate the evolution of their EEG spectrum over time with the disease's progression to provide future BCI-research with the relevant information to classify changes in EEG evolution. Comparison of power spectral density (PSD) of these patients revealed a significant difference in the PSD's of patients in CLIS without any means of communication and the patient in the transition from LIS to CLIS with means of communication. The EEG of patients without any means of communication is devoid of alpha, beta, and higher frequencies than the patient in transition who still had means of communication. The results show that the change in the EEG frequency spectrum may serve as an indicator of the communication ability of such patients.

Keywords Resting-state electroencephalogram (EEG) · Completely locked-in state (CLIS) · LIS (locked-in state) · Power spectrum density (PSD) · Alpha frequency

Introduction

The cardinal feature of a patient in a locked-in state (LIS) is paralysis of most of the voluntary motor function of the body except the oculomotor function with preserved consciousness (Bauer et al. 1979; Chaudhary et al. 2020a). Because of the preserved oculomotor function and consciousness (Schnakers et al. 2008), patients in LIS have several means of communication (Birbaumer et al. 1999; Wolpaw and McFarland 2004; Kübler et al. 2005; Sellers et al. 2010; Lesenfants et al. 2014; Wolpaw et al. 2018; Tonin et al. 2020). A patient can be in LIS because of the severe brain injury or pontine stroke (Sacco et al. 2008; Sarà et al. 2018; Pistoia et al. 2010; Conson et al. 2010), or progressive neurodegenerative motor neuron disorders (Birbaumer 2006; Birbaumer et al. 2012; Chaudhary et al. 2015, 2016a, b). Amyotrophic lateral sclerosis (ALS) is a severe of all progressive neurodegenerative disorder leading to complete paralysis with symptoms involving both upper and lower motor neurons (Rowland and Shneider 2001). Like any other LIS patient, an ALS patient in LIS are paralyzed with preserved voluntary eye movement control, eye blinks or twitching of other muscles, and intact consciousness. The LIS is not a final state for a patient who has ALS. As the disorder progresses, ALS leads to a state of complete paralysis, including eye movements, transferring patients to the completely locked-in state (CLIS)

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(Bauer et al. 1979; Chaudhary et al. 2020a). The transition from LIS to CLIS is usually a gradual process that is patient specific. During this transition phase from LIS to CLIS, the patient starts losing their eye movement control and ultimately losing the ability to open their eyes is lost. ianllt, the patients in CLIS have their eyes closed all the time, even in the CLIS, patients are assumed to preserve their cognitive functions (Kübler and Birbaumer 2008).

Many studies have compared electrophysiological signatures from ALS patients and controls (Jayaram et al. 2015; Nasseroleslami et al. 2019; Dukic et al. 2019; Maruyama et al. 2020), reporting features distinguishing the two groups. The most reliable evidence found is a decrease in alpha relative power, with a shift of the peak in the alpha frequency band (generally present in healthy patients' EEG power spectrum) to lower frequencies (Mai et al. 1998; Hohmann et al. 2018). Several other studies with a different patient population such as depression (Goshvarpour and Goshvarpour 2019), Alzheimer's disease (Nobukawa et al. 2019), stress (Subhani et al. 2018), autism (Gabard-Durnam et al. 2019), epilepsy (Myers and Kozma 2018) and Parkinson's disease (Yi et al. 2017) have shown a difference in EEG spectral power, fractal change, power correlation and complexity of resting-state EEG as compared with the healthy participants (Buiza et al. 2018). However, how these features and biomarkers evolve during the ALS progression, reaching a state where they separate patients in different stages of the disease, is still unclear.

This study aims to perform a longitudinal analysis of EEG frequency in three ALS patients, analyzing how the power spectral densities of EEG resting-state recordings evolve in each patient. Two out of three patients considered here are in CLIS (P6 and P9), while the third patient was first in the transition from LIS to CLIS (P11) and, ultimately, in CLIS. The decrease in relative alpha band power is registered in LIS and CLIS patients with respect to controls (Babiloni et al. 2010) (Maruyama et al. 2020), but a direct comparison between these states is still missing. Investigating whether these conditions differ from the electrophysiological point of view can help understand the effects of the transition and possibly monitor the patients for BCI use. In addition, an earlier report on several CLIS patients (Maruyama et al. 2020) needs replication, finding a reduction of higher frequencies in CLIS in a one-session protocol. Whether such a change in spontaneous EEG frequency spectrums indicates functional changes in the central nervous system is now a question of further investigations.

Materials and methods

The Internal Review Board of the Medical Faculty of the University of Tubingen approved the experiment reported in this study. The study was performed per the guideline established by the Medical Faculty of the University of Tubingen and Helsinki declaration. The patient or the patients' legal representative gave informed consent. The clinical trial registration number is ClinicalTrials.gov Identifier: NCT02980380.

Patients

The patients chosen for this study were selected from the available database if the EEG resting-state recordings were in a sufficient number for a longitudinal comparison and covering a time range of at least 1 year. Table 1 lists the most relevant clinical information for each patient and the dates of the acquired EEG recordings.

EEG data acquisition

EEG resting-state recordings were acquired during visits to the patients for BCI experiments before the experimental sessions started. From now on, "visits" refers to a period of several subsequent days in which acquisitions were performed. Usually, a single visit lasted for 4 to 5 days, and two subsequent visits were at least 30 days apart from each other.

During the resting state recordings, patients were lying in their beds, being instructed to relax. EEG electrodes were attached according to the 10-5 system, with reference and ground channels placed respectively to their right mastoid and the forehead. EEG signals were recorded using a V-Amp amplifier and active electrodes (Brain Products, Germany). The numbers and positions of electrodes were different between patients and visits due to clinical and experimental needs, as outlined in Supplementary Table 1.

EEG preprocessing

EEG data were processed using Matlab R2018_b (The MathWorks, Inc., Natick, Massachusetts, U.S.A.) and EEGLAB 14.1.1 (Delorme and Makeig 2004). First, a windowed band-pass filter at 0.5 to 45 Hz was applied to the raw EEG data, followed by down-sampling to 128 Hz. Data were then cleaned from the ocular signal by removing the artifacts using the AAR plug-in (Gómez-Herrero et al. 2006) of EEGLAB. The AAR toolbox process EEG data by first decomposing the time series into spatial components using a Blind Source Separation (BSS) algorithm, then identifying the artifactual components and finally

Table 1 List of patients—the table lists for each patient the respective ID, the age and gender, the ALS type diagnosed, a short report of the progression of the disease, and the month and year of visits

Patient ID	Birthday/sex	ALS type	Medical history	Resting state data acquisition date
P6	40/M	Bulbar	2009: Diagnosis	May 2017
			Sept 2010: Percutaneous feeding and artificial ventilation	September 2017
			Dec 2010: Lost speech and walk	April 2018
			2012: Transition to CLIS	May 2018
				January 2019
P9	24/M	Juvenile	2013: Diagnosis	June 2017
			Aug 2014: Percutaneous feeding and artificial ventilation	November 2017
			2016: Transition to CLIS	March 2018
				June 2018
P11	35/M	Non-bulbar	Aug 2015: Diagnosis	May 2018
			Dec 2015: Lost of speech and walk	August 2018
			Jul 2016: Percutaneous feeding and artificial ventilation	September 2018
			March 2019: Transition to CLIS	November 2018
				December 2018
				January 2019
				February 2019
				March 2019
				August 2019
				September 2019

reconstructing the signals using the non-artifactual components. For this study, the decomposition in independent components was obtained through second-order blind identification (SOBI) algorithm (Belouchrani et al. 1997), and artifactual components were automatically identified based on the value of the fractal dimension of the waveform (Gómez-Herrero et al. 2006). In particular, each EEG recording (comprehensive of all the channels acquired) was processed on sliding windows of 180 s, with an overlap period equal to 60 s, and the components with smaller fractal dimensions were selected as artifactual as they correspond to the ones with less low-frequency components. After ocular artifacts rejection was applied singularly to each EEG resting-state record on the complete set of channels, the Cz channel was selected for further analysis.

PSD was obtained through Welch's overlapped segments averaging estimator, using windows of 5 s length with an overlap of 2 s on a segment of 180 s extracted from the middle of each recording (samples were taken equally before and after the central sample of the complete EEG recording). Then, each PSD was normalized by its median to reduce the effect of different offsets in the recordings. The representative resting-state PSD of each visit was obtained averaging Cz's PSDs from recordings belonging to the same visit.

The relative band-power was then computed from each PSD (for each visit-wise PSD of each patient) to compare relative power values in the three patients quantitatively. The frequency range was divided into delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low beta (12–20 Hz), high beta (20–30 Hz), and gamma (30–45 Hz) bands (Fig. 1).

Results

Statistical tests were applied using Matlab 2018b. Pearson's linear correlation coefficient was computed on subsequent values of relative band-power, obtained for each patient's set of visits, to investigate the correlation with the corresponding timeline. Then, the Mann–Whitney U test was applied to test the power difference between the three patients for each frequency band at the Cz sensor, considering for each of them the whole set of PSDs. The obtained p values were corrected through the False Discovery Rate (FDR) using the Benjamini–Hochberg method (Benjamini and Hochberg 1995) to compensate for the multiple comparisons of 6 frequency bands. The results are reported through the visualization of the PSD profile's evolution within the period of observation for each patient separately. The evolution of PSD of patients 6, 9, and 11 are shown in Figs. 2, 3, and 4, respectively. The results on the variance within visits relative band power and power

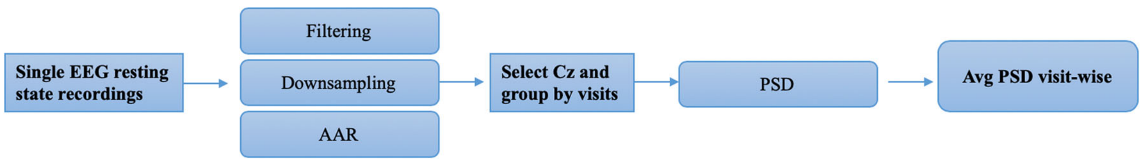

Fig. 1 Schematic workflow showing EEG's processing steps

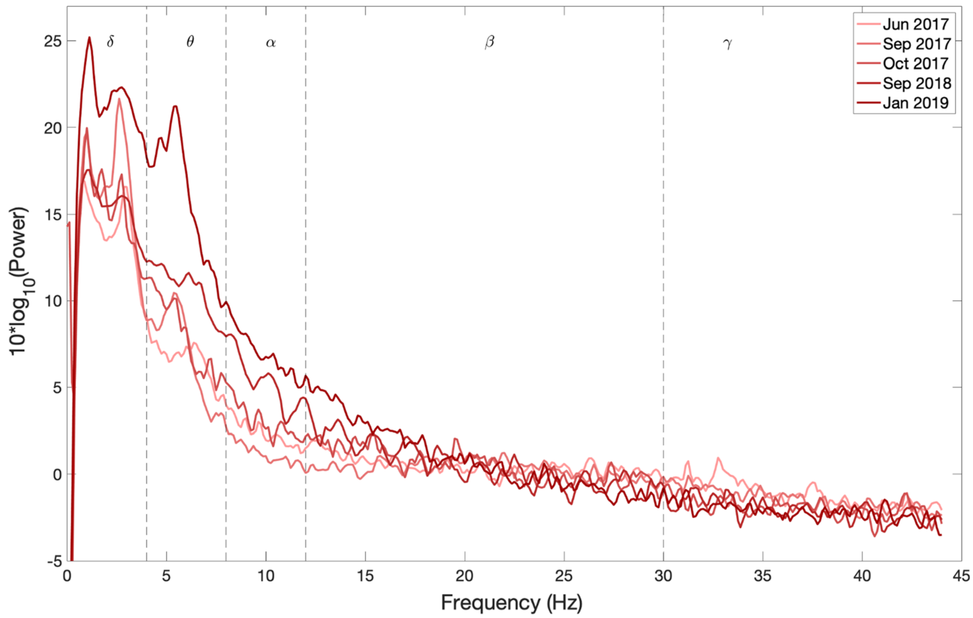

Fig. 2 EEG power spectral density evolution in Patient 6. The PSDs corresponding to different visits is shown in different colors, as explained in the box in the top right corner of the figure. The x-axis represents the frequency in Hz. The y-axis represents the normalized amplitude of the power spectral densities on a logarithmic scale. In dashed lines are shown the frequency bands of interest. The frequency range analyzed is divided in the canonical frequency bands, represented in dashed lines in the figures: delta (1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 12 Hz), beta (12 to 30 Hz) and gamma (30 to 45 Hz)

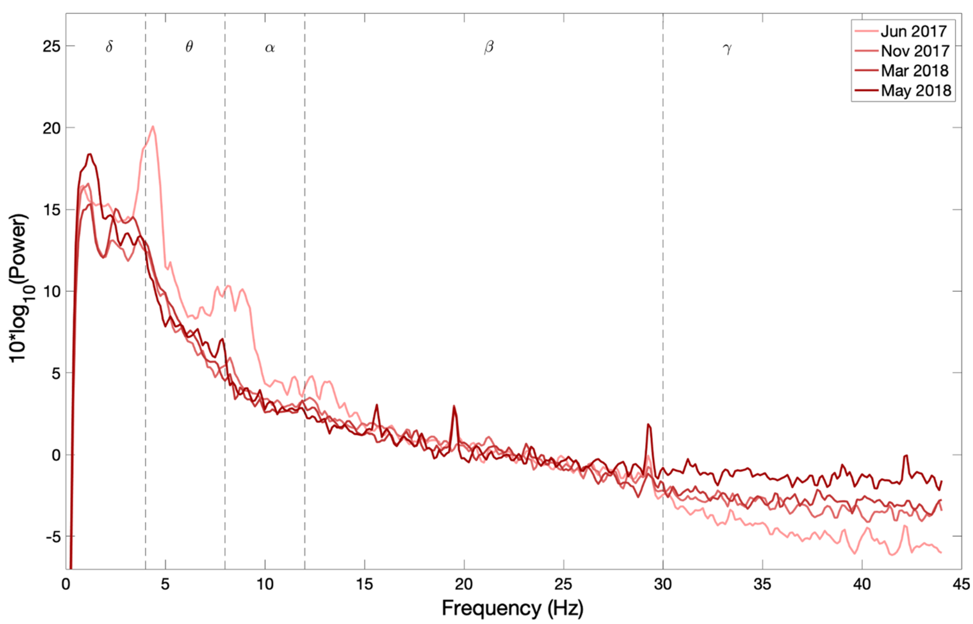

Fig. 3 EEG power spectral density evolution in Patient 9. The details of the figure are the same as explained in the legend of Fig. 2

spectral density of each patient is shown in Supplementary Text 1, where we show that the variance within a visit to be insignificant.

It can be observed from Figs. 2 and 3 that the frequency content of patients 6 and 9, who are in CLIS, are shifted towards delta and theta frequency bands. During the observation period reported in this paper, no general evolution of trends could be seen in patients 6 and 9. While Patient 11 has activity in the alpha band, present in all the recordings within the observation period, as shown in

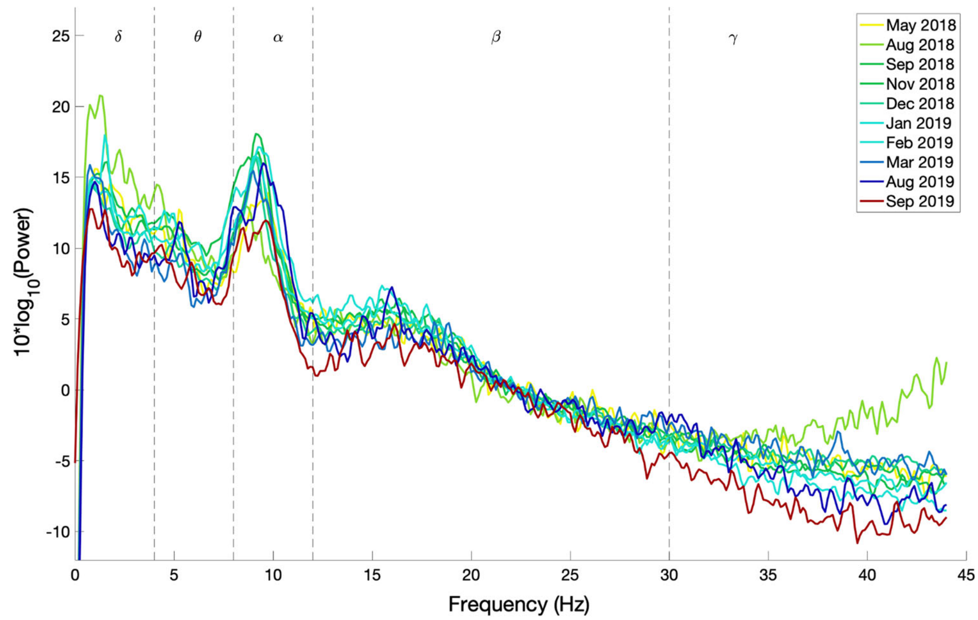

Fig. 4 EEG power spectral density evolution in Patient 11. The details of the figure are the same as explained in the legend of Fig. 2

Fig. 4. Nevertheless, a decrease in the power of the EEG signal as the patient transitioned from LIS to CLIS and, ultimately, in CLIS could be observed. The frequency content of patients' 6 and 9 EEG is very different from the EEG of patient 11. This aspect is more evident in Fig. 5, where the average of the PSDs related to all the visits grouped for patients is presented. These results were confirmed by the results of the Mann–Whitney *U* test shown in Fig. 6, which revealed the significant difference in the relative band power between Patient 11 and the two CLIS patients (Patients 6 and 9) at delta, alpha, and low-beta frequency bands. On the other hand, no significant difference was found over the values of relative power between patients 6 and 9.

Discussion and conclusion

A longitudinal resting-state analysis of patients in LIS and CLIS reveals a trend on the variation of EEG relative band power within the observation period. Patient 6, who is in CLIS since 2012 and was recorded for the first time in May 2017, shows a stable EEG frequency spectrum with dominant frequency in the delta and theta band. Patient 9, who is in CLIS since 2017 and was recorded for the first in June

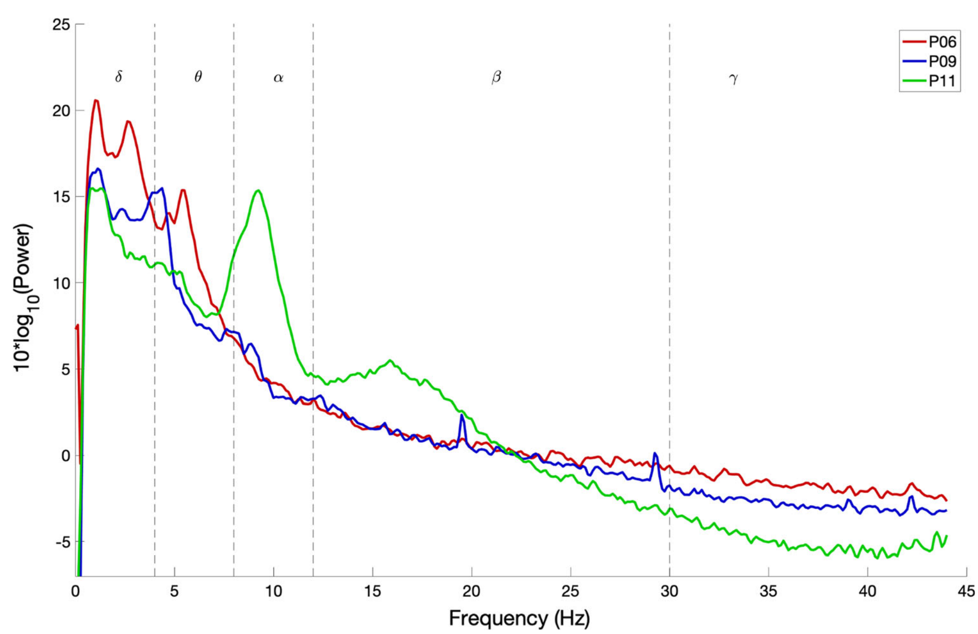

Fig. 5 Comparison of average EEG power spectral densities in Patients 6, 9, and 11. The red, blue, and green traces correspond to the average PSDs at electrode Cz for patients 6, 9, and 11, respectively. The x-axis represents the frequency in Hz. The y-axis represents the normalized amplitude of the power spectral densities in the logarithmic scale. In dashed lines are shown the frequency bands of interest as described in the legend of Fig. 2

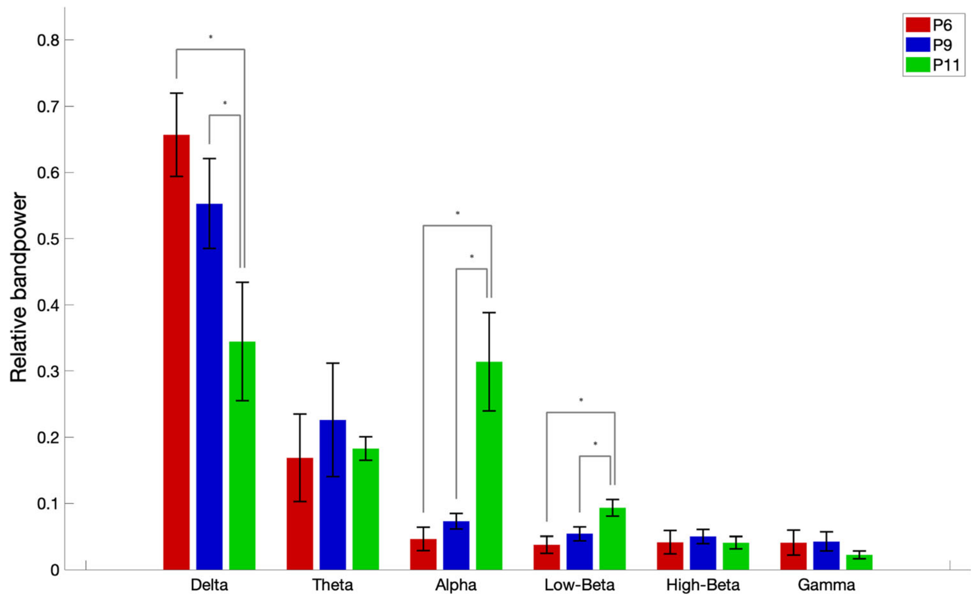

Fig. 6 Relative band power at electrode Cz. Error bars represent standard deviations. The figure depicts the significant power differences between patients 6, 9, and 11 in the two-tailed Wilcoxon rank-sum test with False Discovery Rate correction are marked: *$p < 0.05$. The x-axis represents the different frequency bands in Hz, and the y-axis represents the relative band power

2017 also shows a trend similar to patient 6. When we started recording Patient 11 in May 2018, the patient had control over his eye-movements but was unable to communicate with the eye-tracker based communication system because of his inability to fixate his gaze. During every visit to each patient, brain–computer interface (BCI)-based communication was attempted after resting-state recording. With patients 6 and 9, functional near-infrared spectroscopy (fNIRS) based communication was attempted, except for the visit 1 of patient 6, we were not able to establish a reliable means of communication using fNIRS based BCI communication system (Chaudhary et al. 2017) with these two patients. The fNIRS based BCI communication system was employed for patient 6 and 9 because it was demonstrated earlier that EEG-based BCI system had failed so far to provide a means of communication to the patients in CLIS (Kübler and Birbaumer 2008) except for a short one-session period report (Okahara et al. 2018) while fNIRS based BCI communication system showed some promise (Gallegos-Ayala et al. 2014). Since the patient 11 still had eye-movement an electrooculogram (EOG) based BCI communication was developed and implemented to provide a means of communication to the patient. The EOG-based communication by patient 11 is described in Tonin et al. (2020). As described in Tonin et al. (2020), patient 11 was able to employ his eye movement ability to communicate his thoughts and desires until February 2019, albeit with increasing difficulties due to the progressive paralysis of his eye muscles associated with the progression of the amyotrophic lateral sclerosis. From February 2019, the patient 11 could not employ his eye-movement to drive the EOG-based communication system (please refer to (Tonin et al. 2020) for further details). Patient 11 could not communicate reliably with his eyes from March 2019 onwards. He was implanted with microelectrodes in the motor region to provide him a means of communication (Please refer to Chaudhary et al. 2020b for details). The patient although in CLIS was able to form phrases and sentences to express his desires and wishes (Chaudhary et al. 2020b). His EEG spectrum remained constant throughout the observation period reported in this paper.

Patients 6 and 9, although of different ages and being in CLIS for different time periods, have the same EEG spectrum, which is significantly different from patient 11, who was first in LIS, then in the transition from LIS to CLIS and ultimately in CLIS during the period of observation reported in this paper. The main difference between patients 6 and 9 and patient 11 is that since we started following patients 6 and 9, they never had any means of communication. While we were able to provide a means of communication to patient 11 despite his degrading oculomotor function. It can be stated that from the patients reported in this longitudinal analysis, patients without any means of communication have different EEG spectrums than a patient who, despite being in CLIS, has a means of communication. It can also be hypothesized that if a patient has a means of communication despite being in CLIS the general shift in EEG spectrum to the lower bands might not occur, but to generalize these results to other patients in LIS and CLIS with and without means of communication, there is a need to perform such a longitudinal study on the large patient population. Also, a contrary causality is possible: with loss of normal EEG power spectrum and the underlying neurological functionality a loss of communication may be the consequence.

These results are partly supporting an earlier report from our lab of a remarkable reduction of higher frequencies in CLIS (Maruyama et al. 2020), all without any means of communication. It can also be hypothesized that the reason for the failure to establish communication with patients already in CLIS might be due to general shift of their EEG spectrum to the lower bands and absence of alpha and higher frequency bands since all the current EEG based BCI communication systems rely on the alpha and higher frequency bands (Jayaram et al. 2015; Lazarou et al. 2018). Nevertheless, it can also be argued that lack of alpha, in general, might also indicate reduced cognitive processing or compromised vigilance state of the patient (Klimesch 1999). However, in a recent study reported by Khalili-Ardali et al. (2019), patient in CLIS was shown to have the ability to process sentences with motor semantic content and self-related content better than control sentences indicating comprehension and some level of cognitive processing in CLIS in ALS patients. It can also be argued that the patients might be asleep during the period of data acquisition, but recently we showed in a larger sample of patients in CLIS (Malekshahi et al. 2019) that despite a general decrease in their EEG spectrum, patients in CLIS still have an intact sleep and wake cycle.

Thus, there is a need to perform long-term longitudinal studies with patients in LIS, the transition to LIS, and CLIS and parallel cognitive evaluation with BCI assistance to elucidate the evolution in their EEG signature, which afterward may then be used in the development of more efficient non-invasive BCI-systems.

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Appendix 5.

Y. Maruyama, N. Yoshimura, A. Rana, A. Malekshahi, A. Tonin, **A. Jaramillo-Gonzalez**, N. Birbaumer, U. Chaudhary (2020). Electroencephalography of completely locked-in state patients with amyotrophic lateral sclerosis, *Neuroscience Research*, 162, 45-51. https://doi.org/10.1016/j.neures.2020.01.013

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Electroencephalography of completely locked-in state patients with amyotrophic lateral sclerosis

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A B S T R A C T

Patients in completely locked-in state (CLIS) due to amyotrophic lateral sclerosis (ALS) lose the control of each and every muscle of their body rendering them motionless and without any means of communication. Though some studies have attempted to develop brain-computer interface (BCI)-based communication methods with CLIS patients, little information is available of the neuroelectric brain activity of CLIS patients. However, because of the difficulties with and often loss of communication, the neuroelectric signature may provide some indications of the state of consciousness in these patients. We recorded electroencephalography (EEG) signals from 10 CLIS patients during resting state and compared their power spectral densities with those of healthy participants in fronto-central, central, and centro-parietal channels. The results showed significant power reduction in the high alpha, beta, and gamma bands in CLIS patients, indicating the dominance of slower EEG frequencies in their oscillatory activity. This is the first study showing group-level EEG change of CLIS patients, though the reason for the observed EEG change cannot be concluded without any reliable communication methods with this population.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive disease that affects patients' motor control. ALS patients suffer from progressing impaired motor control, and often their options for communication methods become limited. In the advanced stage of ALS called locked-in state (LIS), patients lose most voluntary body movements but still can communicate using their eye movements or any other muscular response. However, in the further advanced stage called completely locked-in state (CLIS), patients lose all muscular control including their eyes and thus all communication methods are lost, although cognitive function of CLIS patients is assumed to be functioning (Kotchoubey et al., 2003; Fuchino et al., 2008).

Some studies have attempted to establish brain-computer interface (BCI)-based communication methods with CLIS patients using brain signals such as electrocorticography (ECoG), electroencephalography (EEG), and functional Near-Infrared Spectroscopy (fNIRS) (Kübler and Birbaumer, 2008; Murguialday et al., 2011; Gallegos-Ayala et al., 2014; Okahara et al., 2018; Ardali et al., 2019; Han et al., 2019). Though some of such attempts partly succeeded in communication (Okahara et al., 2018; Han et al., 2019), it is still a quite challenging problem. Characterization of EEG in CLIS patients can assist in the development of EEG-BCI-based communication methods with CLIS patients because the knowledge of the EEG frequency characteristics is crucial in the correct selection and exclusion criteria of classification algorithms for BCIs (Nicolas-Alonso and Gomez-Gil, 2012).

Though EEG of non-late-stage ALS patients during resting state have been reported in some studies (Mai et al., 1998; Santhosh et al., 2005; Iyer et al., 2015; Jayaram et al., 2015; Fraschini et al., 2016, 2018; Nasseroleslami et al., 2019) and reviews (Kellmeyer et al., 2018; Proudfoot et al., 2019), little EEG information is available of late-stage ALS patients such as LIS and CLIS. Only one case

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Table 1
Demographic data and EEG measurement conditions of the participants.

Participant ID	Gender	Age (years)	ALS duration (years)	Recording time (seconds)	EEG sensor positions
ALS-CLIS Patients					
P1	F	72	10	311	FCC3, FCC4, FCC5, FCC6, Cz[a]
P2	M	62	4	603	AF3, AF4, FC1[a], FC5[a], FC6[a], CP1[a], CP5[a], CP6[a]
P3	F	79	7	584	FC3, FC4, FC5[a], FC6[a], Cz[a]
P4	F	26	4	487	FC1[a], FC2, FC5[a], FC6[a], CP1[a], CP2, CP5[a], CP6[a]
P5	M	58	7	600	FC1[a], FC2, FC5[a], FC6[a], CP1[a], CP2, CP5[a], CP6[a]
P6	M	37	8	623	FC5[a], FC6[a], C5, C6, Cz[a], T9, T10
P7	F	56	7	753	FC3, FC4, FC5[a], FC6[a], Cz[a]
P8	F	33	6	630	FC1[a]
P9	M	23	4	1032	F3, F4, C3, C4, Cz[a]
P10	M	25	5	641	FC5[a], FC6[a], C5, C6
Healthy Participants					
H1	M	26		684	
H2	F	29		1166	AF3, AF4, FC1[a], FC2, FC3, FC4,
H3	F	51		682	FC5[a], FC6[a], C5, C6, Cz[a], CP1[a],
H4[b]	M	50	N.A.[c]	1268	CP2, CP5[a], CP6[a], Oz
H5	M	65		1258	
H6	M	49		1272	
H7	M	50		1214	

[a] EEG sensors used in the analysis.
[b] Data of H4 was excluded from the analysis due to recording failure and artefact contamination.
[c] Not applicable.

study investigated power spectral densities (PSDs) of 2 ALS-CLIS patients (Hohmann et al., 2018). This study quantitatively reported shifts of the alpha peak frequencies in the CLIS patients toward the lower frequency ranges compared with healthy participants and ALS patients who showed ALSFRS-R (The Revised ALS Functional Rating Scale) (Cedarbaum et al., 1999) scores larger than 0. Other single case studies also reported dominance of low EEG frequencies in ALS-CLIS patients (Hayashi and Kato, 1989; Kotchoubey et al., 2003). However, group-level comparison between ALS-CLIS and healthy people has not been performed yet.

In this study, therefore, to describe the EEG characteristics of ALS-CLIS patients at group level, we investigated the resting-state PSDs of ALS-CLIS patients. The PSD analysis was performed for signals recorded from fronto-central, central, and centro-parietal sensors that could be placed over the scalp of the bedridden patients.

2. Materials and methods

The Institutional Review Boards of the Medical Faculty of the University of Tübingen and Tokyo Institute of Technology approved the study reported in this study. This study is in full compliance with the ethical practice of Medical Faculty of the University of Tübingen and follows the criteria of the Helsinki Accords. Written informed consent for this study was obtained from the patients' legal representatives and the healthy participants.

2.1. Participants

We recorded EEG signals from 10 ALS-CLIS patients and 7 healthy participants. The number of healthy participants was decided so that mean and variance of age were not significantly different in each comparison, considering the different numbers and positions of sensors between the patients due to clinical needs. Table 1 shows the demographic data and EEG measurement conditions. The mean age (standard deviation) was 47.1 (19.7) in patients and 45.7 (12.6) in healthy participants. All patients were in home care and bed-ridden, artificially ventilated and fed. CLIS was defined as inability to communicate with eye movements or any other voluntary muscle with use or non-use of eye trackers for more than 6 months. (After failure of eye-trackers caretakers tried to "read" "yes"- signals from eye or face muscles, in none of the patients any reliable communication was possible. A detailed description of the patients can be found in Malekshahi et al., 2019). All of the patients showed regular circadian patterns of slow wave sleep and waking (Malekshahi et al., 2019).

2.2. EEG acquisition

In the EEG measurement, the CLIS patients and the healthy participants were instructed to relax, try not to think anything, and refrain from sleeping. Eyes of the CLIS patients were closed (they can only be opened actively by caretakers). Healthy participants were additionally instructed to keep their eyes closed and not to move throughout the measurement. EEG sensors were attached according to the 10-5 system, with one reference channel attached to their right mastoids. EEG signals were recorded using a V-Amp amplifier and passive electrodes (Brain Products GmbH, Gilching, Germany). In the measurement of the patients, electrooculogram (EOG), chin electromyogram (EMG), and Near-Infrared Spectroscopy (NIRS) sensors were also attached to faces and heads for other clinical and research purposes. Due to clinical needs, the numbers and positions of sensors were different between the patients, while they were identical across the healthy participants (Table 1). The EEG data were measured in the afternoon for all the CLIS patients and healthy participants to equalize their conditions in terms of the circadian rhythm. The EEG data from one of the healthy participants (H4) was excluded from the analysis due to recording failure of EEG sensors and artefact contamination.

2.3. EEG processing

EEG signals were processed using Matlab R2016b (The MathWorks, Inc., Natick, Massachusetts, U.S.A.) and EEGLAB 14.1.1 software (Delorme and Makeig, 2004). In the preprocessing, a high-pass finite impulse response (FIR) filter at 0.5 Hz and a low-pass FIR filter at 45 Hz were applied to the raw EEG signals, followed by down-sampling to 100 Hz to save computational cost. Subsequently, we extracted five 1-minute epochs (i.e., 5-minute data in total) containing minimal artefacts such as muscle activities and body movements by visual inspection.

Considering the difference of sensor positions in CLIS patients due to clinical limitation, we decided to use 7 sensors FC5, FC6, Cz, FC1, CP1, CP5, and CP6 (Table 1) for the PSD comparison analysis.

Specifically, FC5 and FC6 were used for 7 patients (patient ID: P2, P3, P4, P5, P6, P7, and P10), Cz was used for 5 patients (patient ID: P1, P3, P6, P7, and P9), FC1 was used for 4 patients (patient ID: P2, P4, P5, and P8), and CP1, CP5, and CP6 were used for 3 patients (patient ID: P2, P4, and P5). For these 7 sensors (FC5, FC6, Cz, FC1, CP1, CP5, and CP6), PSDs of these patients were compared with PSDs of all the 6 healthy participants (H1, H2, H3, H5, H6, and H7), respectively. For each sensor, PSD for each 1-minute epoch was calculated by Fast Fourier Transform (FFT) of 1-second time window with 0.25-second overlap, and each participant's PSD was obtained by averaging five 1-minute PSDs. Hann window was applied as the window function. We averaged 1185 PSDs (237 PSDs per 1-minute epoch × 5 epochs) to get each participant's representative resting-state PSD. From the PSD, delta (1−3 Hz), theta (4−7 Hz), low alpha (8−10 Hz), high alpha (11−13 Hz), beta (14−30 Hz), and gamma (31−40 Hz) band power was calculated by averaging power in the corresponding frequencies.

2.4. Statistical analysis

Statistical tests were performed in free software R (R Core Team, 2018). Due to small sample sizes, we applied a two-tailed Wilcoxon rank sum test to test the power difference between the CLIS patients and the healthy participants for each frequency band and sensor. The obtained p-values were False Discovery Rate (FDR) corrected using the Benjamini-Hochberg method to compensate for the multiple comparison of 6 frequency bands and 7 sensors (Benjamini and Hochberg, 1995). Additionally, at sensors where significant difference of frequency band power was observed in the above comparison, correlation between frequency band power and ALS duration in the CLIS patients was tested based on Spearman's rank correlation coefficient for each frequency band. The obtained p-values were FDR corrected for the multiple comparisons (Benjamini and Hochberg, 1995).

3. Results

For each comparison the mean and the variance of age were not significantly different between the CLIS patients and the healthy participants (two-tailed *t*-test and *F*-test).

On Figs. 1A and B, we show filtered EEG time series of a representative CLIS patient (Fig. 1A) and a healthy participant (Fig. 1B) at sensor Cz. Figs. 1C and D show PSDs at Cz for the 5 CLIS patients who could use Cz for the recording (patient ID: P1, P3, P6, P7, and P9 as described above and in Table 1) and the 6 healthy participants, and their mean PSDs are compared in Fig. 1E. These figures show the dominance of slow oscillations in the CLIS patients. In the same manner, we also calculated PSDs of the other sensors (FC1, FC5, FC6, CP1, CP5, and CP6), and frequency band power of the CLIS patients and the healthy participants at all of the sensors are statistically compared and summarized in Fig. 2. Figs. 2A–F show power in the delta, theta, low alpha, high alpha, beta, and gamma bands, respectively. In the high alpha band (Fig. 2D), power between the two groups was significantly different at sensor FC5 ($p = 0.044$). In the beta and gamma bands (Figs. 2E and F), power between the two groups was significantly different at sensors FC1, FC5, FC6, and Cz ($p = 0.044$, 0.016, 0.016, and 0.030 respectively in the beta band and $p = 0.044$, 0.016, 0.024, and 0.030 respectively in the gamma band).

In the correlation analyses, we included only sensors FC1, FC5, FC6, and Cz because significant differences of frequency band power between the CLIS patients and the healthy participants were observed at these sensors. Relationships between frequency band power and ALS duration in the CLIS patients at these 4sensors are depicted in Figs. 3A–F. Spearman's rank correlation coefficients at sensors FC1, FC5, FC6, and Cz were −0.32, 0.17, −0.24, and −0.82 respectively in the delta band, −0.32, −0.37, −0.71, and −0.87 respectively in the theta band, −0.63, −0.51, −0.88, and −0.46 respectively in the low alpha band, −0.95, −0.51, −0.88, and −0.46 respectively in the high alpha band, −0.95, −0.75, −0.73, and −0.46 respectively in the beta band, and −0.95, 0.15, −0.47, and −0.41 respectively in the gamma band. No correlation coefficients were statistically significant after FDR correction.

4. Discussion

We investigated resting-state EEG of ALS-CLIS patients to provide insight into their electric brain activities and possible state of consciousness. The CLIS patients showed significant power decrease in the high alpha band at sensor FC5 and in the beta and gamma bands at sensors FC1, FC5, FC6, and Cz. This group-level comparison using EEG data of CLIS patients and healthy participants demonstrated clear EEG power differences.

Different state of consciousness and arousal is the most discussed reason for the power decrease in the alpha and beta bands. Patients with Alzheimer's dementia show a decrease of the absolute power in the alpha and beta bands together with an increase in the delta and theta bands in comparison with healthy participants during eyes-closed resting state (Pucci et al., 1998). Some ALS patients may also show cognitive impairment in various domains such as executive function, language, and fluency (Phukan et al., 2007; Raaphorst et al., 2010; Goldstein and Abrahams, 2013; Beeldman et al., 2016). Mild cognitive deficits are more frequently observed in the advanced stage of ALS than in the early stage (Crockford et al., 2018). However, there is also a report with LIS patients suffering from ALS who showed no signs of cognitive decline during testing using an eye-tracking system (Linse et al., 2017). None of the studies cited here found a significant relationship between the reduction of band power and cognitive performance. At present, testing of cognitive capacities becomes increasingly difficult with progressing paralysis and finally impossible in LIS and CLIS. Thus, any conclusion about such a relationship remains highly speculative. However, a decreased state of central arousal during waking seems plausible associated with the complete immobility and consequent deprivation of environmental stimulation.

There are inconsistent reports about the relationship between the decrease of the gamma band power and cognitive impairment. Herrmann and Demiralp suggested relationship between the alteration of the gamma band activity and disturbed cognitive function (Herrmann and Demiralp, 2005), while van Deursen et al. reported that patients with Alzheimer's dementia showed power increase in the gamma band during eye-open resting state in comparison with healthy participants (van Deursen et al., 2008). In comparison with healthy people, we should not ignore the effect of absence of muscle activities in CLIS patients because high frequency bands such as the gamma band are easily contaminated by muscle activities (Pope et al., 2009). Though we instructed the healthy participants not to move during the EEG recordings, the decrease of the gamma band power in the CLIS patients in comparison with the healthy participants can be partly due to the loss of muscle activity. Accordingly, it is premature to associate the gamma band power reduction with cognitive impairment without reliable findings from a cognitive testing procedure.

Another reason for the power decrease in the alpha band could be reduced vigilance and outward attention, since the alpha peak frequency is suggested to be associated with the activities in brain regions modulating attention in healthy people (Jann et al., 2010). The "extinction of goal-directed thinking" hypothesis formulated by Kübler and Birbaumer predicts the reduction of arousability and vigilance in CLIS patients due to suppressed social-cognitive inter-

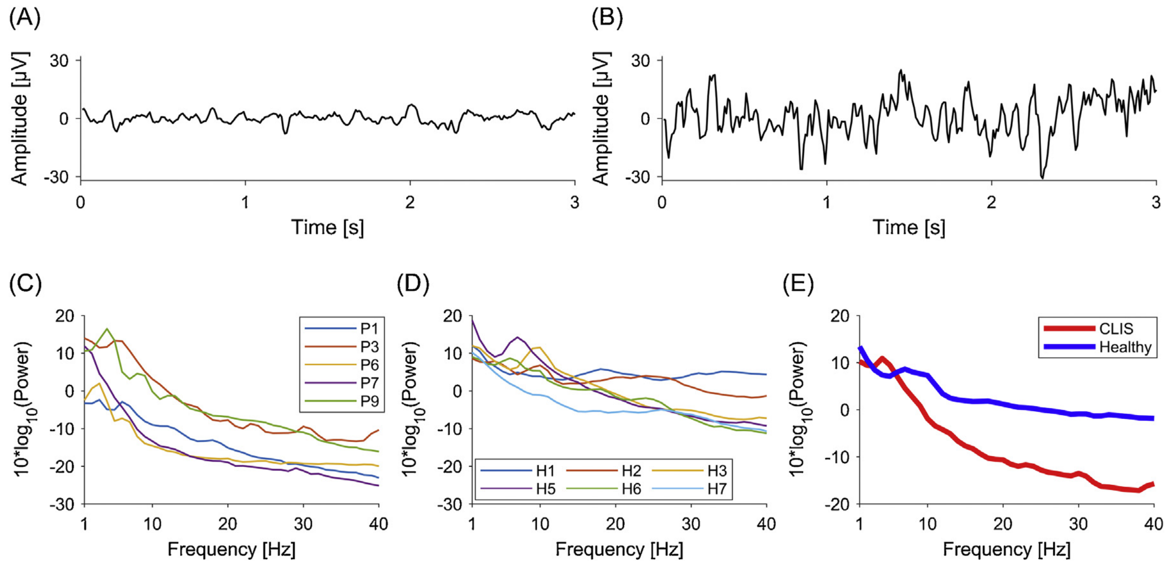

Fig. 1. EEG time series and power spectral densities of the CLIS patients and the healthy participants at sensor Cz. (A) EEG of a CLIS patient (P1). (B) EEG of a healthy participant (H3). (C) PSDs of the 5 CLIS patients (P1, P3, P6, P7, and P9). (D) PSDs of the 6 healthy participants (H1, H2, H3, H5, H6, and H7). (E) Mean PSDs of the 5 CLIS patients and the 6 healthy participants.

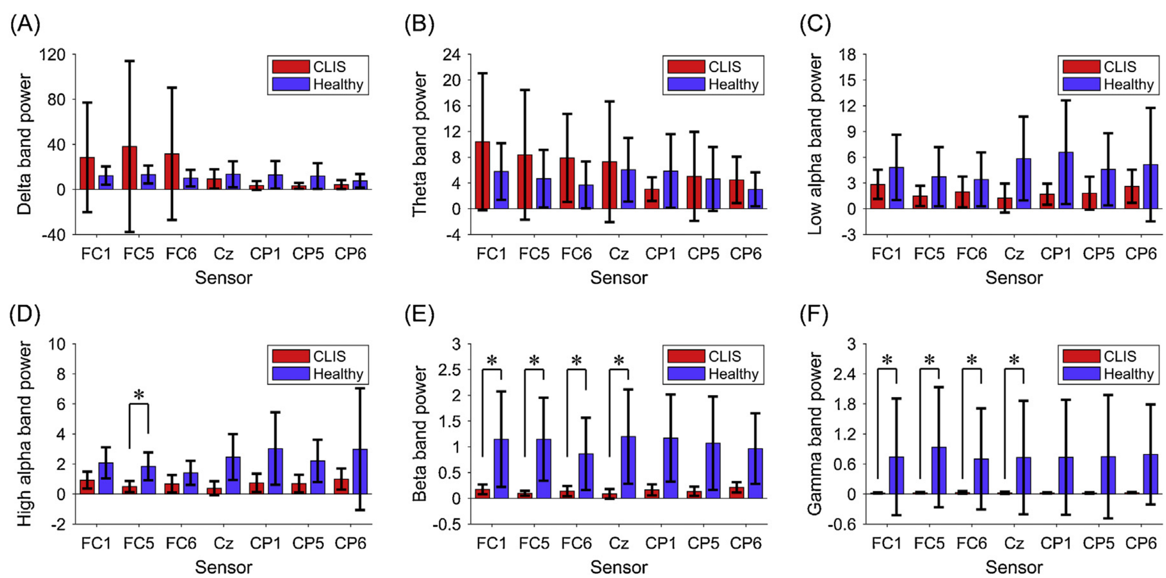

Fig. 2. Mean frequency band power at sensors FC1, FC5, FC6, Cz, CP1, CP5, and CP6. Error bars represent standard deviations. Significant power differences between the CLIS patients and the healthy participants in two-tailed Wilcoxon rank sum test with False Discovery Rate correction are marked: *p < 0.05. (A) Delta band (1–3 Hz). (B)Theta band (4–7 Hz). (C) Low alpha band (8–10 Hz). (D) High alpha band (11–13 Hz). (E) Beta band (14–30 Hz). (F) Gamma band (31–40 Hz).

action (Kübler and Birbaumer, 2008). However, it is also impossible to affirm a reduced vigilance and outward attention in CLIS patients without any existing behavioral evidence. To investigate the attentional and cognitive function in CLIS patients and their relationship with the EEG characteristics, functioning BCI systems allowing more flexible communication than simple yes/no responses are necessary (Ardali et al., 2019).

Both, the decrease of the alpha and gamma band power may be in part due to loss of motor control. Most EEG-based BCIs use power changes in the alpha band in accordance with preparation and start and stop of imagined or executed body movements. These phenomena are called event-related desynchronization (ERD) for movement and event-related synchronization (ERS) for stopping movements, and are commonly observed in EEG signals recorded from central area (Pfurtscheller and Aranibar, 1979). Although the exact neuro-physiological mechanisms of the phenomena have not been clarified yet, CLIS patients may have less neural activation in the motor related areas, which may be related to the power decrease in the alpha band. Gamma band power is also reported to be involved in action execution in studies using ECoG (Pistohl et al., 2008; Nakanishi et al., 2013; Babiloni et al., 2016). On the other hand, some BCI studies reported that LIS and non-late-stage ALS patients succeeded in controlling a speller or a web browser using neuronal signals from intracortical electrodes placed in the hand area of dominant motor cortex (Vansteensel et al., 2016; Pandarinath et al., 2017; Nuyujukian et al., 2018). Considering the success of the BCI-use in these studies, the power decrease in the frequency bands may just indicate shifts of alpha frequency to lower frequencies such as theta or delta, which has been suggested in previous studies (Hohmann et al., 2018; Malekshahi et al., 2019). Our results may also indicate this tendency of a shift of alpha as shown in Fig. 1.

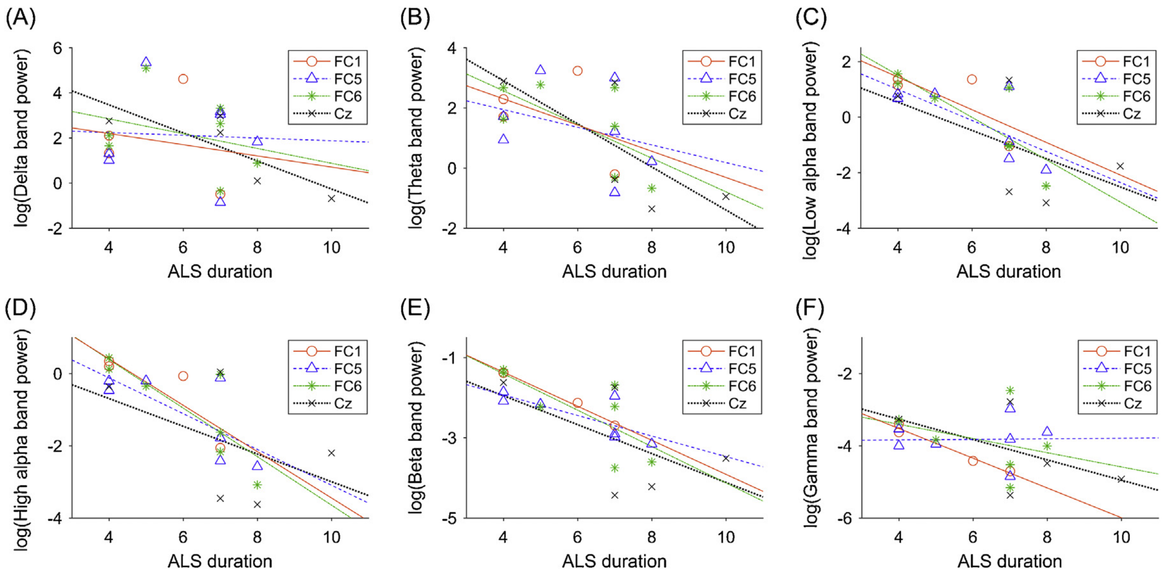

Fig. 3. Scatter plot of ALS duration and frequency band power at sensors FC1, FC5, FC6, and Cz. Red circles, blue triangles, green stars, and black crosses represent individual patients' data for FC1, FC5, FC6, and Cz, respectively. The corresponding lines represent linear approximation calculated by a least-squares method. (A) Delta band (1−3 Hz). Spearman's correlation coefficients (ρs) were −0.32, 0.17, −0.24, and −0.82 at sensors FC1, FC5, FC6, and Cz respectively. (B)Theta band (4−7 Hz). ρs were −0.32, −0.37, −0.71, and −0.87 at sensors FC1, FC5, FC6, and Cz respectively. (C) Low alpha band (8−10 Hz). ρs were −0.63, −0.51, −0.88, and −0.46 at sensors FC1, FC5, FC6, and Cz respectively. (D) High alpha band (11−13 Hz). ρs were −0.95, −0.51, −0.88, and −0.46 at sensors FC1, FC5, FC6, and Cz respectively. (E) Beta band (14−30 Hz). ρs were −0.95, −0.75, −0.73, and −0.46 at sensors FC1, FC5, FC6, and Cz respectively. (F) Gamma band (31−40 Hz). ρs were −0.95, 0.15, −0.47, and −0.41 at sensors FC1, FC5, FC6, and Cz respectively.

We calculated the correlation coefficients between the EEG power and the disease duration. Though we found no significant correlation in this study and it is difficult to reach a conclusion with such a limited number of patients, the frequency band power at most sensors tended to decrease as the ALS duration was long. In addition to the disease duration, other factors such as progression rate of the disease, age, and medication may be responsible for such hypothetical relationships with the demonstrated power reduction. An important factor affecting the difference between CLIS patients and healthy participants may result from artificial respiration over extensive time periods, a rule in CLIS patients. Hyper- as well as hypoventilation is strongly related with EEG-slowing (Hoshi et al., 1999). However, both, long-term hyperventilation and lack of oxygen lasting minutes or more, are causing reduced central and subjective arousal and are thus compatible with our conclusion of lowered arousal level in CLIS. If resting-state EEG of ALS patients progressing toward CLIS can be recorded longitudinally before and after artificial respiration, it will reveal the relationship between the EEG power and ALS progression and respiration-related changes. Furthermore, if ALS patients would use a BCI-based communication method already in the early stage of the disease, the BCI-use might play a role as a device to prevent the power decrease in the higher frequency bands due to continued cognitive demands and increased environmental stimulation. For stroke patients, an ERD-based BCI has been used as a rehabilitation to restore or reorganize their neural processing for their partially paralyzed body (Ramos-Murguialday et al., 2013). To investigate whether the use of BCI-based communication has the effect of preventing the power decreases and/or changing subjective arousal and activation in ALS patients, studies applying BCI for ALS patients from the early stage are needed. In addition, although the population of CLIS is small, a study with more CLIS patients in comparison with non-late-stage ALS patients is necessary to further quantify their EEG signatures.

In conclusion, this study showed altered oscillatory brain activities of CLIS patients compared with healthy participants. We found significant power decrease in the high alpha, beta, and gamma bands at fronto-central and/or central channels in the CLIS patients suggesting reduced central arousal. We think the observed EEG change may indicate a shift of the alpha band toward lower frequencies. This overall slowing may indicate a different state of vigilance and attention and may not allow the application of comparable cognitive tasks as in healthy subjects for which most BCI paradigms were developed. Thus, BCIs that entail tasks that seem difficult for LIS and CLIS patients should be replaced. In addition, many BCIs that rely on the classification of ERD/ERS using the defined frequency band of 8–15 Hz will not function because in LIS and CLIS frequency bands below 8 Hz seem to be relevant. Changes of the target frequencies may be needed because the target brain activities may be represented in the slower frequency ranges in CLIS patients. Further investigation using longitudinal recordings and use of BCIs are required to clarify the effect of BCI-use as a rehabilitation method and if the power decrease correlates with loss of motor control, cognitive changes, reduced vigilance, and/or emergency treatment effects such as artificial respiration and feeding.

Author contributions

NY, NB, and UC conceptualized and designed the study. AR, AM, AT, AJ, and UC collected the data. YM performed analysis. NY supervised analysis. YM, NY, NB, and UC wrote the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Appendix 6.

A. Jaramillo-Gonzalez, S. Wu, A. Tonin, A. Rana, M. Khalili-Ardali, N. Birbaumer, U. Chaudhary (2021). A dataset of EEG and EOG from an auditory EOG-based communication system for patients in locked-in state, Nature Scientific Data, 8, 8.
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SCIENTIFIC DATA

OPEN

DATA DESCRIPTOR

A dataset of EEG and EOG from an auditory EOG-based communication system for patients in locked-in state

Andres Jaramillo-Gonzalez[1], Shizhe Wu[1], Alessandro Tonin[2], Aygul Rana[1], Majid Khalili Ardali[1], Niels Birbaumer[1,3] & Ujwal Chaudhary[1,2] ✉

The dataset presented here contains recordings of electroencephalogram (EEG) and electrooculogram (EOG) from four advanced locked-in state (LIS) patients suffering from ALS (amyotrophic lateral sclerosis). These patients could no longer use commercial eye-trackers, but they could still move their eyes and used the remnant oculomotor activity to select letters to form words and sentences using a novel auditory communication system. Data were recorded from four patients during a variable range of visits (from 2 to 10), each visit comprised of 3.22 ± 1.21 days and consisted of 5.57 ± 2.61 sessions recorded per day. The patients performed a succession of different sessions, namely, Training, Feedback, Copy spelling, and Free spelling. The dataset provides an insight into the progression of ALS and presents a valuable opportunity to design and improve assistive and alternative communication technologies and brain-computer interfaces. It might also help redefine the course of progression in ALS, thereby improving clinical judgement and treatment.

Background & Summary

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that, in its final stages, paralyzes affected individuals impairing their ability to communicate[1–4]. Those patients with intact consciousness, voluntary eye movement control, who can blink their eyes or twitch their muscles are said to be in a locked-in state (LIS)[5,6]. Patients in LIS rely on eye-tracking based assistive and augmentative communication (AAC) technologies to communicate[7,8]. In the case of patients who survive attached to life-support systems, the progression of the disease ultimately destroys oculomotor control, leading to the loss of gaze-fixation and impeding the use of eye-tracking based communication technologies[9–11]. Nevertheless, even in the late stages of this condition, some remaining controllable muscles of the eyes continue to function for an unspecified length of time, which can be used to provide a means of communication to these patients[11,12].

An auditory electrooculogram (EOG) based communication system[12] was developed to provide a means of communication to ALS patients without gaze-fixation and who were unable to use the commercial AAC eye-tracking devices, but who had remnant oculomotor control to form words, phrases, and sentences using the system described in Tonin & Jaramillo-Gonzalez *et al.*[12]. Four ALS patients with progressively decreasing EOG signal amplitude in the range of ±200 µV to ±40 µV were able to select letters to construct words to form sentences and hence communicate freely using an auditory speller system. The auditory speller system is based on a binary system in which a patient is asked to respond to auditory questions by moving the eyes to say "yes" and not moving the eyes to say "no". The system must use the auditory modality because, in these patients, vision is often impaired due to drying and necrosis of the cornea and the partly or fully paralyzed eye-muscles. The study design and paradigm are described in detail in the Methods section.

This data descriptor outlines the EEG and EOG recordings from four different patients recorded during their use of the auditory communication system, having first trained progressively, and then ultimately controlling the

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system to communicate. Electromyography (EMG) recordings are available for some sessions, according to the clinical conditions.

There have been other studies with similar goals, but only one has an available online dataset[13], with different features. To our knowledge, in the available open-access specialized repositories[14–16], there are no datasets with similar properties to the one described here. It must be emphasized that the data described here are both the EOG and EEG signals recorded with a dedicated set of electrodes for each type of signal simultaneously. These EEG and EOG data are recorded from patients with ALS in the most advanced stage, whose disease progression is not well defined and is, to a certain extent, unknown. The data highlight a phase in ALS where communication becomes difficult and gradually impossible with existing commercial AAC. It includes recordings of over the course of a year during which one of the users became unable to use the system because of disease progression. As a consequence, we believe that the study of this dataset might help towards improving the clinical definition of ALS in its very advanced state, the testing of hypotheses on the brain's electrophysiological changes during this progression and evaluating the impact of advanced ALS on the cognitive state of the patients. Nevertheless, even though the data is quite specific, further investigation of the data can support novel clinical and therapeutic practices. It could help develop augmentative and alternative assistive communication technologies and brain-computer interfaces that can be generalized to other types of disorders and patients with pervasive communication deficits and motor impairments due to CNS damage, such as stroke or high spinal cord injury. Lastly, although the system can be considered successful in enabling communication, other analytical methods can still improve the system's speed and efficiency, for example, offline testing of other feature extraction methods or testing and comparing the performance with different machine-learning methods to classify the patients' response.

Methods

The Internal Review Board of the Medical Faculty of the University of Tubingen approved the experiment reported in this study. The study was performed according to guidelines established by the Medical Faculty of the University of Tubingen. The patient, or the patient's legal representative, gave informed consent with permission to publish the data. The clinical trial registration number is: ClinicalTrials.gov - Identifier: NCT02980380. The methods described here are complementary to an in-depth description of the results derived from this dataset that have been presented in related work[12].

Participating patients. Four ALS patients with amyotrophic lateral sclerosis with a functional rating scale revised (ALSFRS-R)[17] score of 0 in the locked-in state (LIS) were visited on subsequent months starting from Feb 2018 to May 2019. Team members travelled to the patient's home to perform the communication sessions, depending on the health status and convenience of the patient. The medical history of patients is described in our related work[12]. Every visit (V), lasted for a few days (D), during which the patient performed different session (S), as detailed in the Online-only Tables 1–4, with the precise dates of all the visits and details of the sessions.

Auditory communication system. *Prerequisites for performing the study.* In agreement with the patients' caretakers and considering the patients' health and wellness and optimization of resources, it was established that the visits should be performed every two months approximately, with each visit no longer than four days. However, on some occasions the condition of the patients led to shorter visits, from three days to a single day. (see Online-only Tables 1–4). For each visit, guided by the same criteria of health and wellness of the patient, two team members transported all equipment and set up all systems in the patient's home or accommodation.

Before the beginning of the study, at least 100 questions with known "yes" or "no" answers were formulated and recorded by a family member or caretaker in their own voice, in close proximity to the patient. Each question with a "yes" answer is paired with a similar question with "no" answer (e.g., "Paris is the capital of France" and "Berlin is the capital of France"). Each question is saved as an audio file with an explicit identifier, a question with a "yes" answer is saved with a 001_NUMBER identifier, and a question with "no" answer is saved with a 002_NUMBER identifier. The value of the label NUMBER is the same for a semantically paired sentence. The same procedure was repeated with biographical-related questions with at least 100 for every patient. Sentences are then stored on a laptop and accessed and played by the communication system during the sessions.

Study and paradigm. The study consisted of patients performing four different types of sessions, namely, Training, Feedback, Copy speller, and Free speller session, to train and enable the patient to employ an oculomotor strategy to control the spelling system successfully. During the visit, the patient performed different sessions, as depicted in Fig. 1. The patients developed a strategy to respond during successive trials to an auditory question (the questions previously recorded) by moving the eyes to say "yes" and by not moving the eyes to say "no". To control the activities during the trials, specific paradigms were designed for the different sessions, as depicted in Fig. 2.

The different sessions performed by the patients are described below.

a. Training session
The study on a single day always started with Training sessions during which the patients were instructed to listen to a sequence of 20 personal questions consisting of 10 sentences with a "yes" answer and 10 with "no" answer, presented in pseudo-random order. After the system presents an auditory question, patients are asked to move their eyes to respond "yes" and not to move the eyes to respond "no" during a response time window. The duration of the response segment depended on the patient's performance, i.e., if the patient could move his/her eye with ease, the duration was kept shorter and vice versa. Therefore, this window has a range from 3 to 10 seconds. For each Training session, the set of triggers indicating the sequence of events were recorded on the raw file, using the labels shown in Fig. 2a. Alongside, the system creates a questions sequence text file (Block_X_senlist.txt) that includes the list of identifiers of the presented audio/

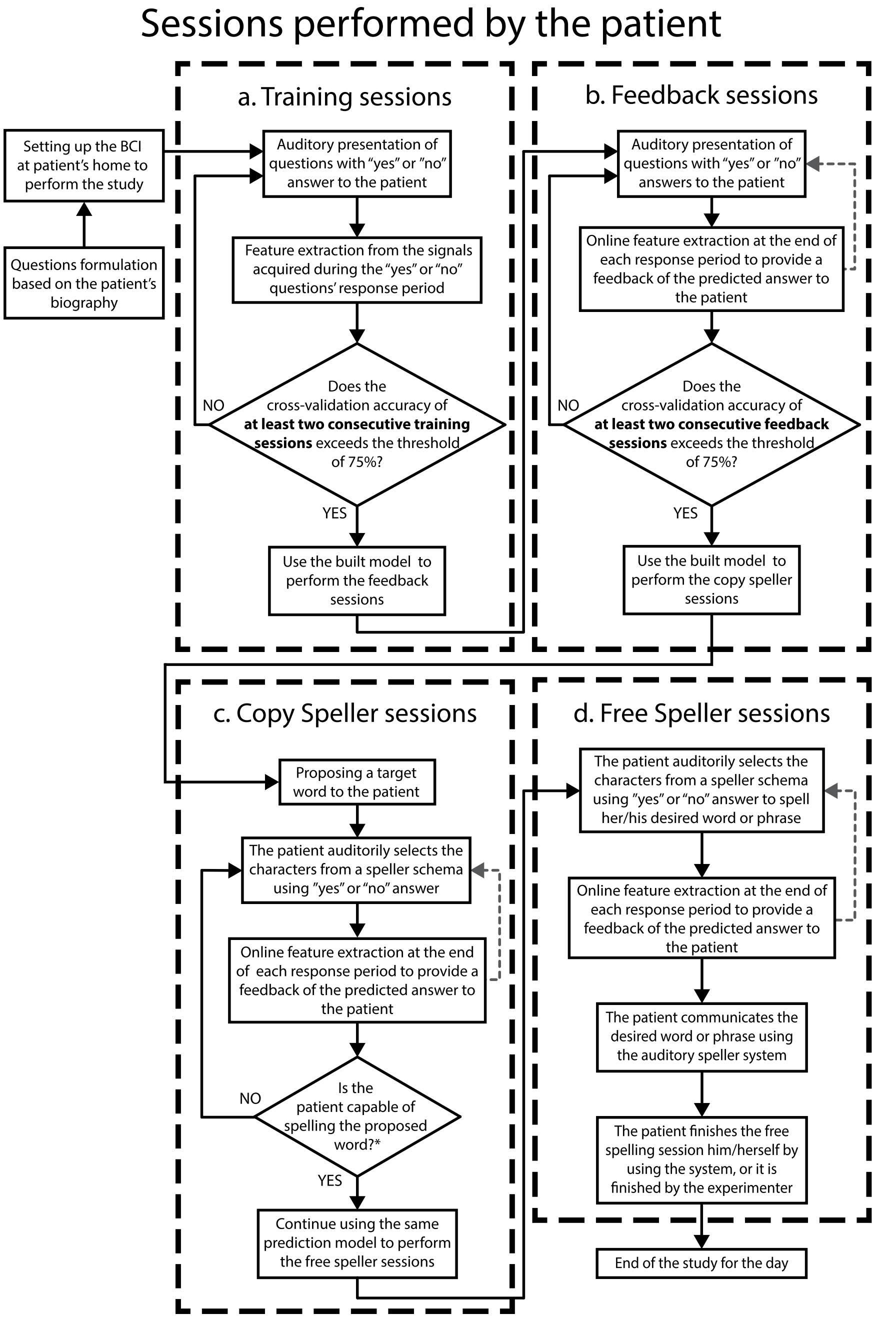

Fig. 1 The procedure performed during a single day. The figure depicts the sequence of the types of sessions performed by patients and the criteria to progress from one type of session to the next. The patients first performed the Training sessions during which the patient learned to move his/her eyes to generate the signal to control the auditory communication system. At the end of the Training session, a classification model was built, and when the accuracy of the built model was greater than 75% the patients performed the feedback session. During the feedback sessions the patients were provided the feedback of their response, i.e., whether their answer was classified as "yes" or "no". When the feedback accuracy exceeded 75% the patients first performed a copy speller session and then a free speller during which they could spell whatever they desired.

question files during the session (e.g., 001_13012a.wav), including also the label of the corresponding type of answer ("0" for sentences with "no" as an answer, and "1" for sentences with "yes" as an answer). The. txt lists are included inside the raw data folder structure, as described in the section Data Records. After at least two consecutive Training sessions with a classification accuracy result greater than 75%, the patient progresses to the Feedback sessions (see Fig. 1).

b. Feedback session
As in the Training session, the patients were presented with a sequence of a familiar question, but, at the end of the response segment, they were provided with auditory feedback as to whether their answer was

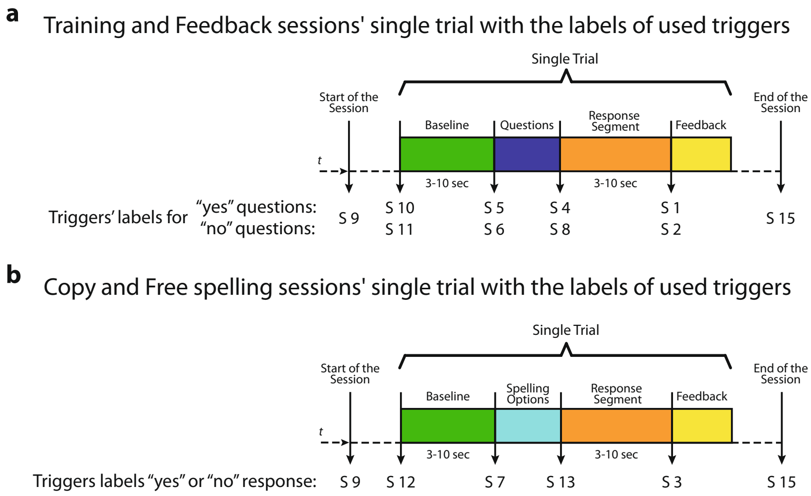

Fig. 2 Different types of trials in the study. (**a**) Paradigm describing the sequence of events and sequence of the triggers' labels used in a single trial for the Training and Feedback sessions. In these types of sessions, 20 questions with "yes" and "no" answers, known by the patient, are presented in a pseudo-random order. (**b**) Paradigm describing the sequence of events and sequence of the triggers' labels used during a single trial for the Copy and Free spelling sessions. In these sessions, instead of questions, the patient is presented with options that allow him/her to navigate through his/her predetermined spelling scheme (e.g., sectors, letters). For both spelling sessions, the limit in the number of trials depends only on the patient's attempts to spell the given target (i.e., Copy speller sessions) or her/his desired sentence (i.e., Open speller sessions). For any type of session recorded, the recording's start and end are indicated by an "S 9" and an "S 15" trigger.

recognized as "yes" or "no" by the system. For each Feedback session, the triggers indicating the events' sequence were recorded on the raw file, using the labels shown in Fig. 2a. The system creates a sentence list (Block_X_senlist.txt) in the same way it was created for the Training sessions. In the case of Feedback sessions, in addition to the sequence of the questions text file, the system creates a result file (Date_result_f1_X.txt) listing the predicted results, i.e., "1" if the answer was recognized as "no", "0" if the answer was recognized as "yes", and "2" if the answer was unable to be classified by the system. The system gives the patient auditory feedback with the sentence: "Your answer was classified as yes/no". Both.txt lists are also included inside the raw data folder structure, as described in the section Data Records. After at least two consecutive Feedback sessions with a classification accuracy result greater than 75%, the patient progresses to the Copy spelling sessions (see Fig. 1).

The sequence of events and triggers (with their labels) for a single trial of the Training and Feedback sessions is depicted in Fig. 2a. Each of these trials consists of the segment of baseline (i.e., no sound presented), stimulus, during which the question is presented auditorily to the patients, followed by the segment of response time, in which the patient moves or does not move the eye according to his/her answer, and lastly the segment of feedback. For a Training session trail, the feedback is "thank you" to mark the end of the response while for a Feedback session trail, the feedback is "yes" or "no" depending on the answer classified by the system.

c. Copy spelling session
During the Copy spelling sessions, the patients were asked to spell a specific word described in our previous work[12]. For each Copy spelling session, the set of triggers indicating the sequence of events was recorded on the raw file, as shown in Fig. 2b. For the Spelling sessions, there are no questions sequence text files, but there are results files (Date_result_f1_X.txt) with the label of the predicted answer, listing the predicted results as "1" if the answer was recognized as "no", "0" if the answer was recognized as "yes", and "2" if the system was unable to classify the answer. The.txt lists are also included in the raw data folder structure described in the section Data Records.

d. Free spelling session
After completing the Copy spelling session, the patients were asked to spell whatever he/she desired. For each Free spelling session, the set of triggers indicating the sequence of events were recorded on the raw file, as shown in Fig. 2b. As in the Copy spelling case, each Free spelling session created a result file (Date_result_f1_X.txt) using the same label code. The.txt lists are also included in the raw data folder structure described in the section Data Records.

The trials for the Copy and Free spelling sessions do not consist of the pre-recorded personal questions, but instead, of "yes"/"no" questions asking the patient whether to select or not, a particular letter, group of letters, or command, from his/her particular speller scheme[12]. Copy and Free spelling sessions differ in terms of the instruction given to the patient. During the Copy spelling sessions, the patient was asked to spell a specific word, while during the Free spelling sessions, the patient was asked to spell whatever he/she desired. Consequently, instead

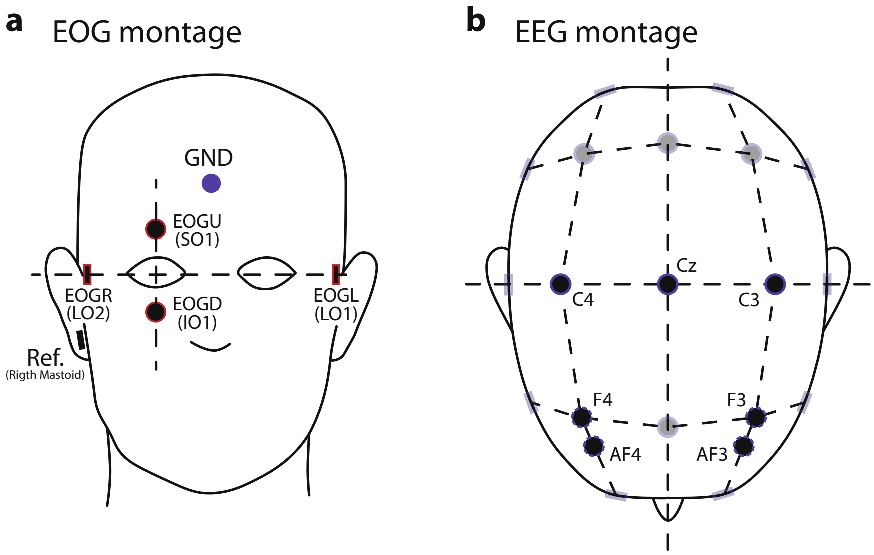

Fig. 3 EOG and EEG setup. (**a**) Montage for the minimum number of EOG channels for each recorded session, using the locations LO1 (left cantus) and LO2 (right cantus) for horizontal eye movement, and SO1 (above superior orbit) and IO1 (below inferior orbit) for vertical eye movement. We used the labels EOGL, EOGR, EOGU, and EOGD, respectively, for the *online* study. (**b**) Montage for the minimum number of EEG electrodes for each recorded session, emphasizing the central motor (C4, Cz, C3) and prefrontal areas. In this latter case, the location of used electrodes might vary between F3 and F4, or Af4 and Af3. Nevertheless, the total number of electrodes might vary between days of the visits due to the patient's wellness conditions. The exact number of electrodes and labels used can be verified in the Online-only Tables S1–S4.

of being a fixed number, the number of trials in these sessions depends on the number of attempts performed by the patient to spell the given target (for the Copy speller sessions) or his/her desired sentence (for the Free speller sessions).

The sequence of events and triggers (with their labels) for a single trial for the Copy and Free spelling sessions is depicted in Fig. 2b. The trials consist of the segment of baseline (i.e., no sound presented), stimulus, where instead of questions the patient is presented with auditory options that allow him/her to navigate through his/her predetermined spelling scheme[12] (e.g., sectors, characters, letters), followed by the response time segment in which the patient move or not move the eye according to his/her answer. Lastly, the feedback segment, during which depending on the answer classified by the system, "yes" or "no" auditory feedback is given to the patient.

Regardless of the session type, the recording time's start and end are labeled by "S 9" and "S 15" triggers. During each trial, the sequence of events is presented to the patient and simultaneously, in a synchronized manner, a system of digital triggers is created by a Matlab script interacting with the V-Amp amplifier, to indicate the onset of each event in the time series. Both Fig. 2a,b show the sequence of triggers (their labels) as used in each trial. Information on the onset and labels of each event is also provided (see section Data Records).

We have to add that during the setting up of the system or the sessions' execution, patients' care and wellness were a high priority; therefore, under any request or signal of unease, sessions or even the day's study were stopped.

System for data acquisition. The communication system is composed of the different elements described below.

- Laptop: The present setup uses a laptop with 8 GB RAM, Windows 7 operating system, and 3.3 GHz processor.
- EEG amplifier and recorder: For each session, EEG and EOG channels were recorded according to the 10-20 EEG electrode positioning system, with a 16 channel EEG amplifier (V-Amp DC, Brain Products, Germany) with Ag/AgCl active electrodes.
- EOG channels: at least four electrodes were recorded (positions SO1 and IO1 for vertical eye movement, and LO1 and LO2 for horizontal eye movement).
- EEG channels: at least seven channels located in central and prefrontal areas were recorded (exact locations per day in the Online-only Tables 1–4).
- EMG channels: on a limited number of sessions electrodes located on the chin of the patient or any other face muscle with assumed remaining function.

All the channels were referenced to an electrode on the right mastoid and grounded to electrode FPz on the forehead. For the montage, electrode impedances were kept below 10 kΩ. The sampling frequency was 500 Hz. The standard montage for the minimum number of available EOG and EEG electrodes is specified in Fig. 3. The precise number and location of electrodes available for each session are detailed in the Online-only Tables 1–4, including recording EMG electrodes.

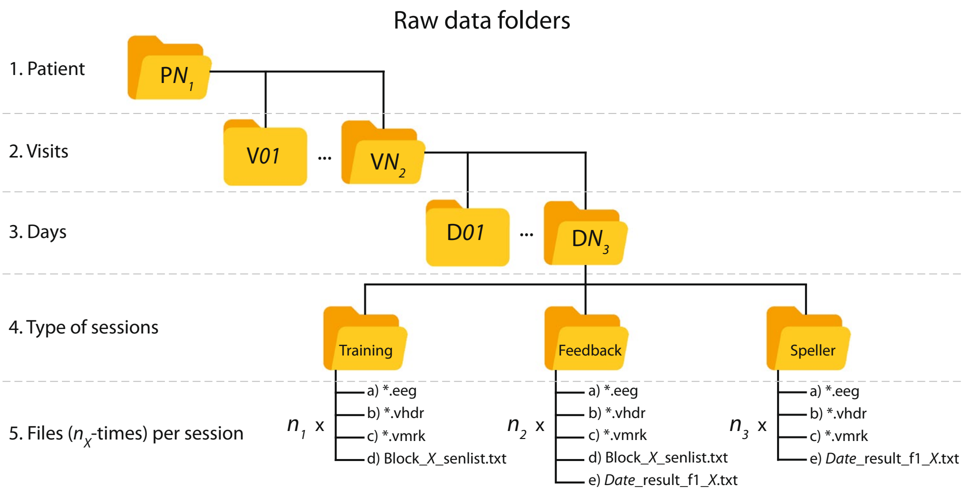

Fig. 4 Raw data folder structure. Structure of nested folders containing the raw recordings of the study. According to the patient identifier, the upper level is the folder, which can be $PN_1 = 11,13,15$ or 16. In the next level, VN_2 indicates the total number of visits available for that patient, and inside it, *DN3* indicates the number of days that the visit lasted. Each day's folder stores subfolders for the Training, Feedback, and spelling (that stores recordings from both the Copy and Free speller sessions). Each of these folders contains a set of files that are the outcome of a recorded session (detailed in the section Data Records), times the number that particular type of session (i.e., n_1, n_2, and n_3) was respectively performed during the day.

- Serial cable: This cable is used to connect the Laptop and the EEG amplifier to send the triggers with the custom Matlab code to mark the EEG-EOG recording with the different segments' starting point.
- Loudspeakers: Loudspeakers connected to the laptop performs the function of delivering the audio stimuli to patients during the Training/Feedback/Copy spelling/Free spelling sessions, as described below.

Data Records

Raw data folders. The data stream was recorded directly from the EEG amplifier and stored with the proprietary BrainVision Recorder format[18,19] during the sessions. According to the dongle key available during the visit, the data were stored in two possible formats, necessary to access and use BrainVision Recorder, 42% of data were recorded in *.ahdr and the rest 58% in *.vhdr format. For consistency here, we present the data in *.vdhr after converting the other 42% of *.ahdr format data also to *.vhdr format. Thus, as an output of this recording scheme, three output files per recording had the same name but different extension:

a. Header file (*.vhdr), containing recording parameters and further meta-information, as the scaling factor necessary to convert the recorded raw amplitude to milivolts.
b. Marker file (*.vmrk) describes the events and their onset during the data recording, in this case, the sequence of triggers.
c. Raw EEG data file (*.eeg) is a binary file containing the EEG and EOG data and additional recorded signals.

Nevertheless, to assist with handling the unmodified raw data, we have used the BrainVision Analyzer[20] software to export all the recordings to the more accessible.vhdr format, but without altering anyhow the content of the data itself.

For storing the raw data, a database was created using a nested structure of five levels (see Fig. 4), from the top:

1. Patient folder, where PN_1 can be either P11, P13, P15, or P16.
2. Visits folder, where VN_2 indicates the total number of visits available for each particular patient.
3. Day folder, where DN_3 indicates the number of days that the particular visit lasted.
4. Type of sessions, where data has been separated according to the type of sessions. Training, Feedback, and Spelling sessions (consisting of both Copy and Free spelling sessions).

At the 5th level, according to the type of session, there might be up to five types of files stored, times the number of that particular session recorded on the day, i.e., n_1, n_2, and n_3 (see Fig. 4). Namely, the hosted files can be:

(a) *.vhdr, the exported version of the *.ahdr file.
(b) *.vmrk, the exported version of the *. amrk file.
(c) *.eeg, that is a binary file with the recorded data.
(d) Block sentence list (Block_*X*_senlist.txt), where *X* is the counter of the number of ongoing sessions. This type of *.txt file was only created for Training and Feedback sessions.
(e) Result list (*Date*_result_f1_*X*.txt), with the *Date* in which the recording was made, and *X* is the counter of the ongoing sessions. This type of *.txt file was only created for Feedback and both Speller sessions.

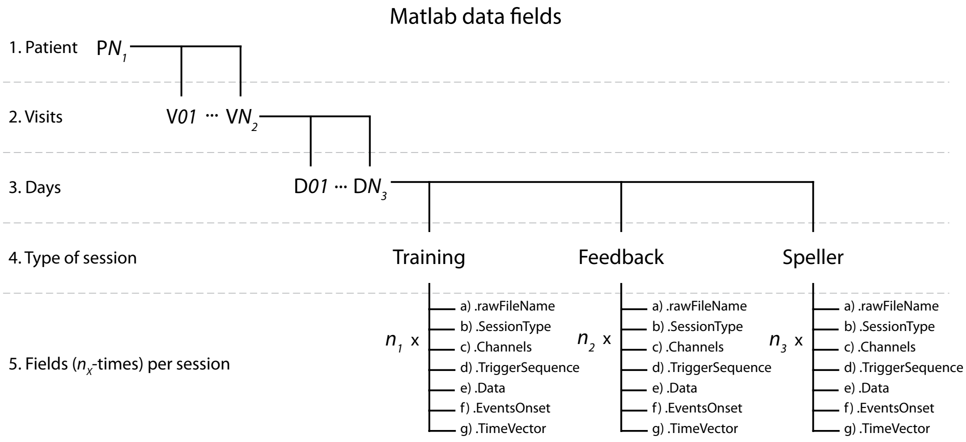

Fig. 5 Matlab data fields structure. Nested structure elements containing the values and features of recordings from the study. According to the patient identifier, the upper level is the main structure, which can be $PN_1 = 11,13,15$ or 16. In the next level, VN_2 indicates the total number of visits available for that patient, and inside it, D*N3* indicates the number of days that the visit lasted. Inside each day, there are structures for the Training and Feedback sessions and the spelling sessions (containing recordings from both the Copy and Free speller sessions). Each of these contains a set of structures that result from exporting the *.vhdr raw files for each recorded session, times the number of that particular session type (i.e., n_1, n_2, and n_3) was performed during the day. Read the Data Records section for details on the data exporting.

Matlab data fields. Additionally, another format has been chosen to present and share the data obtained from exporting the original raw files (details in the section Usage Notes). In this rectangular form, a Matlab variable is stored (*.mat), corresponding to the patient's name, i.e., P11. In the variable, nested structures were created using a somehow similar architecture for the raw files, as detailed in Fig. 5. The levels, from upper to lower, are:

1. Patient structure, where PN_1 can be either P11, P13, P15, or P16.
2. Visits structure, where VN_2 indicates the total number of visits available for each particular patient.
3. Day structure, where DN_3 indicates the number of days that the particular visit lasted.
4. Type of sessions structure, where data has been separated according to the type of sessions. Training, Feedback, and Spelling sessions (containing both copy and free spelling sessions).

At the 5th level, according to the type of session, there are seven fields stored, times the number of that particular session recorded on the day, i.e., n_1, n_2, and n_3 (see Fig. 6). The hosted fields are:

(a) .rawFileName: character type variable with the name of the original raw file that was exported
(b) .SessionType: character type variable with the label of the type of session that the data belongs to
(c) .Channels: cell array with *1xK* dimensions, with *K* being the total number of EEG, EOG and EMG channels recorded, where each cell element is the label of a channel.
(d) .TriggerSequence: cell array with *1xM* dimensions, including the *Mth* events of all the trials recorded and the session as a sequence of triggers, with the labels indicated in Fig. 2., e,g., S 9, S 10, S 5, S 4, S 1, S 11, …, S 15
(e) .Data: a *KxR* dimensional matrix of numerical values, being *K* the number of channels recorded, and *R* the number of data points in the time domain of the recording, each element being the amplitude values of the recording. It is highly relevant to consider that the default amplitude of the recording needs to be multiplied for a scaling factor of 0.0488281 (±410 mV range in 24 bits) to convert to μV[21]. The scaling factor can be verified inside every *.vhdr file produced for every recording
(f) .EventsOnset; a *1xR* dimensional vector of numerical values, being *R* the number of data points in the time domain of the recording, and to each time point we have assigned the numerical value of the trigger labels (see Fig. 2) occurring at that time point, e.g., 9, 10, 5, 4, 1, 11, …, 15, and a value of zero otherwise. This vector aims to help quickly locate each event's onset and nature in the time domain
(g) .TimeVector: a *1xR* dimensional vector of numerical values, being *R* the number of data points in the time domain of the recording, where an element of *R* indicates the time value in seconds of the recording.

As an example of the previous variable description, Fig. 6 illustrates the data structure using P11's data from visit V01 and day D03.

All the datasets described in this section can be freely downloaded from the open access repository[22].

Technical Validation

The raw data referred to in this descriptor was recorded using a Brain Products V-Amp amplifier, without any type of hardware or software filter besides the physical instrumental restriction of the amplifier (wideband filter in the range of 0 Hz (DC) – 320 Hz or 4 kHz for the high-speed mode)[21].

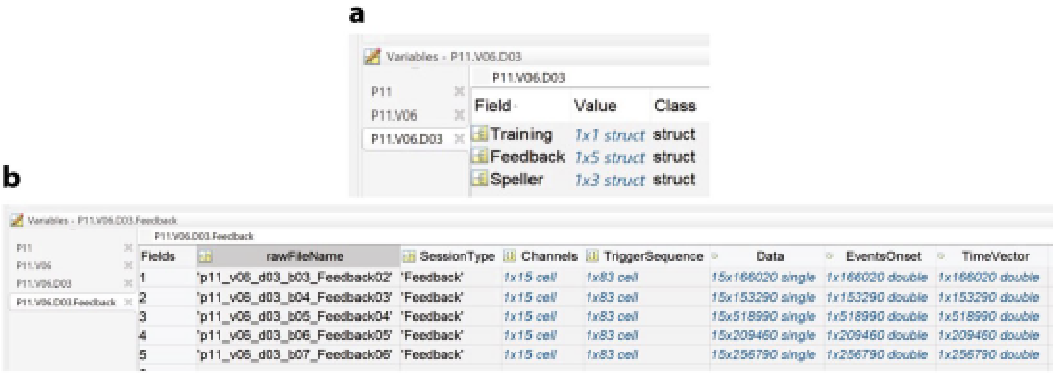

Fig. 6 Example of a Matlab structure of the data using P11's data. The figure illustrates the data structure using P11's data from visit V06 and day D03. (**a**) Indicates the selection of patient variables and the data fields corresponding to a particular visit and day and inside it, the type and number of sessions performed on the given day. (**b**) Depicts the presence of different fields upon selecting a session type, in this case, the number of Feedback sessions performed by P11, upon selection of Field named Feedback, and their different elements, as shown in the figure. Read the Data Records section for the detailed description.

The raw data recorded with BrainVision Recorder software (v2.1.0) in *.ahdr, *.amrk, *.eeg formats were exported using BrainVision Analyzer software[20] (v2.2.0) to obtain the formats[19] *.vhdr, *.vmrk and *.eeg.

The data given as a Matlab format variable (*.mat) has been exported from the raw files taking advantage of the EEGLAB[23] toolbox (https://sccn.ucsd.edu/eeglab/index.php, v2019.0) and the "bva-io" plugin (https://sccn.ucsd.edu/eeglab/plugin_uploader/plugin_list_all.php, v1.5.13), to save in the described variable structure desired features of the original raw file, as detailed in the Data Records section. No special parameter was used for exporting these data, and therefore we consider both raw and exported to the same values. Nevertheless, the amplitude of the recorded data (either.eeg or exported files using the "bva-io" plugin) is defined by the ADC bit resolution of the device, that is a ± 410 mV range in 24 bits, and therefore, the amplitude value needs to be multiplied by the scaling factor of 0.0488281[21] to be converted to µV (microvolts) units. The resolution of each recording can be found per channel inside each *.vhdr given file.

The Matlab script used to export the raw files to Matlab variables (see Code Availability section) includes a deactivated code line that can be used to convert to µV the amplitude.

EOG electrodes were located and placed according to the standard 10-20 system with EEG neoprene caps (Neuroelectrics, Barcelona, Spain), inserted in the cap using plastic holders. Once the whole set of electrodes was in place, they were filled with SuperVisc electrolyte gel (Easycap, Germany, GmbH). Impedance was measured on the whole set using an ImpBox (Brain Products, Germany, GmbH), to achieve a target impedance of 10 KΩ. Researchers in charge of the study ensured that the recorded activity had the proper impedance and a clean signal for all the channels. Recordings are not affected by muscular or blinking artifacts, besides eye movements related to the patients' intentions.

Usage Notes

Performance of the communication system. The communication system can present a question every nine seconds with an information transfer rate of 6.7 bits/min. The system's optimal speed can be improved depending on the speller scheme's design for each individual patient and the corpus of sentences stored for word prediction. Descriptive statistics on each patient's performance can be found in the related publication[12].

A minimal criterion for communicating using the system is the presence of eye-movements recordable with sate of the art EOG recording devices in the microvolt range. For one of the patients, the progression of the disease over the course of a year eventually prevented him from controlling his oculomotor activity. He was however capable of producing undifferentiated EOG activity with low amplitude in the range of ± 30 µV which reached that minimal criterion. The other patients never arrived at such a total loss of control when the data described here was recorded. Therefore, the duration of the transition period to CLIS, and whether voluntary communication with non-invasive physiological recording technologies, as described here, will be possible in CLIS, is still a matter of future research.

Date and time of the recordings. The original timestamp of the beginning of a recorded session can be found both inside the *.vhdr and the *.vmrk files, as the occurrence of the first marker in the recording. It can also be found as the timestamp of the sentence lists (Block_X_senlist.txt), or indicating the end of a session in the results text files (*Date*_result_f1_*X*.txt).

Name of the raw files. During the study, files recorded with BrainVision Recorder software (v2.1.0) (i.e., *.vhdr, *.vmrk and *.eeg) were labeled by the experimenters, and therefore, human error or discrepancies might have been committed during the labeling process. To clarify any possible confusion, the Online-only Tables 1–4 include a set of columns that show the correspondence between the name of the raw file, the session's sequence, and any *.txt files attached to it.

Patient	Visits	Days	Sessions		
			Training	Feedback	Speller
P11	9	27	68 (including 2 lost files)	56	26
P13	4	14	28	22	21
P15	2	7	7	16 (including 1 lost files)	18
P16	2	9	27	22	8

Table 1. The number of sessions in the dataset. Detail of the number of visits and total days of the study, and the total number of different types of sessions recorded for each patient. Indicated in parenthesis are the numbers of lost recordings. Copy speller and free speller sessions are considered in the same column. A more detailed description of the days, dates, and sessions can be verified in the Online-only Tables 1–4.

The text lists (Block_*X*_senlist.txt and *Date*_result_f1_*X*.txt) were created automatically by a Matlab script running during each session.

From the given recordings, either raw or Matlab fields, it can be noticed from the labels that some files or sessions are lacking. This is because during the visits, sessions belonging to another paradigm for a different and unrelated study were also recorded, and they have been deliberately removed from the actual data descriptor to focus on the auditory communication recordings. Removed files are indicated in the Online-only Tables 1–4. Additionally, a number of files were lost or corrupted; the precise number and sessions are indicated in Table 1 and Online-only Tables 1–4.

EEG locations and inconsistency. Working with patients who have critical health conditions means being completely dependent on their current (minute by minute) state. These limitations were considered in the design of the study. The number of EEG electrodes was limited by restrictions of accessibility of some scalp regions. Since the patients lie on their backs most of the time, it is impossible to access occipital areas.

Nevertheless, the most relevant restriction is the time constraint, that is, to place a minimal number of EEG electrodes in appropriate locations, in the minimum possible time, so to maximize the time available to work with the patient before tiredness or another need (for example, sucking of saliva) prevents them from participating in the study. Consequently, the montages of electrodes might be affected by inconsistency in EEG electrode locations, even for the same patient, and different visits, since it is always dependent on changing circumstances of health and time.

Therefore, the criterion we follow aims to reach with the minimal number of electrodes the greatest coverage of the prefrontal and mesial surfaces of the brain (besides the EOG electrodes), under the assumption that the cognitive activity implicated in the processing of these questions might elicit changes in the electrical activity of the aforementioned cortical regions.

Regardless of that, we managed to keep a constant number of seven EEG electrodes and four EOG electrodes for most of the patients, for most of the visits, as can be verified in the Online-only Tables 1–4.

Audio files. The audio files (recorded questions) used in this research contains personal information of the patients and their relatives and consequently, to make these audio files fully open and public will compromise their identities. These data[24] have been uploaded with restricted access, therefore any researcher or laboratory interested in accessing the data to perform the analysis will have to sign an identity protection agreement document provided as a "Data Use Agreement" Supplementary material with this manuscript.

Code availability

The given Matlab data variables were obtained by exporting the raw files (i.e., *.vhdr, *.vmrk, and *.eeg) using the EEGLAB[23] toolbox (v2019.1.0) and exporting the data using the "bva-io" plugin (v1.5.13). We wrote a short Matlab script (ExportingCode_vhdr2mat.m) to export and save the desired features of the recordings, as thoroughly detailed in the section Data Records. The code is included in the same repository as the rest of the data, and it is accompanied by a brief document (ExportingCode_vhdr2mat.docx) explaining details of the code.

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Author contributions

Andres Jaramillo-Gonzalez – Performed 35% of the Auditory communication system (ACS) sessions and data collection; Data curation; Manuscript writing. Shihze Wu – Data curation and validation. Alessandro Tonin – Performed 35% of the ACS sessions and data collection. Aygul Rana – Performed 35% of the ACS sessions and data collection. Majid Khalili Ardali – Discussion in Laboratory. Niels Birbaumer – Study design and conceptualization; Manuscript correction. Ujwal Chaudhary – Study design and conceptualization; Performed 65% of the ACS sessions and data collection; Supervision; Manuscript writing.

Competing interests

The authors declare no competing interests.

Additional information

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Appendix 7.

U. Chaudhary, B. S. Chander, A. Ohry, **A. Jaramillo-Gonzalez**, D. Lulé, N. Birbaumer (2021). Brain-Computer Interfaces for assisted communication in paralysis and quality of life. *International Journal of Neural System*.
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This publication is not open-access and can only be accessed through the publisher.

Appendix 8.

U. Chaudhary, I. Vlachos, J. B. Zimmermann, A. Espinosa, A. Tonin, **A. Jaramillo-Gonzalez**, M. Khalili-Ardali, H. Topka, J, Lehmberg, G. M. Friehs, A. Woodtli, J. P. Donoghue, N. Birbaumer (2021). Spelling Interface using Intracortical Signals in a Completely Locked-In Patient enabled via Auditory Neurofeedback Training, *Nature Communications,* 13, 1236.
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Spelling interface using intracortical signals in a completely locked-in patient enabled via auditory neurofeedback training

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Patients with amyotrophic lateral sclerosis (ALS) can lose all muscle-based routes of communication as motor neuron degeneration progresses, and ultimately, they may be left without any means of communication. While others have evaluated communication in people with remaining muscle control, to the best of our knowledge, it is not known whether neural-based communication remains possible in a completely locked-in state. Here, we implanted two 64 microelectrode arrays in the supplementary and primary motor cortex of a patient in a completely locked-in state with ALS. The patient modulated neural firing rates based on auditory feedback and he used this strategy to select letters one at a time to form words and phrases to communicate his needs and experiences. This case study provides evidence that brain-based volitional communication is possible even in a completely locked-in state.

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder that leads to the progressive loss of voluntary muscular function of the body[1]. As the disorder typically progresses, the affected individual loses the ability to breathe due to diaphragm paralysis. Upon accepting artificial ventilation and with oro-facial muscle paralysis, the individual in most cases can no longer speak and becomes dependent on assistive and augmentative communication (AAC) devices[2,3], and may progress into the locked-in state (LIS) with intact eye-movement or gaze control[4,5]. Several invasive[6–10] and non-invasive[11–16] brain-computer interfaces (BCIs) have provided communication to individuals in LIS[17–20] using control of remaining eye-movement or (facial) muscles or neural signals. Once the affected individual loses this control to communicate reliably or cannot open their eyes voluntarily anymore, no existing assistive technology has provided voluntary communication in this completely locked-in state (CLIS)[17–20]. Non-invasive[11–16] and invasive[6–10] BCIs developed for communication have demonstrated successful cursor control and sentence formation by individuals up to the stage of LIS. However, none of these studies has demonstrated communication at the level of voluntary sentence formation in CLIS individuals, who lack stable and reliable eye-movement/muscle control or have closed eyes, leaving the possibility open that once all movement - and hence all possibility for communication - is lost, neural mechanisms to produce communication will concurrently fail. Several hypotheses have been formulated, based on the past BCI failures, to explain the inability of ALS-patients in CLIS to select letters to form words and sentences ranging from extinction of intentions[21] related to protracted loss of sensory input and motor output, cognitive dysfunction, particularly when it occurs in association with fronto-temporal degeneration. A successful demonstration of any BCI enabling an individual without reliable eye-movement control and with eyes closed (CLIS) to form a complete sentence would upend these hypotheses, opening the door to communication and the investigation of psychological processes in the completely paralyzed ALS patients and probably also other disease or injury states leading to CLIS.

Here, we established that an individual was in the CLIS state and demonstrated that sentence-level communication is possible using a BCI without relying upon the patient's vision. This individual lacked reliable voluntary eye-movement control and, consequently, was unable to use an eye-tracker for communication. The patient was also ultimately unable to use a non-invasive eye-movement-based computerized communication system[22]. To restore communication in CLIS, this participant was implanted with intracortical microelectrode arrays in two motor cortex areas. The legally responsible family members provided informed written consent to the implantation, according to procedures established by regulatory authorities. The patient, who is in home care, then employed an auditory-guided neurofeedback-based strategy to modulate neural firing rates to select letters and to form words and sentences using custom software. Before implantation, this person was unable to express his needs and wishes through non-invasive methods, including eye-tracking, visual categorization of eye-movements, or an eye movement-based BCI-system. The patient started using the intracortical BCI system for voluntary verbal communication three months after implantation. With ALS progression, the patient lost the ability to open his eyes voluntarily as well as visual acuity, but he is still employing the auditory-guided neurofeedback-based strategy with his eyes closed to select letters and form words and sentences. Therefore, a CLIS patient who was unable to express his wishes and desires is employing the BCI system to express himself independent of vision.

Results

One day after the implantation, attempts were initiated to establish communication. The patient was asked to use his previously effective communication strategy employing eye movements to respond to questions with known "yes" and "no" answers, which did not result in a classifiable neural signal, no difference in spike rate and multi-unit-activity (MUA). Passive movements of the patient's right fingers, thumb, and wrist evoked consistent neural firing rate modulations on several electrodes on both arrays. However, when we instructed the patient to attempt or imagine hand, tongue, or foot movements, we could not detect consistent responses. Subsequently, the communication strategy was changed on the 86th day after implantation, and neurofeedback-based paradigms (described in the Online Methods section) were employed, as shown in Fig. 1. In this setting, the patient was provided auditory feedback of neural activity by mapping a spike rate metric (SRM) for one or more channels to the frequency of an auditory feedback tone, as displayed in Fig. 1 (described in the "Neurofeedback communication" section of Online Methods, see sample Supplementary Video V1). The patient was able to modulate the sound tone on his first attempt on day 86 and subsequently was able to successfully modulate the neural firing rate and match the frequency of the feedback to the target for the first time on day 98. Employing the neurofeedback strategy, the patient was able to modulate the neural firing rate and was able to use this method to select letters and to free spell from day 106 onwards. The Results reported here include data from days 106–462 after implantation. Three of the authors (UC, NB and AT) frequently traveled to the patient's home to perform communication sessions about every two weeks for 3 or 4 consecutive days until February 2020. Because of the COVID pandemic from March 2020 to June 2020, all the sessions were performed via secured remote access to the patient's laptop. During these sessions, the patient's wife performed locally all required hardware connections, and the experimenters, either UC or AT, controlled the software remotely. During the experimental period reported here, the authors UC, AT, and NB performed experimental sessions on 135 days. The patient was hospitalised due to unrelated adverse events between days 120 and 145, 163 and 172, and 212 and 223 after implantation, during which time no sessions were performed.

Each session day, we started with a 10-minutes baseline recording, where the patient was instructed to rest. During this time period the experimenter ran a software program to determine the firing rate of different individual channels and select their parameters for the first neurofeedback session-block. Two different types of neurofeedback sessions were performed consecutively on each day, "feedback without reward" and "feedback with reward" with the goal (1) to select channels suitable for voluntary control by the patient and (2) to train the patient to control the selected channels' spiking activity voluntarily. The first paradigm ("feedback without reward") provided successive target tones, and the patient was asked to match the frequency of the feedback tone to the target tone. The second paradigm ("feedback with reward") was the same. However, upon reaching and holding (during a configurable number of interactions, each interaction lasting 250 ms) the feedback tone within a predefined range around the target frequency, an additional reward sound was delivered for 250 ms, indicating successful performance to the patient. Holding the feedback tone at the high (low) end of the range for a minimum of 250 ms was then interpreted as a successful "yes" ("no") response. After the first "feedback without reward" session, individual channels' firing rate distributions were automatically calculated. The experimenter selected channels with differential modulation for the high and low target tones and

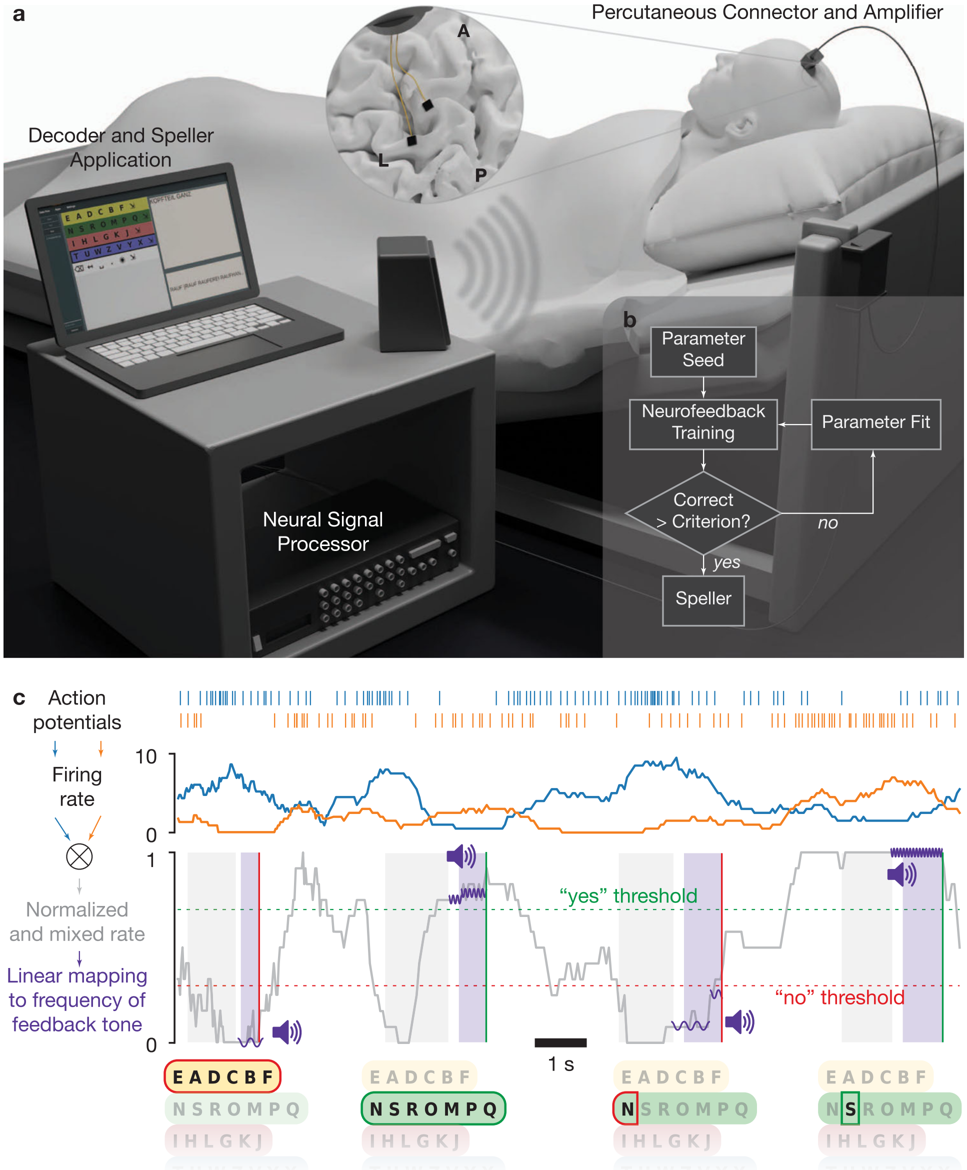

Fig. 1 Setup and neurofeedback paradigm. a Experimental setup. Two microelectrode arrays were placed in the precentral gyrus and superior frontal gyrus (insert, L: left central sulcus, A-P: midline from anterior to posterior). An amplifying and digitizing headstage recorded signals through a percutaneous pedestal connector. Neural signals were pre-processed on a Neural Signal Processor and further processed and decoded on a laptop computer. **b** Daily sessions began with Neurofeedback training. If the performance criterion was reached, the patient proceeded to speller use. If the criterion was not reached, parameters were re-estimated on neurofeedback data, and further training was performed. **c** Schematic representation of auditory neurofeedback and speller. Action potentials were detected and used to estimate neural firing rates. One or several channels were selected, their firing rates normalized and mixed (two channels shown here for illustration; see Online Methods). Options such as letter groups and letters were presented by a synthesized voice, followed by a response period during which the patient was asked to modulate the normalized and mixed firing rate up for a positive response and down for a negative response. The normalized rate was linearly mapped to the frequency of short tones that were played during the response period to give feedback to the patient. The patient had to hold the firing rate above (below) a certain threshold for typically 500 ms to evoke a "Yes" ("No") response. Control over the neural firing rates was trained in neurofeedback blocks, in which the patient was instructed to match the frequency of target tones.

updated the parameters for subsequent sessions. Employing this iterative procedure on each day, we performed several neurofeedback blocks within a particular day to remind the patient of the correct strategy to control the firing rate, each typically consisting of 10 high-frequency target tones and 10 low-frequency target tones presented in pseudo-random order and also to tune and validate the classifier. Typically, if the patient could match the frequency of the feedback to the target in 80% of the trials, we proceeded with the speller.

Neurofeedback sessions. Figure 2a shows individual neurofeedback trials, including an error trial, of one representative block. Over the reported period, there were 1176 feedback sessions as shown in Supplementary Fig. S1. In the 281 neurofeedback blocks preceding the speller blocks, 4936 of 5700 trials (86.6%) were correct (Fig. 2b), i.e., for target tone up (higher frequency) the decision was up (a "yes" answer), and for target down (low frequency) the decision was down (a "no" answer). The difference in error rates between 'up' and 'down' trials, i.e., the fraction of trials

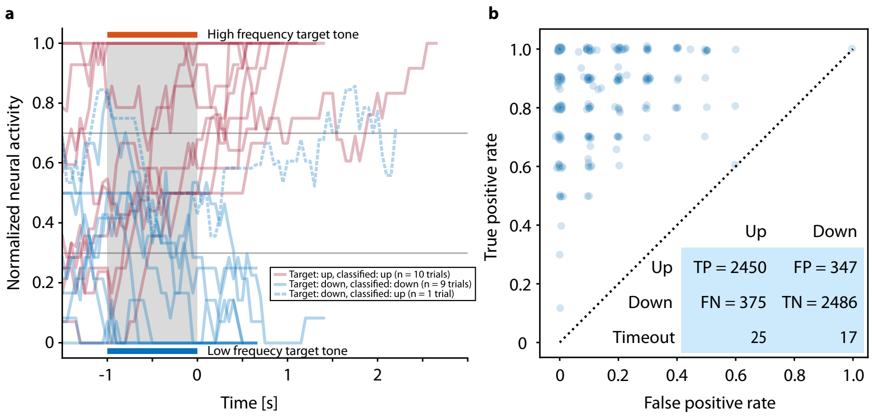

Fig. 2 Neurofeedback task and classification. a Representative example for normalized and mixed firing rate during ten high (red) and ten low (blue) target tone frequency feedback trials of day 247. The patient was asked to match the target tone by modulating the normalized and weighted firing rate, and he succeeded in all but one trial of this example. Trials were completed as soon as the firing rate was held above or below the upper or lower threshold, respectively. As defined in the Materials and Methods section, these feedback blocks were performed every day of recording for training, parameter selection, and validation of the selected parameters. The grey-shaded region from −1 to 0 s depicts the time period during which the high or low target tones were presented to the patient. The horizontal line at 0.3 and 0.7 shows the lower and upper threshold, respectively. Source data are provided as a Source Data file. **b** True positive rate vs. false positive rate of the trials in auditory neurofeedback blocks directly preceding speller blocks on days 123–462. Each circle represents one neurofeedback block; circles are jittered for better visibility. The blue insert at the bottom right corner shows the contingency table of all neurofeedback trials directly preceding speller blocks on days 123–462. In the blue insert—TP stands for true positive, i.e., up trials classified as up; FP stands for false positive, i.e, up trials classified as down; FN—stands for false negative, i.e., down trials classified as up; TN—stands for true negative, i.e., down trials classified as down; Time out denotes the trials that were unclassified. Source data are provided as a Source Data file.

in which the modulated tone did not match the target tone, (13.2% and 12.2%, respectively), was significant (Pearson's χ^2 test: $p < 0.01$). The patient maintained a high level of accuracy in the neurofeedback condition throughout the reported period: on 52.6% of the days, the accuracy was at least 90% during at least one of the feedback trials blocks, i.e., the patient was able to match the frequency of the feedback to the target 18 out of 20 times. We observed considerable within-day variability of neural firing rates and hence performance of the neurofeedback classifier, necessitating manual recalibration throughout the day (see Supplementary Fig. S1). In the last feedback sessions before speller sessions, the median accuracy was 90.0%, the minimum was 50.0% (chance level). In 17.1% of the sessions, accuracy was below 80.0%.

Speller sessions. We continued with the speller paradigm when the patient's performance in a neurofeedback block exceeded an acceptance threshold (usually 80%). To verify that good performance in the neurofeedback task translated to volitional speller control (based on correct word spelling), we asked the patient to copy words before allowing free spelling. On the first three days of speller use, the patient correctly spelled his own, his son's, and his wife's names. After an unrelated stay at the hospital, we again attempted the speller using the same strategy on day 148.

Afterward, we relied on a good performance in the neurofeedback task, i.e., the patient's ability to match the frequency of the feedback to the target in 80% of trials, to advance to free spelling. The selection of two letters from a speller block on day 108 is shown in Fig. 3. Supplementary Video V2 presents a representative speller block.

Over the reported period, out of 135 days, speller sessions were attempted on 107 days, while on the remaining 28 days use of the speller was not attempted because the neurofeedback performance criterion was not reached. The patient produced intelligible output, as rated independently by three observers, on 44 of 107 days when the speller was used (Fig. 4). On average, 121 min were spent spelling and the average length of these communications was 131 characters per day. The patient's intelligible messages comprised 5747 characters produced over 5338 min, corresponding to an average rate of 1.08 characters per minute. This rate varied across blocks (min/median/max: 0.2/1.1/5.1 characters per minute). Over the reported period, there was no apparent trend in spelling speed. There were 312 pairs of speller blocks and preceding neurofeedback blocks. The speller output was rated 0 for unintelligible by raters, 1 for partially intelligible, 2 for intelligible. The Spearman correlation between Neurofeedback task accuracy and subsequent speller intelligibility was 0.282 ($p = 4.002e{-}07$). The Spearman correlation between Neurofeedback accuracy and number of letters spelled was 0.151 ($p = 7.671e{-}03$). The information transfer rate (ITR) during intelligible speller sessions was 5.2 bits/minute on average (min/median/max: 0.3/4.9/21.4 bits/minute).

On the second day of free spelling, i.e., on the 107th day after implantation, the patient spelled phrases, spelled in three-time episodes, thanking NB and his team ('erst mal moechte ich mich niels und seine birbaumer bedanken' – 'first I would like to thank Niels and his birbaumer'). Many of the patient's communications concerned his care (e.g. 'kop?f immerlqz gerad' – 'head always straight', day 161; 'kein shirt aber socken' – 'no shirts but socks [for the night]', day 244; 'mama kopfmassage' – 'Mom head massage', day 247; 'erstmal kopfteil viel viel hoeh ab jetzt imm' – 'first of all head position very high from now', day 251; 'an alle muessen mir viel oefter gel augengel' – 'everybody must use gel on my eye more often', day 254; 'alle sollen meine haende direkten auf baubch' – 'everybody should put my hand direct on my stomach', day 344; 'zum glotze und wenn besuchen da ist das kopfteil immer gaaanz rauf' – 'when visitors are here, head position always very high' on day 461. The patient also participated in social interactions and asked for entertainment ('come tonight [to continue with the speller]', day 203, 247, 251, 294, 295, 'wili ch tool balbum mal laut hoerenzn' – 'I would like to listen to the album by Tool [a band] loud', day 245, 'und jetwzt ein bier' – 'and now a beer', day 247 (fluids have to be inserted through the gastro-tube), 251, 253, 461. He even gave suggestions to improve his speller performance by spelling 'turn on word

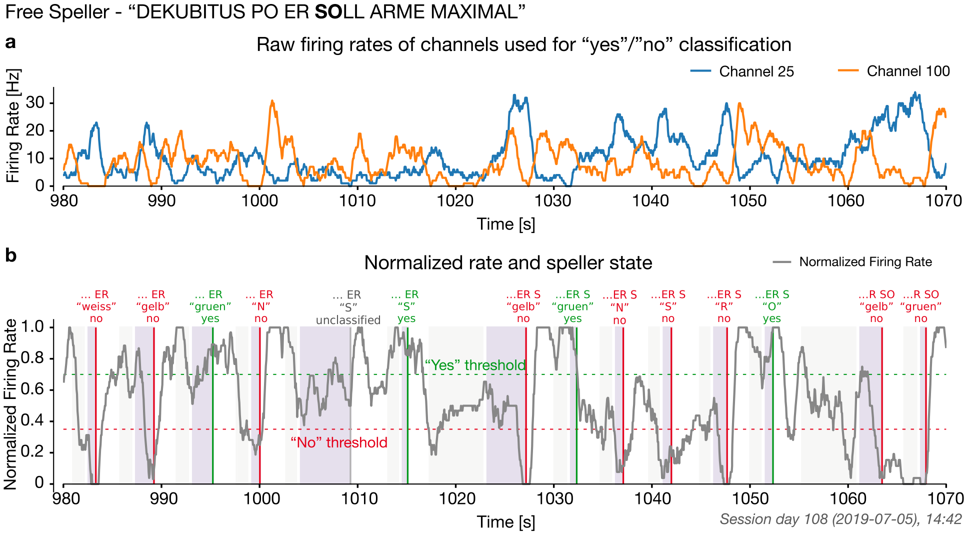

Fig. 3 Example of letter selection during a free spelling block. a Firing rate of the channels 25 and 100 used for "yes"/"no" classification on day 108. **b** Normalized firing rate and the speller state during the same 90 s period of a speller block. "Yes"/"no"/ timeout decisions are marked by vertical lines and the option selected in green and not selected in red. This example is part of the phrase "dekubitus po er soll arme maximal", referring to bedsore and instructing the aide to change arm position. Source data are provided as a Source Data file.

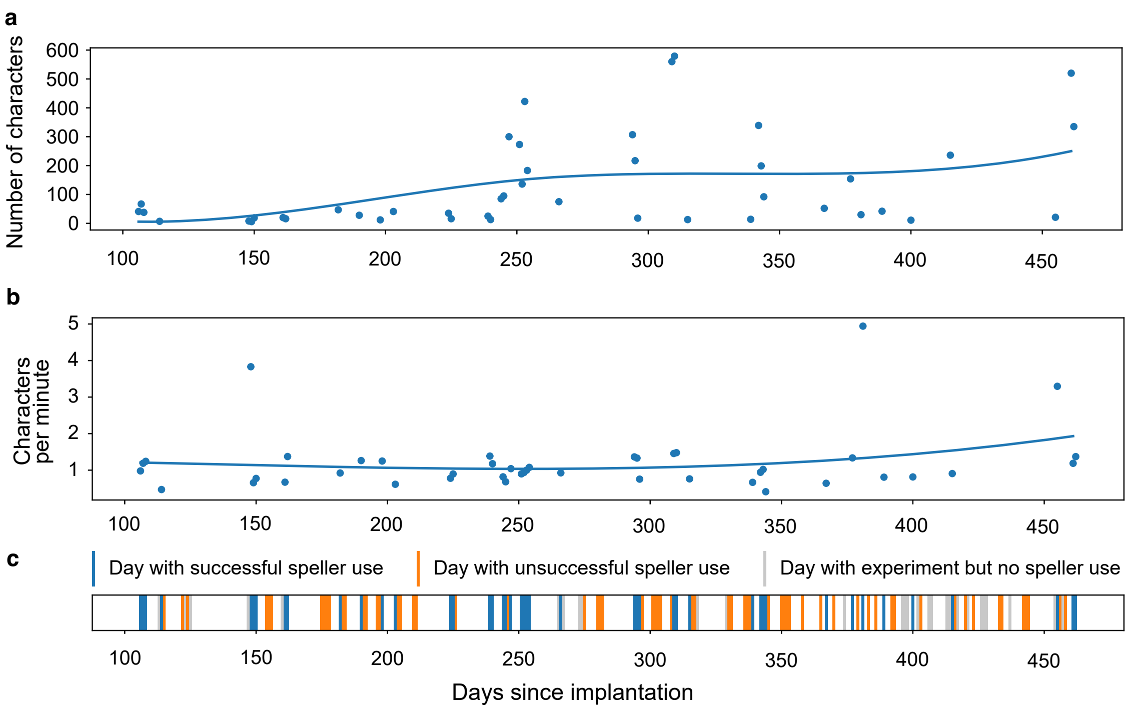

Fig. 4 Overview of BCI use. a Number of characters spelled by the patient during speller sessions whose output was rated 'intelligible' (rating described in text), aggregated by day. **b** Characters selected per minute in 'intelligible' speller sessions, aggregated by day. **c** Speller use during the period presented. Sessions span 135 days. Green bars represent days on which speller was used and yielded intelligible output (44 days). Yellow bars represent days on which speller use was attempted, but no intelligible output was produced (63 days). On 28 days, speller use was not attempted (red). Source data are provided as a Source Data file.

recognition' on day 183, 'is it easy back once confirmation' on Day 253, 'tell alessandro i need to save edit and delete whole phrases and all of that into the list where (patient's son name) on day 295, 'why cant you leave the system on. ifind that good' on day 461, in English as the patient knew that the experimenter UC and AT are not native German speakers and mostly spoke in English with the patient. On day 247 he gave his feedback on speller as, 'jungs es funktioniert gerade so muehelos', - 'boys, it works so effortlessly'. The patient expressed his desire to have different kind of food in his tube as, 'mixer fuer suppen mit fleisch' – 'instructed his wife to buy a mixer for soup with meat' on day 247'; 'gulaschsuppe und dann erbsensuppe' – 'Gulash soup and sweet pea soup' on day 253; 'wegen essen da wird ich erst mal des curry mit kartoffeln haben und dann bologna und dann gefuellte und dann kartoffeln suppe' – 'for food I want to have curry with potato then Bolognese and potato soup on day 462. He interacted with his 4 years old son and wife, '(son's name) ich liebe meinen coolen (son's name) – 'I love my cool son' on day 251; '(son's name) willst du mit mir bald disneys robin hood anschauen'- 'Do you want to watch Disney's Robin Hood with me' on day 253; 'alles von den dino ryders und brax autobahnund alle aufziehautos' – 'everything from dino riders and brax and cars' on day 309; '(son's name) moechtest du mit mir disneys die hexe und der zauberer anschauen auf amazon' – 'would you like to watch Disney's witch and wizard with me on amazon' on day 461; 'mein groesster wunsch ist eine neue bett und das ich morgen mitkommen darf zum grillen' – 'My biggest wish is a new bed and that tomorrow I come with you for barbecue' on day 462.

Discussion

We demonstrate that a paralyzed patient, according to the presently available physiological and clinical criteria in the completely locked-in state (CLIS), could volitionally select letters to form words and phrases to express his desires and experiences using a neurally-based auditory neurofeedback system independent of his vision. The patient used this intracortical BCI based on voluntarily modulated neural spiking from the motor cortex to spell semantically correct and personally useful phrases. Properties of the multielectrode array impedance and recordings across sessions are shown in the Supplementary Fig. S2. In all blocks, measurable spike rate differentiation between "yes" and "no" during the neurofeedback trials and "select" and "no select during speller blocks appeared in only a few channels in the SMA (supplementary motor area) out of all active channels, as shown in Supplementary Fig. S3a. After the establishment of successful communication after day 86, similar channels from the Supplementary Motor Cortex array were used for communication sessions with the patient, as shown in Supplementary Fig. S3b. Mainly electrode 21 and neighbouring electrodes were used, which demonstrated differential control of the feedback tones during the neurofeedback sessions before spelling. Because the neurofeedback procedure was the prerequisite for successful communication after 86 days of attempted, but unsuccessful decoding, a multichannel decoding algorithm was not implemented following our clinical judgment based on learning principles[23] that such a substantial change in the procedure might impede or extinguish the successful control of the patient and spelling. In addition, after this failure, we attempted a neural feedback approach, based on learning principles, capitalizing on the observation that neural firing rates could be used to achieve levels suitable to make yes/no choices. For the speller sessions, only one to four channels were used for control, as shown in Supplementary Fig. S3. There was insufficient time to explore other decoding approaches, and we wanted to establish that communication was feasible at all in CLIS. We cannot explain why the other electrodes did not provide modulation suitable for multichannel decoding. Perhaps with further sessions and other strategies, not possible in this experiment, we might have identified faster, or more accurate approaches. Speller use duration was highly variable, ranging from a few minutes to hours. As shown in Fig. 4, the patient generated a different number of characters on different days. He spelled only under 100 characters on some days, while on other days, he produced more than 400 characters. Despite the huge variation in the number of characters spelled, the number of characters spelled per minute was mostly around 1 character per minute, and ITR averaged 5 bits/minute. Communication rates are lower than in other studies using intracortical arrays[7–9], but comparable to EEG P300 spellers for ALS patients[24,25] and much faster than an SSVEP EEG BCI for advanced ALS patients[12]. These apparent poor performances are primarily due to the completely auditory nature of these systems, which are intrinsically slower than a system based on visual feedback. Lastly it was noteworthy that free voluntary spelling mainly concerned requests related to body position, health status, food, personal care and social activities suggesting that even with this slow speller the patient could relay his needs and desires to caretakers and family.

Our study showed communication in a patient with CLIS. It is worth mentioning that no universally accepted clinical definition exists to distinguish LIS from CLIS; the current standard criteria to differentiate LIS from CLIS is the presence or absence of means of communication. During the transition from LIS to CLIS, patients are initially left with limited, and finally, no means of communication. The time course of this transition process is patient and disease specific. In theory, other voluntary muscles than eye-movements could have been used for Electromyography (EMG)-based communication attempts. Particularly face muscles outside the extraocular muscles may remain under voluntary control in some cases even after the loss of eye-muscle control. To the best of the authors' knowledge, no study has extensively investigated the remaining muscle activity of CLIS patients, but in previous studies[22,26] the authors showed that during the transition from LIS to CLIS some remaining muscles of the eyes continue to function and can be used for successful communication.

In the case of the patient described here, extensive electrooculogram (EOG) recordings were performed to demonstrate that no other measurable neuromuscular output existed- a way to confirm CLIS. The patient employed an EOG-based BCI for communication successfully for the last time in February 2019 when the amplitude of EOG signal decreased below 20 μV. Nevertheless, extensive post-hoc EOG analysis showed a significant difference in the maximum, mean, and variance feature of the eye movement corresponding to "yes" and "no" even after the patient's inability to employ the EOG-based system. This failure to communicate despite the presence of a significant difference in some of the features may be due to the limitations of the EOG-based BCI system. However, as differences of eye movement amplitudes were only detectable over tens of trials and not reliably from session to session, EOG was not a practical signal for communication. In this study, caretakers and family members denied the existence of any possible reliable communication from February 2019 onwards, when this study occurred. Thus, we conclude based on our reported measurements that the patient described was in a CLIS a few weeks before and also after implantation. This statement does not exclude the possibility that even more sensitive measurements of somatic-motor control could reveal some form of volitional control, which would render the diagnostic statement of CLIS at least for this case inaccurate. Nevertheless, by the measures we describe here no muscle-based signals useful for communication were evident, leading us to conclude that this patient could be classified as in the chronic complete locked in state but was able to communicate using an implanted BCI system usefully.

The present BCI communication demonstrates that an individual unable to move for protracted periods is capable of meaningful communication. Still, the current neurofeedback based BCI system has several limitations, as several software and hardware modifications would need to be implemented before the system could be used independently by the family or caretakers without technical oversight. The BCI-software is presently being modified to improve communication quality and rate and the self-reliance of the family.

In this study, communication rates were much lower compared to other studies using intracortical arrays, which include communication with a point-and-click screen keyboard[7–9], and decoding of imagined handwriting in a spinal cord injured patient[27]. People with ALS and not apparently completely locked-in have been able to use multi neuron-based decoders for more rapid communication than seen here. The differences might be both technical—a failure of the electrode—or biological, i.e., related to the disease state. While the multielectrode array (MEA) used here typically shows some variable level of degradation in the quality and number of recordings over time, such arrays reportedly provide useful signals for years[28,29].

Our MEA retained impedances in the useful range across the entire experimental period of this study (Fig. S2) and neurons were recorded on many channels suggesting that the loss of recordable neural waveforms cannot explain performance differences. The most striking difference in the present data was the inability to record neurons that modulated with the participant's volitional intent. This could be the result of the disease processes on the neurons themselves or the protracted loss of sensory-motor input itself. The observation that control was intermittent may reflect changes in neural connectivity or the ability to be activated. Lack of any somatic sensory feedback, especially that from muscles, might impede voluntary modulation of neural activity. Participants with ALS enrolled in previous trials apparently had at least some residual voluntary control of muscles, whereas this participant had lost all control by the time of implantation. Additionally, advanced ALS may have led to cognitive or affective changes such as shortened attention span or modified motivational systems that may have made it difficult to achieve reliable modulation of large numbers of neurons (dozens to hundreds) achieved in other ALS participants with similar BCI systems implanted. Altered cortical evoked response amplitudes and latencies[30] seen in this individual may be a reflection of these abnormal states. CLIS patients with ALS show highly variable and often pathological neurophysiological signatures[31] such as heterogeneous sleep-waking cycles[32] that may also affect the ability to engage neurons. Lastly, auditory cues may engage motor processes that will activate neurons in frontal areas outside of the motor cortex[33], which may have contributed to the changes with the auditory task used here.

To conclude, this case study has demonstrated that a patient without any stable and reliable means of eye-movement control or identifiable communication route employed a neurofeedback strategy to modulate the firing rates of neurons in a paradigm allowing him to select letters to form words and sentences to express his desires and experiences. It will be valuable to extend this study to other people with advanced ALS to address the aforementioned issues systematically.

Methods

The medical procedure was approved by the Bundesinstitut für Arzneimittel und Medizinprodukte ("BfArM", The German Federal Institute for Drugs and Medical Devices). The study was declared as a Single Case Study and has received a special authorization ("Sonderzulassung") by BfArM, according to §11 of the German Medical Device Law ("Medizin-Produkte-Gesetz") on December 20, 2018, with Case Nr. 5640-S-036/18. The Ethical Committee of the Medical Faculty of the Technische Universität München Rechts der Isar provided support to the study on 19 Jan 2019, along with the explicit permission to publish on 17 February 2020. Before the patient transitioned into CLIS, he gave informed consent to the surgical procedure using his eye movements for confirmation. The patient was visited at home by authors HT and JL, and thorough discussions were held with the legally responsible family members (wife and sister) in order to establish convincing evidence of the patient's informed consent and firm wish to undergo the procedure. The legally responsible family members then provided informed written permission to the implantation and the use of photographs, videos, and portions of his protected health information to be published for scientific and educational purposes. In addition, a family judge at the Ebersberg county court gave the permission to proceed with the implantation after reviewing the documented consent and a visit to the patient. The patient received no compensation for the participation.

Patient. The patient, born in 1985, was diagnosed with progressive muscle atrophy, a clinical variant of non-bulbar ALS, selectively affecting spinal motor neurons in August 2015. He lost verbal communication and the capability to walk by the end of 2015. He has been fed through a percutaneous endoscopic gastrostomy tube and artificially ventilated since July 2016 and is in home care. He started using the MyTobii eye-tracking-based assistive and augmentative communication (AAC) device in August 2016. From August 2017 onwards, he could not use the eye-tracker for communication because of his inability to fixate his gaze. Subsequently, the family developed their own paper-based spelling system to communicate with the patient by observing the individual's eye movements. According to their scheme, any visible eye movement was identified as a "yes" response, lack of eye movement as "no". The patient anticipated complete loss of eye control and asked for an alternative communication system, which motivated the family to contact authors NB and UC for alternative approaches. Initial assessment sessions were performed in February 2018. During this interval, the detection of eye movements by relatives became increasingly difficult, and errors made communication attempts impossible up to the point when communication attempts were abandoned. The patient and family were informed that a BCI-system based on electrooculogram (EOG) and/or electroencephalogram (EEG) might allow "yes" - "no" communication for a limited period.

The patient began to use the non-invasive eye movement-based BCI-system described in Tonin et al.[21]. The Patient was instructed to move the eyes ("eye-movement") to say "yes" and not to move the eyes ("no eye-movement") to say "no". Features of the EOG signal corresponding to "eye-movement" and "no eye-movement" or "yes" and "no" were extracted to train a binary support vector machine (SVM) to identify "yes" and "no" response. This "yes" and "no" response was then used by the patient to auditorily select letters to form words and hence sentences. The patient and family were also informed that non-invasive BCI-systems might stop functioning satisfactorily, and in particular, selection of letters might not be possible if he became completely locked-in (where no eye movements could be recorded reliably). In that case, implantation of an intracortical BCI-system using neural spike-based recordings might allow for voluntary communication. As the patient's ability to communicate via non-invasive BCI systems deteriorated, in June 2018, preparations for the implantation of an intracortical BCI system were initiated. To this end, HT and JL and GF were approached in order to prepare the surgical procedure and ensure clinical care in a hospital close to the patient's home. The patient was able to use the non-invasive BCI system employing eye-movement to select letters, words, and sentences until February 2019, as described in Tonin et al.[21,34]. By the time of implantation, the EOG/EEG based BCI system failed, as signals could not be used reliably for any form of communication in this investigational setting. The EOG/EEG recordings and their analysis are described in Supplementary Note 1 and Supplementary Fig. S4. Additionally, the patient reported low visual acuity caused by the drying of the cornea.

Surgical procedure. A head MRI scan was performed to aid surgical planning for electrode array placement. The MRI scan did not reveal any significant structural abnormalities, in particular no brain atrophy or signs of neural degeneration. A neuronavigation system (Brainlab, Munich, Germany) was used to plan and perform the surgery. In March 2019, two microelectrode arrays (8×8 electrodes each, 1.5 mm length, 0.4 mm electrode pitch; Blackrock Microsystems LLC) were implanted in the dominant left motor cortex under general anaesthesia. After a left central and precentral trephination, the implantation sites were identified by neuronavigation and anatomical landmarks of the brain surface. A pneumatic inserter was used[28] to insert the electrode arrays through the arachnoid mater, where there were no major blood vessels. The pedestal connected to the microelectrode arrays connected via a bundle of fine wires (Blackrock Microsystems LLC), was attached to the calvaria using bone screws and was exited through the skin. The first array was inserted into the hand area region of the primary motor cortex[35], and the second array was placed 2 cm anteromedially from the first array into the region of the supplementary motor area (SMA) as anatomically identified. No implant-related medical adverse events were observed. After three days of post-operative recovery, the patient was discharged to his home.

Neural signal processing. A digitizing headstage and a Neural Signal Processor (CerePlex E and NSP, Blackrock Microsystems LLC) were used to record and process neural signals. Raw signals sampled at 30kS/s per channel were bandpass filtered with a window of 250–7500 Hz. Single and multi-unit action potentials were extracted from each channel by identifying threshold crossings (4.5 times root-mean-square of each channel's values). Depending on the activity and noise level, thresholds were manually adjusted for those channels used in the BCI sessions after visual inspection of the data to exclude noise but capture all of the visible spikes above the threshold. Neural data were further processed on a separate computer using a modified version of the CereLink library (https://github.com/dashesy/CereLink) and additional custom software. For communication, we used spike rates from one or more channels. A spike rate metric (SRM) was calculated for each channel by counting threshold crossings in 50 ms bins. The SRM was calculated as the mean of these bins over the past one second.

Custom software written in Python and C + + was used to perform and control all BCI sessions. The software managed the complete data flow of the raw signals provided by the NSP, allowing manual configuration of recording parameters, selection of individual channels for neurofeedback and storing of neural data, and meta-information (timing information of trigger events, etc.) required for offline analysis.

The software enabled the experimenter to configure different experimental protocols, to select an experimental paradigm for each session, and to trigger the start and end of a session. The software-controlled the presentation of auditory stimuli to the patient, including the presentation of feedback from his neural activity. It also provided live feedback to the experimenter regarding ongoing progress, e.g., the currently spelled phrase. Also, the software provided live visualization of neural activity, including the original firing rate activity of selected channels and normalized firing rate activity used for neurofeedback. To secure smooth real-time processing and to avoid potential performance bottlenecks, the software supported multiprocessing. That is, all critical processes, including data acquisition, data storage, neurofeedback, classification, and visualization, were executed in separated cores.

Neurofeedback communication. The patient was provided auditory feedback of neural activity levels by mapping the SRM for one or more channels to the frequency of an auditory feedback tone, as shown in Fig. 1. Single channel spike rates were normalized according to the spike rate distribution of each channel. Selected channels' normalized SRMs were then summed and linearly mapped to the range of 120–480 Hz, determining the frequency of the feedback tone produced by an audio speaker. Feedback tones were updated every 250 ms. The firing rate r_i of each selected channel was constrained to the range $[a_i,b_i]$, normalized to the interval [0,1], and optionally inverted, and the resulting rates were averaged:

$$r(t) = \frac{1}{n}\sum_{i}^{n}\frac{1-c_i}{2} + c_i\frac{\max(\min(r_i(t), b_i),\ a_i)}{b_i - a_i} \tag{1}$$

where $r(t)$ is the overall normalized firing rate, and the c_i are 1 or −1. The normalized rate was then linearly mapped to a frequency between 120 and 480 Hz for auditory feedback. Feedback tones were pure sine waves lasting 250 ms each. Initially, channels were selected randomly for feedback. Then the parameters a_i,b_i,c_i as well as the channels used for control were chosen and iteratively optimized each day in the neurofeedback training paradigms.

The first paradigm ("feedback without reward") provided successive target tones at 120 or 480 Hz, and the patient was asked to match the frequency of the feedback to the target (typically 20 pseudorandom trials per block). In the "feedback with reward" paradigm, was essentially the same, however, upon reaching and holding (during a configurable number of interactions, each interaction lasting 250 ms) the feedback tone within a predefined range around the target frequency, an additional reward sound was delivered for 250 ms indicating successful performance to the patient. Holding the feedback tone at the high (low) end of the range for 250 ms was then interpreted by the patient upon instruction as a Yes (No) response (see Supplementary Video V1 as a typical example). The "feedback with reward" paradigm served to train and validate the responses.

We also validated the Yes/No responses in a question paradigm, in which the answers were assumed to be known to the patient. Furthermore, we used an 'exploration' paradigm to test if the patient's attempted or imagined movements could lead to modulation of firing rates.

Finally, in an auditory speller paradigm, the patient could select letters and words using the previously trained Yes/No approach. The auditory speller paradigm is depicted in Fig. 1c. The speller system described here avoids long adaptation and learning phases because it is identical to the one used previously when he was still in control of eye movements. The original arrangement of the letters in their respective groups was chosen according to their respective frequency in the patient's native German language.

The speller's output was rated for intelligibility by three of the authors (UC, IV, and JZ). Three categories were used: unintelligible, ambiguous, and intelligible. Ambiguous speller output includes grammatically correct words that could not be interpreted in the context as well as strings of letters that could give rise to uncertain interpretations. Intelligible phrases may contain words with spelling mistakes or incomplete words, but the family or experimenter identified and agreed upon their meaning.

To evaluate the performance of the speller, the information transfer rate[36] (ITR) B during speller sessions that were rated as intelligible was calculated as:

$$B = \log_2 N + P\log_2 P + (1-P)\log_2\frac{1-P}{N-1} \tag{2}$$

where N is the number of possible speller selections (30 including space, delete, question mark and end program), and P is the probability that a correct letter was selected. Multiplication with selected symbols and division by session duration yields bits per minute.

Data handling. Software and procedures were designed to provide redundancy and automation to ensure that crucial information is always saved with each recording:

1. The BCI software was implemented with extensive automated logging for each session:
   a. neural data (spike rates) used for BCI control
   b. event timestamps from the neurofeedback training/validation and speller paradigms
   c. configuration used to run the particular session, including channel selection, normalization parameters, thresholds for yes/no detection, task timings, arrangement of letters in speller, etc.
   d. source code of the KIAP BCI software used on that day. The BCI software was kept under version control using git. The hash of the current commit was saved along with any changes compared to that commit.
2. Specific instructions were given to the personnel performing the experimental sessions to acquire raw neural data collected in parallel to the BCI data, which included loading a configuration file, starting data recording before a BCI session, and stopping the recording at the end. Two experimenters were on-site, when possible, to divide system operation and patient interaction tasks.
3. Information about each recording session was entered into a session log in a shared Excel file (which has a history of edits). Information logged include for each session:
   a. kind of experiment
   b. file names of raw data and KIAP BCI data
   c. any additional EEG recordings if performed
   d. names of video files if performed
   e. experimenters present
   f. observations/abnormalities for the session
   g. data recording abnormalities, etc.
4. During the experiments, known issues were fixed, for example, a change in log file format was implemented (as noted in the accompanying dataset), which allowed to more easily interpret the data. The post hoc analysis, i.e., parsing log files and data compilation was checked manually for several sessions. Co-authors reviewed the results and the process.
5. Data handling procedures were implemented to ensure that data integrity was maintained from recording to safe storage.

Dataset reported in this article. The dataset here spans days 106 to 462 after implantation. For the analysis of neurofeedback trials in Fig. 2 and the corresponding main text, only blocks after day 123 were used because of a change in paradigm (before day 123, incorrect trials and time-outs were not differentiated). For Supplementary Fig. 1, all neurofeedback blocks were used, as time-out trials were counted as 'incorrect' as well. All speller sessions performed between days 106 and 462 were included in the analysis. The BCI data of one neurofeedback and one speller session were lost during data transfer and the loss was only discovered after the original data had been deleted. These sessions were therefore excluded from the analysis.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data upon which the findings in this paper are based (neural firing rates, event log files for data presented in Figs. 2, 3, 4, S1, S3; electrode impedances and spike event files for data presented in Fig. S2) are available at https://doi.org/10.12751/g-node.jdwmjd[37]. The EOG data which Fig. S4 is based on is available at https://doi.org/10.12751/g-node.ng4dfr[38]. Source data are provided with this paper. The raw neural recordings is available upon request to J.B.Z., yet owing to the potential sensitivity of the data, an agreement between the researcher's institution and the Wyss Center is required to facilitate the sharing of these datasets. Source data are provided with this paper.

Code availability

The code used to run the BCI system is available at https://doi.org/10.12751/g-node.ihc6qn[39].

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Author contributions

U.C.—Initiation; Conceptualization; Ethics Approval; Performed 95% of the sessions with the patient before and after implantation; Figures; Neurofeedback paradigm; Manuscript writing. I.V.—Software development, integration and testing; Data analysis; Neurofeedback paradigm implementation; Performed 5% of the sessions after the implantation. J.B.Z.—Neurofeedback paradigm implementation; Data analysis; Figures; Manuscript writing. A.E.—Software testing; EEG/EOG analysis; Figures. A.T.—Speller software development; Performed 30% of sessions before implantation and 20% of the sessions after implantation; EEG/EOG analysis; Figures. A.J.-G.—EEG/EOG analysis; Figures. M.K.A.—Graphical user interface. H.R.T.—Ethics Approval; Medical patient care; Clinical and diagnostic neurological procedures. J.L.—Ethics approval; Neurosurgery; Clinical care. G.M.F.—Neurosurgical training. A.W.—Ethics approval; BfArM approval; Neurosurgical training. J.P.D.—Initiation; Conceptualization, writing, review, editing. N.B.—Initiation; Conceptualization; Coordination, Clinical-psycholgical procedures and care; Neurofeedback paradigm; performed 30% of the sessions with UC; Ethics approval; BfArM approval; Manuscript writing.

Competing interests

The authors declare no competing interests.

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Appendix 9.

Majid Khalili-Ardali, Jayro Martínez-Cerveró, Alessandro Tonin, **Andres Jaramillo-Gonzalez**, Shizhe Wu, Giovanni Zanella, Giulia Corniani, Alberto Montoya-Soderberg, Niels Birbaumer, Ujwal Chaudhary (2021). Framework of a binary EEG and fNIRS Brain Computer Interface. *SoftwareX,* in revision.

A General-Purpose Framework for a Hybrid EEG-NIRS-BCI

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Current code version

Nr	Code metadata description	*Please fill in this column*
C1	Current Code version	V 1.5.5
C2	Permanent link to code / repository used of this code version	https://github.com/majidkhalili/HybridBCI
C3	Legal Code License	MIT license (MIT)
C4	Code Versioning system used	Git on Github.
C5	Software Code Language used	Matlab
C6	Compilation requirements, Operating environments & dependencies	Matlab R2018a, Psychtoolbox, DSP System Toolbox (Only for EEG), TextAnalytics Toolbox (Only for speller)
C7	If available Link to developer documentation / manual	https://github.com/majidkhalili/HybridBCI
C8	Support email for questions	Majidkhalili89@aim.com

Abstract

Brain-computer interfaces (BCI), use brain signals to generate a control signal to control external devices to assist paralyzed people in movement and communication. Electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS) are the two most widely non-invasive brain recording techniques to develop BCIs. This article describes a software tool called "HybridBCI with an open-source framework for NIRS and EEG for a Hybrid BCI" application. This HybridBCI has been successfully used to enable brain communication in patients without any means of voluntary communication and has been recently reported by the authors. This software tool is Matlab based, using modular object-oriented programming principles, and experimenters can use it with different platforms and hardware to perform their BCI experiments and integrate their custom modules according to their needs.

Keywords

Brain-computer interface (BCI), EEG, fNIRS, HybridBCI, Locked-in syndrome (LIS), Completely locked-in syndrome (CLIS)

Introduction

Several research labs have developed versions of BCIs to enable communication with the ALS-patients and other patients with paralysis with heterogeneous results[1–6]. Recently Tonin et al. reported the successful use of an eye-movement based BCI for communication with four patients with amyotrophic lateral sclerosis (ALS) in the transition from locked-in state (LIS) to completely locked-in state (CLIS) [7] and the data set was published by Jaramilo-Gonzalez et. al. [8]. Despite the residual oculomotor activity, these patients could not use assistive and augmentative communication devices for communication. An electrooculogram (EOG) based communication system was developed using which the patients employed their remnant eye-movement activity to spell freely and communicate expressing their desires. The study was performed using a software tool, designed by the authors for the BCI application, called HybridBCI. HybridBCI is the result of extensive development of BCI application for communication purposes in LIS and CLIS patients using electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS) signals [7–9]. With this report, we provide the source code for HybridBCI, which can be used for human-computer interface (HCI) applications in patients, including but not limited to LIS and CLIS.

HybridBCI is not just a programming toolbox but also consists of an experimental paradigm allowing the user to implement any type of BCI using EEG, electrooculography (EOG), electromyography (EMG), or fNIRS. HybridBCI benefits from a modular pattern; therefore, if the user wants to implement a particular algorithm, s/he can add only that particular segment without the need to know how the whole system works. HybridBCI is implemented in Matlab [10] widely used by neuroscientists, and due to the interpreting nature of the Matlab, once a new functionality is added, there is no need to recompile the code. Besides, in clinical applications, data organization and experiment logging is crucial, and HybridBCI manages the file organization and properly logs recording sessions. Although several platforms have already been proposed for BCI applications [1,3,4], we are introducing HybridBCI because the primary goal of the HybridBCI is to be used in ALS-CLIS patients with the possibility to be used in other disorders of consciousness. In ALS-CLIS patients, the vision is impaired [7] and visual paradigms cannot be used. Therefore, the experimental paradigm used in HybridBCI is completely auditory based and does not require intact visual perception. In these patients, the EEG is significantly altered, and common EEG biomarkers are missing in some patients [11,12], and even in patients with the same syndrome, a unique pattern cannot be found within a patient over time in different stages of the disease [13]. Therefore, the analysis pipeline should be applicable and modified for each patient individually, and HybridBCI gives us this flexibility in the analysis pipeline, as described below.

This paper proposes an experimental paradigm with an open-source framework of a BCI with a clear and straightforward pipeline from data acquisition to signal analysis and classification with a separate implementation of each part. New features at any step of the pipeline can be added to the software by placing newly implemented .m files in the correct folders.

Paradigm

In the HybridBCI, regardless of the cognitive task used (e.g., mental calculation, the imagination of hand/foot movement, covert thinking, etc.), a list of questions/sentences with answers known by the experimenters is presented auditorily to the BCI user, and the user is asked to perform two different tasks i.e., responding mentally “ yes” or” no” (i.e., true/false or 1/0). The auditory channel is used because many severely ill chronic patients suffer from impaired vision. HybridBCI uses Psychotolbox [14] in presenting auditory stimuli to minimize the software delay. Questions are repeated to the user with an equal, but random distribution of questions with Yes and No answer (i.e.Your name is Majid. Your name is Ujwal) in an experimental block, and blocks are repeated to acquire enough data for classification. The initial experimental blocks are called training blocks since the user is familiarizing with the paradigm, and the data is collected to train a classifier. Once enough trials are acquired, a classifier is trained to classify yes and no answers. If the classification accuracy reaches above chance level, a feedback block is performed in which the user receives feedback on what has been classified, which also serves as a reward. If the feedback accuracy in a feedback block is also higher than chance, the model can be used for other applications with unknown answers. The chance can be calculated as proposed by Müller-Putz et al.[15] based on the number of trials in each block. The proposed block diagram paradigm is depicted in Figure 1. The number of blocks is dependent on the selected task, the number of trials in each block, and the users' condition. The rule of thumb would be to have twenty trials per block in four training blocks and one feedback block, which approximately takes one hour.

Implementation

HybridBCI is implemented in Matlab based on object-oriented programming (OOP) principles, and new features can be added by placing the user implemented .m file in the correct path to guarantee the scalability [5] of the system. As depicted in Figure 2, the core structure of

HybridBCI is based on the two main modules named “HybridBCI.mlapp” and “ModelBuilder.mlapp”, which do not need to be modified by users and are implemented using the Matlab App Designer[16].

1) Hybrid BCI

This module runs and controls the running experiment’s sequence, controls data acquisition functions, handles the triggering, runs “ModelBuilder” and log the experimental report. HybridBCI has three tabs, 'Configuration', 'Experiments', and 'Applications', which are used in an experiment, respectively. In the first tab, the brain signal measuring techniques and their corresponding recording handlers are selected, and the timing of the experiment is set (Figure 3A). These pieces of information and other experimental information, such as the name of experimenters, date and time of the experiment, and auditory stimuli list, are saved for each experimental block in a single .mat file.

a. Trigger

The HybridBCI system's functioning relies on precise labeling and saving the paradigm's events synchronized with the raw data recording. The correct timing is delivered by the HybridBCI module to the acquisition devices through a set of symbols, named triggers. The proper sequence of triggering values for blocks and trials is presented in Table 1. Any triggering device is an instance of a class derived from ‘Device.m’ and needs to implement its’ abstract functions. With this code, implementation of hardware triggering over the LPT port and the software triggering through a TCP/IP protocol for Brain Products GmbH (Germany) for EEG recording and file-based triggering for NIRx Medical Technologies (USA) for NIRS recording are implemented. HybridBCI is designed not to have any cumulative error between blocks and trials.

b. Data acquisition

HybridBCI can run and handles two recording devices simultaneously as needed for NIRS and EEG data acquisition, and it sends triggers to both of them at the same time. For each recording device, a new instance of Matlab is loaded by clicking on the corresponding ‘RUN’ button in the Experiment tab of the HybridBCI module (Figure 3B). New recording devices can be added by placing their .mlapp file in the “..\lib\Devices\EEG|NIRSDevices\”. With this code, data acquisition and/or triggering for BrainVision, StarStim, and NIRx are also implemented and can be provided upon a request.

c. File Management

For each day of recording, a new folder is created in ‘..\Subjects\XX\’, in which the XX denotes the date of recording (e.g. ’22-Nov-2019’), and for each block, a configuration file is saved in it, containing parameters of the performed experiment. Subjects’ audio files are stored with .wav extension in ‘..\Subjects\XX\Audios\Questions\’, which is very helpful in experiments with (C)LIS patients, in which audios needed to be recorded by the individuals’ family members. Audio question files with yes answers are labeled as ‘001_FileName.wav’ while questions with no answer are labeled as ‘002_FileName.wav’. The files are optional but are recommended to be named with valid identifiers since they will be stored in each block's configuration file. A sample of 20 audio files with yes and no answers are provided with this code.

d. Applications

Once a classification accuracy above the chance level is achieved, the same model can be used to run different applications in which the intention of the user is not priory known for experimenters. HybridBCI can automatically run and control the state transitions for any application that derives from ‘Paradigm.m’. ‘Paradigm.m’ is a class with abstract methods that are needed for their functionality in HybridBCI. Once a new paradigm class is defined, it can be accessed and run from the ‘Application’ tab in the ‘HybridBCI’ module (Figure 3C). With this code, two primary examples of such applications are provided, including OpenQuestion, in which the user can answer the questions that the answers are unknown to the experimenters, and Speller in which the user can freely spell what she/he has in mind [7].

2) Model Builder

“ModelBuilder” handles the analysis processing pipeline for NIRS and EEG in six steps (Figure 4) and stores it in a .mat file in the ‘Models’ folder for each subject to be used for giving feedback, running applications, or to perform offline analysis. Each analysis step has a dedicated tab in the GUI and is described below.

a. Data Selection

This tab enables users to select data and reject noisy channels before performing any analysis, which may arise due to displaced EEG electrodes or noisy NIRS channels, or other recording issues (Figure 5A).

b. EEG Preprocessing

EEG preprocessing fulfills the purpose of cleaning the recorded signal from noise and artifacts (such as eye blinking or movement) and performing transformations or reorganizations of the recorded data or any other condition necessary for further analysis [1–3]. Following what is suggested by the quoted references, for a basic EEG pipeline, we include preprocessing functions commonly used in EEG preprocessing, that is, selection of the frequency bands and filtering, simple linear transformations (normalization and baseline correction) and re-referencing operations (common-average reference) (Figure 5).

It is important to note that the application of preprocessing steps depends on several aspects, as the study's goal, the experimental design, the physiological phenomena being investigated and the searched features in the signal, or other custom analysis necessary for the experiment. Therefore, there is no standard sequence of steps for preprocessing the EEG since each preprocessing sequence is tailored depending on the aforementioned variables [3,4]. For example, a survey for optimizing the work with event-related potentials (ERP) in the frame of BCI [5], concludes that the best-practice guidelines for preprocessing are 1) use as many EEG electrodes as is practical to record, avoiding the use of sub-montages or sub-sets of electrodes, 2) spectral filter to remove obvious noise components, with a close to the optimal passband of 0.5-12 Hz, 3) apply spatial filtering for "whitening" [6], for a final stage with a classification method. Naturally, for different experimental designs, the guidelines change as verified in other developed platforms (e.g., [7–10]).

With this requirement in mind, the preprocessing pipeline of this software allows us to select the order in which the preprocessing functions are applied and include other additional functions necessary for a custom EEG preprocessing (e.g., spatial filtering, re-referencing, temporal windowing). Thus, the particular preprocessing pipeline of this software consist – as it can be configured in the EEG Preprocessing tab of the ModelBuilder (Figure 5B) – of the following steps:

I. Filtering

Previous to the filtering, two sets of options are provided for the user: First, *Source Selection*, in which the user can select the types of signals to be considered in the analysis, either EEG, EOG, or EMG channels. Second, *Bands Selections*, in which a group of traditional ranges of oscillations commonly used in EEG analysis [27], Wideband (0.5-30 Hz), Delta (1-4 Hz), Theta

(4-7 Hz), Alpha (7-13 Hz) and Beta (13-30Hz), are offered to the user, with the possibility of using the default given ranges, or manually introducing modifications to each range. Then we apply a second-order Infinite Impulse Response (IIR) notch filter at 50 Hz, and after that, we included two options for filtering: Finite impulse response (FIR) filter and Butterworth IIR filter design. Both filters are applied so that the phase of the signal is not affected by [28]. We propose these two types of filters to allow the user to consider each according to her/his needs and their particular benefits or drawbacks applied to EEG signals [29].

II. Processing Functions

With this code, three of the most common amplitude correction methods are provided. First, Normalization [30], by applying the z-score to the epoch (that is, subtraction of mean of each window and division by the standard deviation [31]). Second, Baseline Correction, which in our case is the simple subtraction of a pre-stimulus value (a predefined baseline) from the epoch, under the assumption that any physiological effect recorded post-stimulus can be highlighted if compared with a pre-stimulus "base" [32]. For this, it must be considered that the definition of a baseline period varies depending on the physiological and analytical nature of the study [33]. Finally, the Common Average Reference (CAR), to approach the recordings to an "inactive reference" – if all the channels were recorded respective to the same physical reference – by subtracting to each amplitude value the average of the amplitude values of all the channels at the same instant [33]. The user can choose the order in which they will be applied from the list of all available functions. User implemented EEG processing functions can be added to the pipeline by placing the .m file in in '..\lib\EEG\Preprocessing\.

c. EEG Feature Extraction

With this code, an initial set of features used in the analysis of EEG in the field of BCI in the time and frequency domain are included [34], including a series of range features for EEG time-series (Figure 5C). Details on the implemented EEG features can be found on supplementary data. User implemented EEG feature can be added to the pipeline by placing the .m file in '..\lib\EEG\Features\'.

d. NIRS Preprocessing

HybridBCI develops the pipeline for the NIRS pre-processing in two steps: first wavelength conversion, second filtering. In the first step, a basic default function is developed to convert the wavelength signal to hemodynamic concentration using the Modified Beer-Lambert Law

(MBLL) [35], while in the second group, the systemic components can be filtered using a bandpass filter function [36].

The NIRS signal is acquired as a pair of wavelengths belonging to the near-infrared spectral range between 650 nm to 950 nm [37]. To get a physiological signal, the most commonly used technique is the MBLL [35] to convert the wavelength to optical density and the hemodynamic concentrations: oxyhemoglobin (HbO), deoxyhemoglobin (HbR), and total hemoglobin concentration (HbT) [38]. In the MBLL, two terms of the equation are the molar extinction coefficient and the differential path length factor that accounts for the real distance the light travels due to the scattering [35]; these two terms depend on many factors (e.g., age and gender of the subject), and their values can be found on the literature [36,39]. The observed hemodynamic signal is the result of the sum of neuronal and systemic components, thus to analyze functional changes, many techniques have been developed to separate the different components and remove external noise (see [40] for an extensive review). With this code, an implementation to convert wavelength data to hemodynamic response is provided, and proper filters are designed to filter hemodynamic responses (Figure 5B). User implemented functionalities can be added to the processing pipeline by placing the .m file in '..\Lib\NIRS\PreProcessing\'.

e. NIRS features

Once the HbO, HbR, and HbT are pre-processed, it is possible to extract features to describe the signal using only the data's relevant characteristics. The developed functions extract the features for each of the three hemodynamic signals working on a single channel level, i.e., without averaging or grouping different channels or different signal types. With this code, preliminary features mostly used for NIRS signals are provided and listed in supplementary data. Any new feature can be added to the pipeline by placing a related m file in '..\Lib\NIRS\Features\'.

f. Dimensionality

Once the pre-processing and feature extraction steps are concluded, the dataset's size in the feature space increases significantly. At this point, we incorporated two steps to reduce the dataset size keeping only those features that have a more significant influence on the final result (Figure 5D).

I. Features consistency

This step is used to test the homogeneity of the features' distribution across the different trials used to train the classifier and results in a training sample with equal or fewer features than initially. This process keeps only those features that are consistent over time and discards the rest. It also reduces the calculations in future stages. For details, see [41–43].

II. Dimension reduction

This step is used to reduce the training data's dimensionality by selecting an ordered set of the most relevant features for classification [44–47]. Given a training sample with *m* features and a percentage *K* specified by the user, a variable selection method is implemented, resulting in a training sample with a number *k* percent of features. The implemented function is a variation on the popular minimum redundancy maximum relevance (mRMR) method, originally created by *Ding and Peng* [44] and *Peng et al.* [45] but using another association measure instead of "mutual information", as proposed by *Berrendero et al.* [46]. Their approach, which appears to work better on small samples [46] and is thus relevant for BCI applications, consists of using squared "distance correlation", which measures dependency between variables and was introduced by *Székely et al.* [47].

g. Classification

HybridBCI can use any classifier that is derived from the abstract class 'Classifier.m' in '..\Lib\Classifiers\'. Classes inheriting from this class need to implement two abstract functions, including training the model with given features as input and predicting a single trial using the same model. With this code, two well-known classification algorithms are provided: Support Vector Machines (SVM's) and k-Nearest Neighbours (k-NN) [48,49] (Figure 5E). For a review of classification methods for EEG based BCI, see [50], and for hybrid EEG and NIRS see, [51].

h. Validation

One of the known issues in machine learning is the problem of overfitting the data, and it refers to the problem that due to the incorrect tuning of the classifier, the model overfits the features space. Therefore, it is necessary to check the classifier's performance on the data other than the data that has been used for training (simulating the online feedback in the BCI experiment). For this reason, the Validation tab in the 'ModelBuilder' is provided to check the performance of each model on other datasets (Figure 5F).

Discussion and conclusion

During several years of research and development in the field of BCI for communication in DoC patients, several versions of this software have been used to perform studies. This version of HybridBCI is the outcome of this process in our lab. A version of HybridBCI was used to enable communication with ALS patients on the verge from LIS to CLIS when all other communication means failed and reported a yes-no communication of more than chance level, and the possibility for free spelling. Details for analysis pipeline and classification results can be found in Tonin et al. (2020) [7]. The code is provided in the Matlab that most of the scientists in cognitive science are already familiar with and easy to develop. HybridBCI has an OOP software design, and due to the interpreting nature of the Matlab programming language, as opposed to compiling based programming languages, new features and functionalities can be added to the system by placing new .m files in the proper path without the need to know the whole system or recompiling the project. The current version of the developed software enables simultaneous interfacing and data acquisition from Brain Products' EEG and NIRX's NIRS device. The software provides a user-friendly interface to enable experimenters to select an appropriate EEG and NIRS data processing pipeline. The experimenters can select the corresponding feature extraction method and machine learning algorithm to classify the brain states. This software only has the functionality to select features from EEG and NIRS signal separately, i.e., it does not have the functionality for hybrid EEG and NIRS feature selection. However, an experimenter can easily implement their desired hybrid feature selection method and integrate it with the HybridBCI software. An experimenter can also implement his/her machine-learning algorithm as per need beyond what has been provided in the current version of the software and integrate it with the HybridBCI, thereby further expanding the HybridBCI software's functionality. Thus, the modular design of the software enables experimenters to further expand on what has been provided in the software.

The HybdridBCI software, through its six years of the developmental process, has been used to enable communication with patients in LIS, in the transition from LIS to CLIS, and finally in CLIS. During its development process, we encountered several challenges, such as lack of vigilance markers in patients in CLIS, lack of clear sleep- cycle markers in CLIS, patients' cognitive status, and patient's engagement in the experiment. We performed extensive studies to elucidate a sleep-cycle marker in CLIS [11], resting-state state EEG in LIS and CLIS[12–14], performed a preliminary study on the cognitive state of patients in CLIS [14,15] and attempted transcranial direct current stimulation (tDCS) technique to target the vigilance network in CLIS. We found that spontaneous brain activity in ALS-CLIS patients is significantly altered. Thus, commonly used indexes of arousal state in healthy people do not necessarily serve the same purpose in these patients' populations, and newly defined indexes should be introduced and validated. As we continue further with our study with patients in LIS, in the transition from LIS to CLIS and finally in CLIS, we aim to implement modules in the software to detect the vigilance and sleep stage of the patient automatically so that the BCI communication sessions will be performed only if the patient is vigilant and not sleeping. Thus, the present HybridBCI software is the first step towards developing a tool to solve the challenge of enabling communication in patients who have none.

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Author contributions

MKH designed the software, implemented the core structure, and wrote the first draft of the paper. JMC improved the core structure and combined different software modules. AT implemented NIRS pipeline, presenting paradigm and classification methods, implemented speller, and wrote the NIRS section. AJG implemented the EEG pipeline and wrote the EEG section. SW improved EEG pipeline and test and debug the system. GZ test and reported the triggering, and improved NIRS pipeline. GC implemented range features. AMS implemented and reported feature consistency and dimension reduction. NB designed the paradigm and provided resources. UC initiated the HybridBCI software, conceptualized, implemented initial paradigms and signal processing pipeline, supervised, acquired fundings and manuscript writing.

Competing interests

The author(s) declare no competing interests.

Code availability

Source code and sample data are available at https://github.com/majidkhalili/HybridBCI.

Ethical Approval

The Internal Review Board of the Medical Faculty of the University of Tubingen approved the experiment reported in this study. The study was performed per the guideline established by the Medical Faculty of the University of Tubingen. The patient or the patients' legal representative gave informed consent with permission to publish the data. The clinical trial registration number is: ClinicalTrials.gov - Identifier: NCT02980380.

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List of Tables

Table 1: The table represents the 14 different triggers used by the HybridBCI for managing the different events. These values are sent to the acquisition systems during the experiment and used to keep track of the timing of the different events.

Table1

Event	Trigger values			
		Yes Question	No Question	Open Question
Block Start	9			
Baseline		10	11	12
Question		5	6	7
Thinking		4	8	13
Feedback		1	2	3
Block End	15			

List of Figures

Figure 1: Block diagram for HybridBCI paradigm for training (yellow), feedback (blue), and any application (green) blocks. If the offline or online classification accuracy of the built model is more than the chance level in each block, the next block can be performed. The ultimate goal is for the patient to use his/her brain signal to freely spell what s/he has in mind.

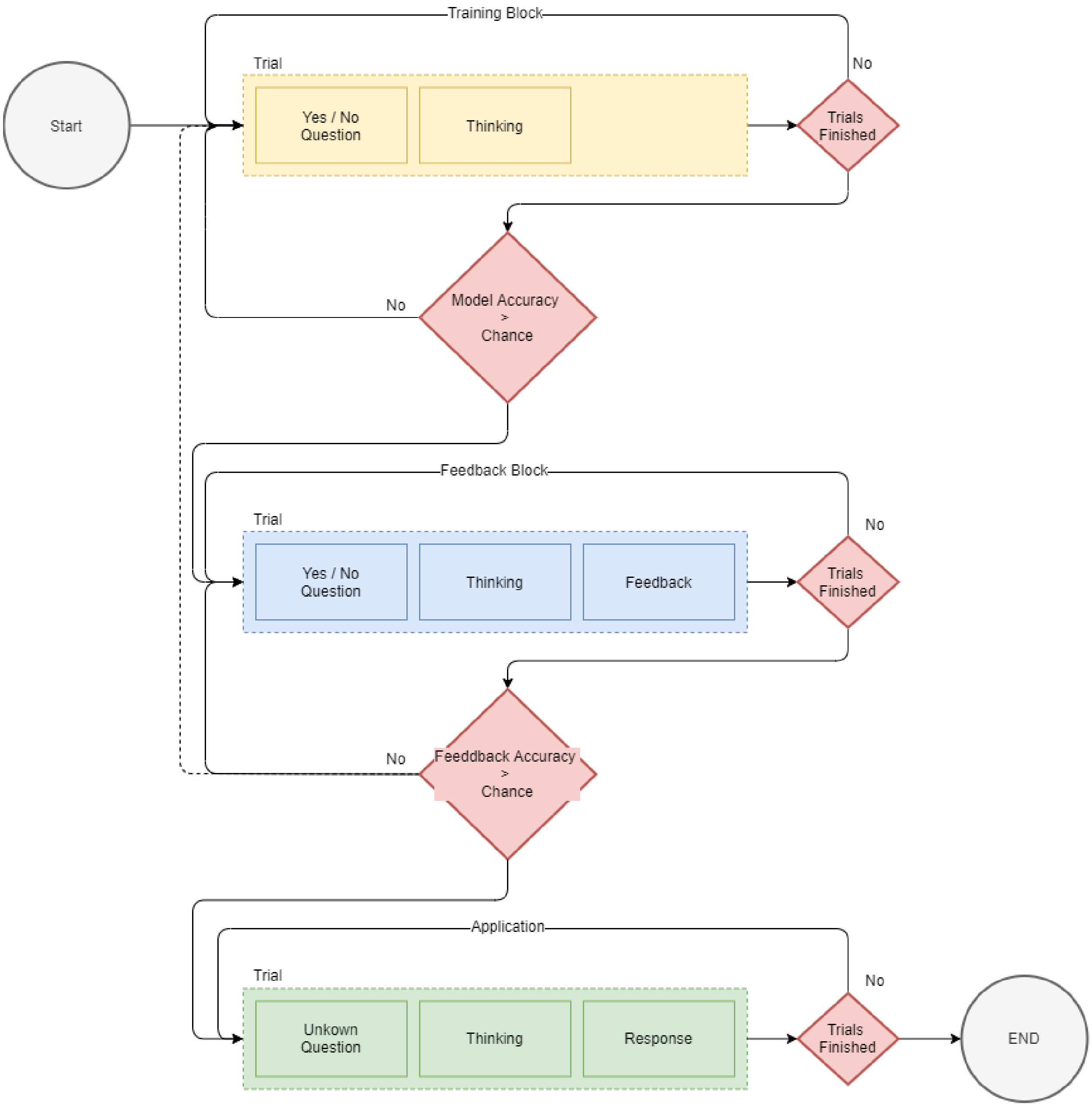
Figure 2: HybridBCI System Design and file organization. Two main software modules, ModelBulder.mlapp and HybridBCI.mlapp (White boxes), and three Matlab instances (Matlab Icons) control the experimental procedure and online data acquisitions. For each functionality of the system, a folder is dedicated (Yello boxes) and the HybridBCI automatically recognizes new .m files in these folders and extends its' functionality accordingly.

Figure 3: HybridBCI Module - A. Configuration tab for Selecting recording devices, setting the timing of the experiment, selecting a list of experimenters, and controlling trigger devices. B. Experiment tab for selecting patients, choosing a task, controlling the number of trials in each block, running data acquisition Matlab instances, and running training and feedback blocks. C. Application tab for selecting the desired application and the model to perform the task.

Figure 4: Six steps of the analysis pipeline used in ModelBuilder. Step 1 is for loading the data and select/deselect channels. Step 2 is designed for the preprocessing of the NIRS and EEG signals based. Step 3 is used to select the desired features to be extracted from NIRS and EEG. In step 4 before passing the features to classifiers in step 5, the dimension of the feature space is reduced. Finally, in step 6 the acquired model is validated on the data that has not been used for training the classifier.

Figure 5: ModelBuilder Module – A. Data tab for selecting data to be used for analysis and rejecting noisy channels. B. Preprocessing pipeline for EEG (top) and NIRS (bottom). C. Selecting features to be extracted from the signal. D. Dimensionality tab for reducing the size of the dataset in features spaces. E. Classifier tab for choosing a classifier to build the model. F. Validation tab for simulating online results and validating a model on previously recorded data.

479 Figure 1



Training Block
Trial
Start
Yes / No
Question
Thinking
No
Trials
Finished
No
Model Accuracy
>
Chance
Feedback Block
Trial
Yes / No
Question
Thinking
Feedback
No
Trials
Finished
No
Feeddback Accuracy
>
Chance
Application
Trial
Unkown
Question
Thinking
Response
No
Trials
Finished
END

480 Figure 2

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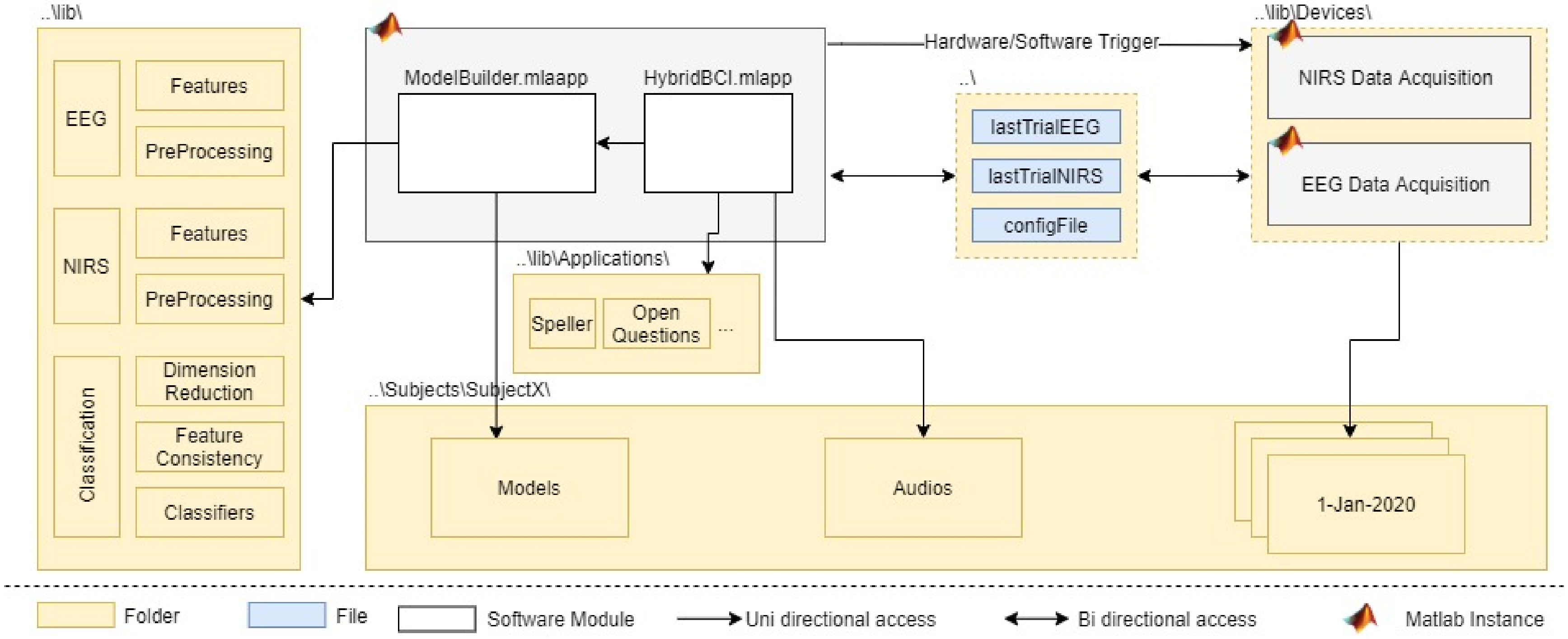

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Figure 3

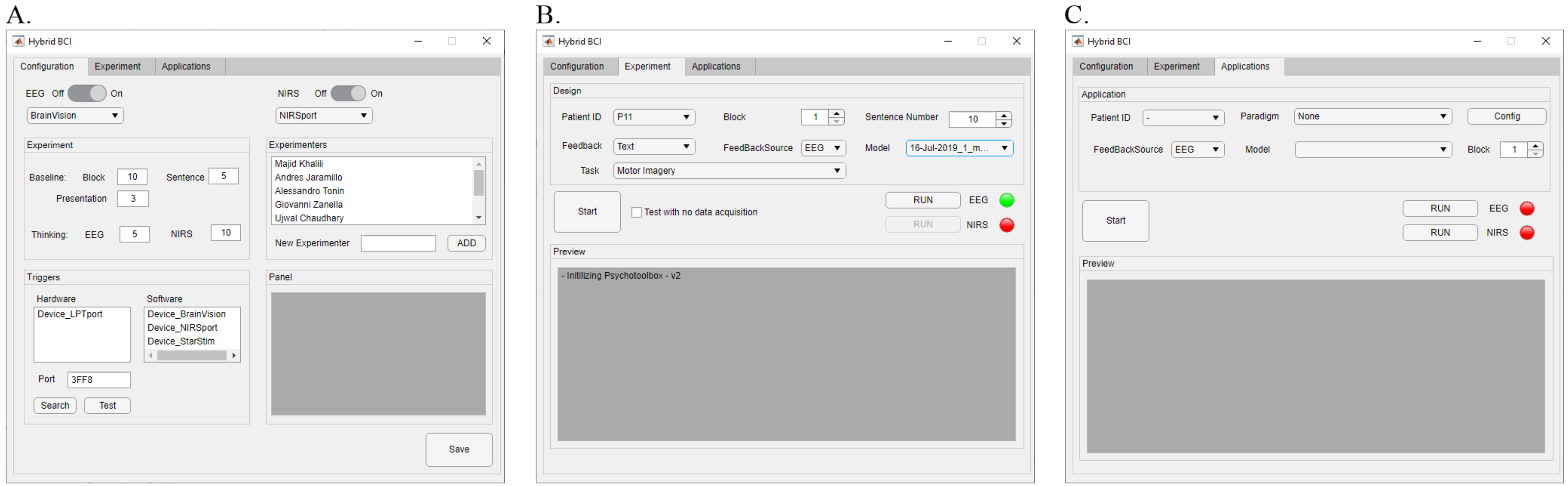
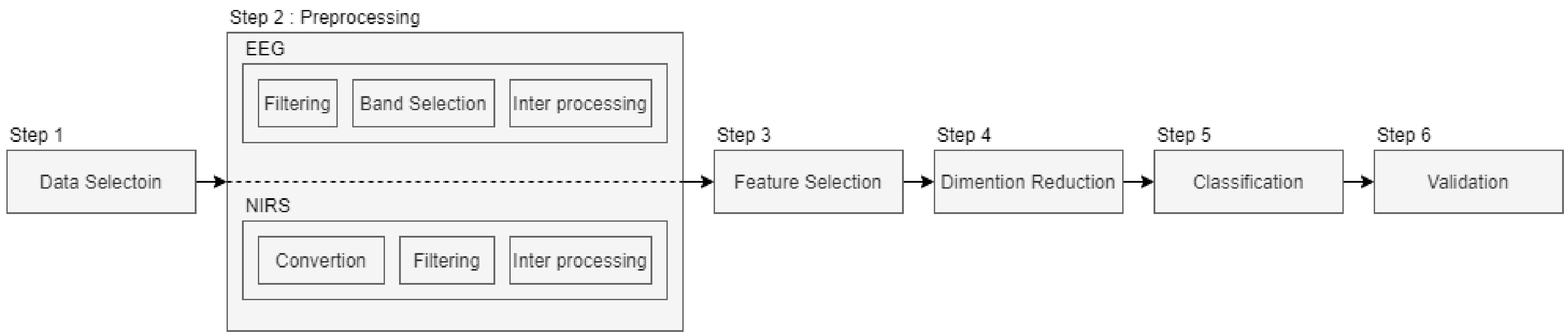
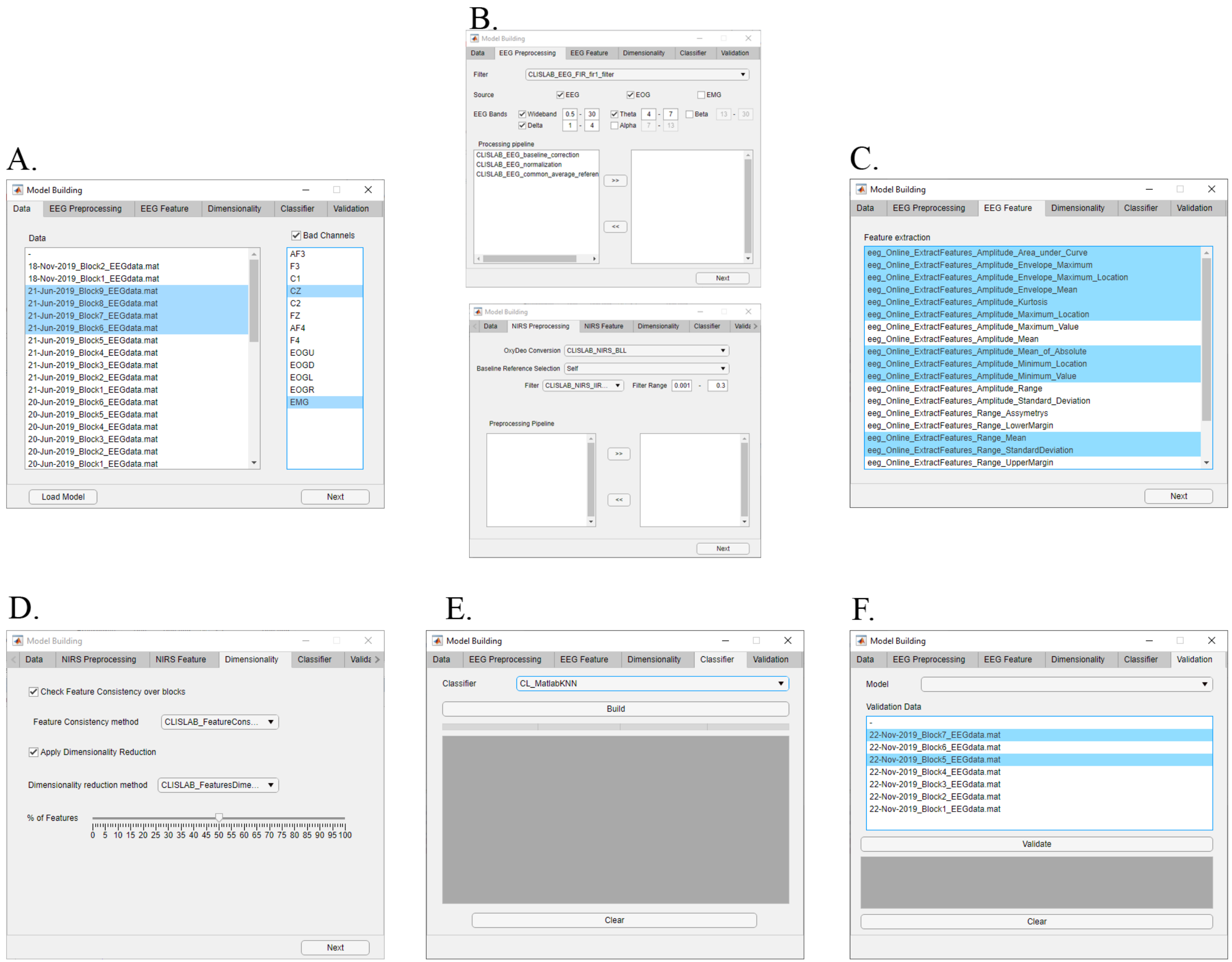

A.
Hybrid BCI
Configuration
Experiment
Applications
EEG Off On
BrainVision
NIRS Off On
NIRSport
Experiment
Baseline: Block 10 Sentence 5
Presentation 3
Thinking: EEG 5 NIRS 10
Experimenters
Majid Khalili
Andres Jaramillo
Alessandro Tonin
Giovanni Zanella
Ujwal Chaudhary
New Experimenter
ADD
Triggers
Hardware
Device_LPTport
Software
Device_BrainVision
Device_NIRSport
Device_StarStim
Port 3FF8
Search
Test
Panel
Save
B.
Hybrid BCI
Configuration
Experiment
Applications
Design
Patient ID P11
Block 1
Sentence Number 10
Feedback Text
FeedBackSource EEG
Model 16-Jul-2019_1_m...
Task Motor Imagery
Start
Test with no data acquisition
RUN EEG
RUN NIRS
Preview
- Initilizing Psychotoolbox - v2
C.
Hybrid BCI
Configuration
Experiment
Applications
Application
Patient ID -
Paradigm None
Config
FeedBackSource EEG
Model
Block 1
Start
RUN EEG
RUN NIRS
Preview

Figure 4



Step 1
Data Selectoin
Step 2 : Preprocessing
EEG
Filtering
Band Selection
Inter processing
NIRS
Convertion
Filtering
Inter processing
Step 3
Feature Selection
Step 4
Dimention Reduction
Step 5
Classification
Step 6
Validation

Figure 5


A.
Model Building
Data
EEG Preprocessing
EEG Feature
Dimensionality
Classifier
Validation
Bad Channels
18-Nov-2019_Block2_EEGdata.mat
18-Nov-2019_Block1_EEGdata.mat
21-Jun-2019_Block9_EEGdata.mat
21-Jun-2019_Block8_EEGdata.mat
21-Jun-2019_Block7_EEGdata.mat
21-Jun-2019_Block6_EEGdata.mat
21-Jun-2019_Block5_EEGdata.mat
21-Jun-2019_Block4_EEGdata.mat
21-Jun-2019_Block3_EEGdata.mat
21-Jun-2019_Block2_EEGdata.mat
21-Jun-2019_Block1_EEGdata.mat
20-Jun-2019_Block6_EEGdata.mat
20-Jun-2019_Block5_EEGdata.mat
20-Jun-2019_Block4_EEGdata.mat
20-Jun-2019_Block3_EEGdata.mat
20-Jun-2019_Block2_EEGdata.mat
20-Jun-2019_Block1_EEGdata.mat
AF3
F3
C1
CZ
C2
FZ
AF4
F4
EOGU
EOGD
EOGL
EOGR
EMG
Load Model
Next
B.
Filter
CLISLAB_EEG_FIR_fir1_filter
Source
EEG
EOG
EMG
EEG Bands
Wideband
Delta
Theta
Alpha
Beta
Processing pipeline
CLISLAB_EEG_baseline_correction
CLISLAB_EEG_normalization
CLISLAB_EEG_common_average_referen
Next
OxyDeo Conversion
CLISLAB_NIRS_BLL
Baseline Reference Selection
Self
Filter
CLISLAB_NIRS_IIR...
Filter Range
0.001
0.3
Preprocessing Pipeline
Next
C.
Model Building
Feature extraction
eeg_Online_ExtractFeatures_Amplitude_Area_under_Curve
eeg_Online_ExtractFeatures_Amplitude_Envelope_Maximum
eeg_Online_ExtractFeatures_Amplitude_Envelope_Maximum_Location
eeg_Online_ExtractFeatures_Amplitude_Envelope_Mean
eeg_Online_ExtractFeatures_Amplitude_Kurtosis
eeg_Online_ExtractFeatures_Amplitude_Maximum_Location
eeg_Online_ExtractFeatures_Amplitude_Maximum_Value
eeg_Online_ExtractFeatures_Amplitude_Mean
eeg_Online_ExtractFeatures_Amplitude_Mean_of_Absolute
eeg_Online_ExtractFeatures_Amplitude_Minimum_Location
eeg_Online_ExtractFeatures_Amplitude_Minimum_Value
eeg_Online_ExtractFeatures_Amplitude_Range
eeg_Online_ExtractFeatures_Amplitude_Standard_Deviation
eeg_Online_ExtractFeatures_Range_Assymetrys
eeg_Online_ExtractFeatures_Range_LowerMargin
eeg_Online_ExtractFeatures_Range_Mean
eeg_Online_ExtractFeatures_Range_StandardDeviation
eeg_Online_ExtractFeatures_Range_UpperMargin
Next
D.
Model Building
NIRS Preprocessing
NIRS Feature
Check Feature Consistency over blocks
Feature Consistency method
CLISLAB_FeatureCons...
Apply Dimensionality Reduction
Dimensionality reduction method
CLISLAB_FeaturesDime...
% of Features
Next
E.
Model Building
Classifier
CL_MatlabKNN
Build
Clear
F.
Model Building
Model
Validation Data
22-Nov-2019_Block7_EEGdata.mat
22-Nov-2019_Block6_EEGdata.mat
22-Nov-2019_Block5_EEGdata.mat
22-Nov-2019_Block4_EEGdata.mat
22-Nov-2019_Block3_EEGdata.mat
22-Nov-2019_Block2_EEGdata.mat
22-Nov-2019_Block1_EEGdata.mat
Validate
Clear