Aus dem Institut für Medizinische Psychologie der
Universität Tübingen

Performance of brain-computer communication in Amyotrophic Lateral Sclerosis

Dissertation
submitted for a doctoral degree in
human sciences

at the
Faculty of Medicine
of the Eberhard Karls Universität
Tübingen

submitted by

Silvoni, Stefano

2017

Dean: Professor Dr. I. B. Autenrieth

First reviewer: Professor Dr. Dr. h.c. mult. N. Birbaumer
Second reviewer: Professor Dr. Dr. h.c. H. Flor

Date of oral examination: 06.11.2017

to Stefania M., for her love, esteem and unconditional support
Chiara V., for her coherence, her openness and her very professional support,
Ujwal C., for his enthusiasm, his unconditional help and his rise & chicken
and Niels B., for his (kid) human character, his brilliance and his far-sightedness

Table of contents

List of tables

List of figures

List of abbreviations

ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale Revised
AAC	Augmentative and Alternative Communication
BCI	Brain Computer Interface
CLIS	Completely Locked-in State
CNV	Contigent Negative Variation
EEG	Electro-encephalography
ERP	Event-Related Potential
fNIRS	functional Near-Infrared Spectroscopy
LIS	Locked-in State
QoL	Quality of Life
SCP	Slow Cortical Potential
SMR	Sensorimotor rithm
SNR	Signal-to-Noise Ratio
SSVEP	Steady State Visual Evoked Potential

1. Introduction

1.1 Background

Persons diagnosed with Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, progressively lose body mobility and verbal communication due to motor neurons degeneration in the neocortex, braistem and spinal cord (Appel et al., 2011). Epidemiological studies of this neurodegenerative disease show that the incidence is between 1.5 and 2.0/100.000 persons per year all over the world (Mitchell & Borasio, 2007) and similar numbers can be found at regional level in Rheinland-Pfalz, Germany, with an incidence of 1.1/100.000 person per year (Wolf et al., 2014).

This dramatic pathological condition is fatal unless individuals opt for artificial ventilation via mask or tracheostomy and feeding via percutaneous endoscopic gastrostomy. Life expectancy of 3 to 5 years (Bensimon et al., 1994; Connolly et al., 2015) covering about 50% of patients' population can be prolonged by supporting respiratory function (Hardiman, 2011). The progression of the disease leads to increased communication difficulties, especially in advanced stages when muscles related to verbal production and speech start to be affected. Palliative measures such as non-invasive mechanical ventilation, speech therapy, respiration therapy, physiotherapy, pharmacological Riluzole treatment and 24h care are important for the quality of life's improvement and life prolongation (Piepers et al., 2006) but they do not halt the neurodegenerative process (Radunovic et al., 2013).

Opting for life and accepting artificial respiration, ALS individuals are faced with vital decisions but progressively lose their communication ability with reduced interactions with family members and surrounding environment. Assistive communication devices, relying on non-verbal signals such as gaze fixation and finger movement, allow patients to interact with the social environment (Fried-Oken et al., 2006). Last functioning muscles are those controlling eyes movements: this condition is called locked-in state (LIS). In this condition patients can communicate by means of augmentative and alternative communication (AAC) devices (Beukelman et al., 2011) or using brain-computer interface (BCI) systems (Wolpaw et al., 2002). Progressively patients enter in the last ALS transition where they are not able to move any muscle, definitely losing their communication capabilities (Murguialday et al., 2011). This condition is known as completely locked-in state (CLIS; Bauer et al., 1979).

Neuropsychological deficits are often found in ALS (Goldstein & Abrahams, 2013) since the involvement of extramotor cortical areas has been shown by neurophysiological, neuropsychological and functional brain imaging tools. Cognitive dysfunction is one of the clinical features in about 50% of patients' population (Ringholz et al., 2005), together with evidences of frontotemporal dementia overlapping motor profile decline in a subset of patients (Strong et al., 2009). Mild cognitive disorders are present in 32% of sporadic ALS patients' samples while moderate and severe cognitive impairments are found in around 19% (Ringholz et al., 2005). Due to the absence of standardized cognitive assessment batteries for ALS the exact numbers may vary considerably between studies. However, disease related motor deficits often alter the results of psychometric tests leading to overestimation of the cognitive decline.

While functional impairment is usually assessed by means of ALS Functional Rating Scale Revised (ALSFRS-R; Cedarbaum et al., 1999), the Edinburgh Cognitive Assessment Screening (ECAS) serves as an effective clinical assessment tool to determine the presence, severity and type of cognitive and/or behavioural changes in ALS (Abrahams et al., 2014). For instance, the ECAS has been consistently validated in a large German sample of ALS patients and healthy controls (Lulé et al., 2014). A few reliable cognitive screenings are available for advanced ALS-stages (Neumann & Kotchoubey, 2004) when verbal/written communication capacities are definitely lost, especially in CLIS condition (Kotchoubey et al., 2003; Fuchino et al., 2008) due to the impossibility to measure motor-behavioural responses. For this reason neurophysiological cognitive assessments are preferred in advanced ALS-stages.

Electroencephalography (EEG) and event-related potentials (ERPs) measurements are mostly used to detect specific cognitive processing dysfunctions related to memory, language and attentional network domains, such as working memory (Volpato et al., 2010), verbal fluency (Hanagasi et al., 2002), executive functions (Paulus et al., 2002) and selective attention (Pinkhardt et al., 2008; Volpato et al., 2016).

The burden of nursing and care of advanced ALS patients is increased when the cognitive profile exhibits clear signs of deficits which negatively influence assisted and BCI-based communication (De Massari et al., 2013). Even emotional changes seem to be altered during the course of the disease leading to reduction of negative emotional valence and lower subjective arousal (Lulé et al., 2007). Subjective quality of life (QoL) is mostly high in ALS (Lulé et al., 2009) and patients maintain a good psychosocial adjustment despite the devastating motor condition (Lulé et al., 2012). Therefore, treatment and maintenance of normal cognitive capabilities and communication are mandatory.

Concerning the communication, the BCI-research community has developed very useful tools in the last fifteen years using different technologies (Daly & Wolpaw, 2008), different neurophysiological signals and different procedural paradigms (Birbaumer et al., 2008; Chaudhary et al., 2016) mainly aimed at maintaining spelling capabilities even in the simple binary form of 'yes' and 'no'. Such ensembles of technologies are based on learned self-regulation of brain states which are fed back and rewarded mostly with neuroelectric signals (Elbert et al., 1984). ALS patients with intact residual motor abilities are still able to interact with social environment, family members and caretakers by means of such non-invasive BCI-technology with clear examples of correct and successful functioning including the LIS condition (Birbaumer et al., 1999; Nijboer et al., 2008b; McCane et al., 2014) even for long time periods (Sellers et al., 2010; Holz et al., 2015) or long-term follow-ups (Silvoni et al., 2013). However, lack of BCI based communication in CLIS stage of the disease has been shown with several single cases (Birbaumer, 2006a) and by a meta-analysis clearly depicting the unsuccessful communication in this last stage (Kübler & Birbaumer, 2008).

The above mentioned BCI studies, quite successful in LIS and unsuccessful in CLIS conditions respectively, posed two scientific questions to the research community at the time of the meta-analysis (i.e. 2008, see also Birbaumer, 2006b): (a1) what causes the BCI outcome variability (i.e. variance)? Similarly, (a2) can healthy people or ALS patients with moderate to severe functional impairment reach excellent and reliable BCI communication performance? And (b) why patients in CLIS are unable to communicate at all by means of BCI?

The first questions (i.e. a1 and a2) arose from sub-optimal and highly variable classification performance of neuroelectric signals during BCI sessions, even though the achieved results in LIS patients were up to 80% (Birbaumer et al., 1999) and sometimes even better (Nijboer et al., 2008b) but almost always greater than and far from chance level (Müller-Putz et al., 2008), thus ensuring reliable communication. A secondary issue linked to the first question was the so called “BCI illiteracy” phenomenon by which researchers attempted to explain, or better categorize, the insufficiency of BCI technology for a small percentage of persons.

Two hypotheses were provided to explain the failure of learned BCI-communication in completely locked-in patients (Birbaumer, 2006a): (i) a drop of cognitive abilities, arousal and attention or (ii) the extinction of output-directed and goal-oriented thoughts which might be incompatible with operant voluntary learning and control of physiological functions. Since reports on cognitive decline in ALS covered only half of the patients’ population (Ringholz et al., 2005) and main findings indicated sub-clinical cognitive deficits only (Ogawa et al., 2009; Volpato et al., 2010), the second hypothesis (comprehensively described in the meta-analysis of Kübler & Birbaumer, 2008, and further deepened in Birbaumer et al., 2012) was not resolved, rather, it represented the starting point for advanced BCI communication research in CLIS patients during the last eight years (Birbaumer et al., 2012; Birbaumer et al., 2014; Chaudhary et al., 2016).

1.2 Factors limiting BCI performance

The above overview introduced ALS patients’ problems occurring in the progression of the disease and some of the difficulties encountered by researchers developing BCI spelling and binary communication systems based on neurophysiological signals self-regulation principles. At least three interdependent aspects are believed to be responsible for non-optimal neurophysiological signals classification performance (or accuracy) which, in turn, represents the outcome of a generic BCI system for communication purposes. They are: (a) the alteration of cognitive and/or emotional/behavioural states which influence BCI outcome (b) the presence of mild cognitive deficits, mostly sub-clinical, which may alter neurophysiological patterns elicited by BCI tasks and (c) the “extinction-of-goal-directed-thought” hypothesis which states the incompatibility of instrumental voluntary learning paradigms in the CLIS condition. Two additional disease related issues contribute to the non-optimal BCI outcome, they are briefly: (d) cornea degeneration which often prevents the use of vision in a BCI task and (e) circadian rhythm and sleep disorders which add difficulties to the proper/adequate detection of users’ vigilance state.

These aspects will be deepened in the following paragraphs for a comprehensive explanation of the problem. A chronological overview of these aspects is presented starting from late nineties to the current period (with some chronological order exceptions). The milestone of the meta-analysis published in 2008 by Kübler and Birbaumer is taken as reference point to render the description more understandable. Indeed, it represents a crucial change in the direction of BCI research for communication purposes in CLIS ALS patients. The following paragraphs will discuss firstly the metrics used to assess BCI performance. Secondly, sub-optimal BCI performance in advanced and LIS ALS patients will be investigated. Thirdly, motivational (i.e. intrinsic, extrinsic), physiological (i.e. vision, sleep), behavioural (i.e. sleep and vigilance) and cognitive deficits (i.e. sub-clinical and severe) in late stages of ALS disease will be outlined. Fourthly, the “BCI illiteracy” phenomenon will be briefly explored. Fifthly, the “extinction-of-goal-directed-thought” hypothesis and probable consequences will be described. Sixthly, the BCI performance in CLIS ALS patients will be discussed. Seventhly, a simple algorithm for ‘pragmatic’ optimal BCI outcome estimation is described. Finally, an overview and conclusions will be presented.

2. Materials and Methods

2.1 Chance-level performance metrics

The reliability of a binary BCI system depends on its capability to correctly classify neurophysiological correlates of ‘yes’ (target) and ‘no’ (non-target) answers in binary discrimination tasks (simple questions asking for affirmative or negative answers). The same concept applies to multi-class detection systems (where more than two items have to be classified). The accuracy of the classification system should be significantly different from results obtained by chance (i.e. above). The reliability/effectiveness of such a BCI system also relies on multiple replications of the experimental results over a long time period.

These characteristics, i.e. the binary classification and the multiple repetition (and replication) of the experimental procedure, are sufficient to define a metric to compare the experimental results. Such metric should allow to estimate the chance level threshold above which the classification accuracy can be considered reliable. In a BCI based communication system such conditions (i.e. binary classification and multiple repetitions) ensure (or strongly suggest) that the results are not due to chance, rather, they rely on the intact cognitive processing of the incoming stimuli (‘yes’/‘no’ questions) to be discriminated.

In a balanced binary BCI discrimination task only two outcome are possible and they are equally distributed (50%): ‘yes’ or ‘no’ (true/false). This characteristic suggests the use of the theoretical background of the binomial distribution, which was introduced by Bernoulli (1713), to define the above mentioned metric. The definition of one possible/realistic metric based on binomial distribution can be found in Müller-Putz et al. (2008). Such metric requires the *a priori* probability of the two outcomes and the number of repetitions of the experimental conditions. Given such information the metric provides an estimation of the chance level confidence interval. The upper limit of this confidence interval can represent the chance level threshold necessary to compare the experimental results (i.e. the classification accuracy) and assess the reliability of the BCI classification system.

Of course, different metrics can be applied to BCI results. The 70% performance-threshold, diffusely employed by BCI researchers as criterion to achieve a reliable BCI control, was introduced by using an algorithm which builds a full binary tree for spelling purposes maximizing the characters selection outcome (Perelmouter & Birbaumer, 2000). In their meta-analysis, Kübler and Birbaumer (2008) used both the 70% performance-threshold and the binomial distribution concepts to define the criteria for successful BCI communication.

In the following cited BCI reports, many different chance-level thresholds were used, depending on BCI conditions and physiological measures, but the most are based on the binomial distribution metric proposed by Müller-Putz et al. (2008) or the 70% performance-threshold criterion (Perelmouter & Birbaumer, 2000).

2.2 Advanced ALS patients' sub-optimal BCI performance

The theoretical, practical and future implications of direct communication between brain and computer to generate control signals were firstly introduced by Jacques Vidal in the seventies (Vidal, 1973). After this first visionary approach and a long history of several thousands of BCI studies, sub-optimal BCI communication performance in healthy subjects and ALS persons with moderate to severe functional impairment was taken up by several research groups all over the world in the last two decades.

Since the late nineties (Birbaumer et al., 1999) self-regulation of slow cortical potentials (SCPs) has been successfully used in BCI settings leading to promising classification accuracies even in five advanced and artificially ventilated ALS patients (including LIS) with a communication outcome ranging from about 77% up to 91% of correct responses classification (Birbaumer et al., 2000). A study on predictors of SCP control revealed that some advanced ALS patients (including LIS) were able to self regulate to a high degree their slow cortical potentials and learned it quickly, while others patients (one nearly completely paralyzed and one in a moderate stage of the disease, not ventilated) just reached the above chance level performance only after an extensive training (Neumann & Birbaumer, 2003). Notably, in the Neumann & Birbaumer (2003) study - which involved five severely impaired ALS patients- it was argued that sub-optimal BCI performance is due to the strong demand to the cognitive system during the task, attentional capabilities and users' motivation. In a similar SCP based BCI controlled study (ten moderate to severely impaired ALS patients and a group of ten healthy participants were recruited) authors argued that self-SCP learning in patients was mainly hampered by the low frequency of weekly training, thus a higher frequency of weekly training seems to be necessary to achieve faster progress (Kübler et al., 2004). However, this hypothesis was never proven in a controlled study with a larger patient sample.

Successively, the use of sensorimotor rhythms (SMR) and event-related potentials has been explored for BCI implementation. Positive results of an SMR based BCI were reported with four advanced ALS patients with a percentage of correct classification around 80% (Kübler et al., 2005). Besides the presence of hyperreflexia (Westphal et al., 1998), no special reasons of sub-optimal performance were reported in this study since the aim was the proposal of an alternative mean to the SCPs. At the same time researchers requested the reduction of the extensive training duration (from months to weeks and days) for both SCP and SMR based BCIs which was achieved by new computational capabilities and motor imagery paradigms in healthy subjects and in one moderate ALS patient (Bai et al., 2008): the training and testing sessions lasted one day with classification accuracies of around 70-85%. Better results were observed in a similar one-day SMR based BCI study with classification accuracies even greater than 90%, but only naïve healthy participants were involved (Blankertz et al., 2008).

The same requirement, short training with classification accuracy above 70% classification, did not hold true for ERP based BCIs because elicitation of cognitive neuroelectric waves depends on the relevance/salience of the applied exogenous stimuli (Sutton et al., 1965; Polich, 2007). ERP based BCIs were proven to be successfully applicable to three ALS patients since first initial results of Sellers & Donchin (2006) with both visual and auditory stimuli. Similar tests (using the visual modality only) were conducted in a large sample of intermediate ALS patients with a follow-up assessment of BCI skills (Piccione et al., 2006; Silvoni et al., 2009) and in a cohort of eight ALS patients (Nijboer et al., 2008b). Classification accuracies ranging from 60% to 80% were reported (with excellent single cases close to 100%), clearly indicating the validity of the additional "ERP" option to the already existing "SCP" and "SMR" ones. Even in these studies, no specific reasons of non-optimal performance were proposed: task's complexity, pathological/abnormal shape of the recorded ERPs, possible co-presence of frontotemporal dementia, habituation effects, memory load (Sellers & Donchin, 2006), enhanced complexity of the tasks in terms of quality and number of stimuli with respect to the classic oddball paradigm, amount of sustained processing and attentive resources engaged in the BCI task and sparse electro-myographic (EMG) and electro-oculographic (EOG) artefacts detection issues (Silvoni et al., 2009) probably due to hyperreflexia. While these aspects were largely ignored, one important finding was confirmed: the absence of significant relationships between the functional impairment in ALS and the ability to achieve good BCI control (Nijboer et al., 2008b; Silvoni et al., 2009), at least before entering the last stage of the disease. In a parallel study employing an auditory ERP based BCI in a small sample of four severely impaired ALS patients (3 of them LIS) the communication performances were poor (in the range 25-58%) and lower than that obtained in the same patients with a similar visual ERP based BCI (Kübler et al., 2009). The authors ascribed the non-optimal results to the difficulty of decoding the auditory stimuli (which where numbers associated to a visual speller matrix) and the strong demand to the short-memory system.

Almost contemporarily, two additional neurophysiological methods were investigated for BCI development: the steady-state visual evoked potentials (SSVEPs) and functional near-infrared spectroscopy (fNIRS). Steady-state visual evoked potentials are neuroelectric oscillations elicited at the occipital cortex during high-frequency (>6 Hz) periodic visual stimuli presentation. Changing the visual stimulation frequency it is possible to differentiate target and non-target stimuli eliciting different harmonics. Users can select the target stimulus according with BCI task. Differently, near-infrared spectroscopy measures oxygenation changes of cortical brain regions. Since brain areas oxygenation can be modulated by the task it is possible, in principle, to use such a neurometabolic signal to drive a BCI. This non-invasive technique can be easily applied at the bedside of patients who have severe impairments (Chaudhary et al., 2016).

Studies on SSVEPs method reported initial tests with classification accuracies of 80-90% (Müller-Putz et al., 2005; see Wang et al., 2008 for an overview), similar to previous techniques, but mostly applied to healthy individuals. In a more recent online experiment the classification outcome of 80% was reported in one severely impaired ALS patient (Lim et al., 2013). Although SSVEPs represent a cost-effective and promising solution for BCI implementation, most of the researchers tended to explain the sub-optimal performance focusing on technical problems or paradigms' optimization (Wang et al., 2008) such as the characteristics of the exogenous stimulator, the used flickering frequencies, the right placement of EEG electrodes and algorithms to enhance signal-to-noise ratio (SNR). An exception is represented by a quite recent study which involved seven severely impaired (some of them LIS) ALS patients in a SSVEP based BCI task (Hsu et al., 2016). Classification accuracies around 80% were reported for three ALS good-performers. The remaining four patients were not able to successfully complete the BCI experiment, hence they were excluded from the analysis. The authors argued that ageing factors affected SSVEPs amplitude and visual sensitivity negatively. Additional arguments to explain the results were the reduced SNR in ALS patients, difficulties in following the instructions and consequent loss of attention, cognitive dysfunction and impairment of emotional/social cognition.

Differently, the fNIRS technology harnesses/employs cortical oxygenation changes as neurometabolic signals to decode users' intention and practice the self-regulation of such signals based on learning principles (Coyle et al., 2004). This interesting and new technique quickly led to exciting results during offline discrimination of haemodynamic responses following a motor imagery task in five healthy individuals (Sitaram et al., 2007) with classification accuracies around 90%. Despite the long time constants and the consequent slow time course of neurometabolic signals in fNIRS based BCI systems, the potential of this technique has been proven crucial in a later BCI experiment conducted in one CLIS ALS patient as we will see in the following paragraphs (see Gallegos-Ayala et al., 2014).

Since the time of the meta-analysis (Kübler & Birbaumer, 2008), and even before, many attempts to improve BCI outcome were carried out especially focusing the effort on programming, mathematical/algorithm and engineering levels or changing communication paradigms' structure and respective parameters. Some interesting reviews on this topic are: Daly & Wolpaw, 2008; Shih et al., 2012; Birbaumer et al., 2014; Chaudhary & Birbaumer, 2015; Chaudhary et al., 2016. Conversely, other studies on SMR and ERP based BCIs investigated the reasons of non-optimal performance, cognitive strategies, predictors and neural correlates of the classification accuracy, thus their relevance to the present topic is clear.

Concerning SMR based BCIs, it was found that the strength of the SMR idling rhythm in the EEG is an essential property to predict successful performance (Blankertz et al., 2010). Such predictor explained about one third of the classification accuracy variance in eighty healthy volunteers. Reasons of sub-optimal performance (i.e. in the range 69-77%) were mainly ascribed to (self assessed) fatigue and the possible misexecution (i.e. wrong strategy) of the motor imagery task (e.g. only visually imagining the movements instead of kinesthetically).

A complementary study to the previous one on SMR and ERP based BCIs examined the relationships between mood, motivation and BCI classification accuracy (Nijboer et al, 2010) in a sample of seven severely impaired ALS patients (two of them LIS). The authors found significant relationships between motivational factors and BCI performance in three patients (challenge/mastery confidence in two patients and incompetence fear in one patient), but not with mood; nevertheless, the small cohort of ALS patients showed high motivation to BCI training and good mood. Interestingly, QoL was rated as satisfactory to good and without significant relationships with the physical impairment. The non-optimal BCI performance (from 46% to 88%) was explained mainly by: the abnormal cognitive potentials shape in the ERP based BCI (reduced P300 amplitude and prolonged P300 latency), the required amount of selective attention for both BCI types and the repetitive interruptions of the BCI sessions because of movement related electromyographic artefacts, again likely due to hyperreflexia.

Neurophysiological correlates of errors (Halder et al., 2013) and classification accuracy (Mak et al., 2012) were found also in two groups of ALS patients, eleven and twenty respectively (some of them were artificially ventilated), during short-term visual ERP based BCI communication sessions.

In the former report (Halder et al., 2013) the authors used a short oddball task and a BCI web browsing task. They observed significant correlations between early ERPs amplitudes (in the range 100÷350ms; N1, P2, and N2 peaks) and number of errors, positive at fronto-central sites and negative at parieto-occipital electrodes. These findings were argued to be neurophysiological signatures of selective attention to target/non-target stimuli involving both inhibition and filtering mechanisms. Since the oddball task and the BCI web browsing task had different inter-stimulus intervals, 800 ms and 187.5 ms respectively, it can not ruled out, however, that the browsing task might had elicited different ERP waveforms because the superposition of different cognitive processes during the recording of brain responses. Nevertheless, this difference did not prevent an averaged above chance-level accuracy of 73% for all patients (Halder et al., 2013). Once again, the absence of significant relationships between errors and ALSFRS-R index was confirmed.

In the latter study (Mak et al., 2012) the authors used a short visual ERP based BCI task and found tight relationships between three types of EEG features and classification accuracy: (i) root-mean-square amplitude of target responses, (ii) target stimulus negative peak and (iii) theta frequency power. A multivariate regression model based on these predictors explained more than 50% of the classification accuracy's variance. Very interestingly, while the first two EEG features (i.e. root-mean-square amplitude of target responses and target stimulus negative peak) have known implications as for target/non-target ERPs classification (such as abnormal ERP's properties lead to worse performance), the observed negative correlation with theta frequency power was plausibly argued to reflect decreased alertness during BCI operations (i.e. related to vigilance level and/or drowsiness of the patients). In addition, the authors split on-line classification recordings in low-accuracy and high-accuracy ones. Theta spectral power was significantly higher in low-accuracy recordings with respect to the high-accuracy ones (Mak et al., 2012) in line with previous observations on cognitive performance during sustained attention tasks (Klimesch, 1999).

In a study investigating two different principles ('exogenous' and 'endogenous') for orienting covert visuospatial attention in ten moderate ALS patients an ERP based BCI was used (Marchetti et al. 2013). The 'exogenous' (bottom-up, automatic) orienting of the focus can be elicited by abrupt sensory changes in the periphery of the visual field (e.g. a blinking cue), while the 'endogenous' (top-down, voluntary) one is driven by voluntary cognitive interpretation of the presented stimulus (Posner, 1980), for instance a word indicating a direction. The authors proved the superiority of the interface based on the 'endogenous' orienting compared to the 'exogenous' one with classification accuracies in the range 65-71%. No reasons of non-optimal performance were reported because the main aim was the comparison of the two cognitive strategies which proved that the 'endogenous' orienting can be effectively implemented to increase the performance of a visual ERP based BCI (Marchetti et al. 2013). Two additional longitudinal studies investigated the stability of BCI performance over time (i.e. 2.5 years, one LIS ALS patient case report; Sellers et al., 2010) and the absence of ageing and disease progression effects on BCI communication skill (i.e. three years follow-up, twenty-four moderate ALS patients; Silvoni et al., 2013). Because the aims were focused on technological and ageing/clinical aspects respectively, no reasons of sub-optimal performance were reported in these two studies.

In a more recent work, the visual ERP based BCI outcome in a large sample of severely impaired and LIS ALS patients (i.e. twenty-five) indicated that very good and reliable communication skill (characterized by mean classification accuracy of 92%) can be achieved only if the visual system is not impaired (McCane et al., 2014): ptosis, diplopia, nystagmus were found in eight patients with very poor performance (for some of them below chance level). Evidences of a positive correlation between classification accuracy and P300 amplitude (in the range 250-500 ms) and a negative correlation between classification accuracy and 'later negative peak' (in the range 420-680 ms) were found. The P300 amplitude variations -dependent on difficulty of the task, amount of cognitive, attentive and working memory resources involved in the task- are well known (Polich, 2007) as well as the positive relationship between P300 amplitude and BCI classification accuracy (the bigger the P300 amplitude the better the classification accuracy). Conversely, the meaning of the 'later negative peak' is less investigated in BCI studies, but it could be the expression of the attention's reorienting mechanism in preparation of next incoming stimulus. The contingent negative variation (CNV) has similar characteristics (Walter, 1964) and is associated with arousal processes and attention. Hence, if the 'later negative peak' is a kind of CNV, then the negative relationships with BCI classification accuracy is plausible because it indicates a 'good' preparation of the user to the task (the more attention/preparation the better the classification accuracy). Another interpretation could be the expression of an error-related negativity (Falkenstein et al., 1991), but it can be in contrast with the found negative relationship. However, in this study (McCane et al., 2014), nor underlying mechanism nor meaning of the 'later negative peak' was provided. Additionally, significant differences of P300 amplitude and 'later negative peak' between high-performers (BCI performance greater than 70%) and low-performers (BCI performance lower than 40%) were reported. Besides these observations, again, no significant relationship between ALSFRS-R index and BCI outcome was found. This report contributed also to the understanding of the so called "BCI illiteracy" problem as will be explained in one of the following paragraphs (see *The ill-posed "BCI illiteracy" problem* paragraph).

The same research group (McCane et al., 2015) even assessed the absence of significant differences in performance between fourteen severely impaired and LIS ALS patients (classification accuracy of 96%) and an age-matched group of healthy participants (classification accuracy of 99%). The comparison showed that ALS patients' N200 and P300 peaks were located more over anterior sites than in control subjects and the most prominent ERP components tended to have longer latencies. In this last study (McCane et al., 2015), no particular mention of the cognitive processes underlying ERPs responses recorded during BCI task and attentive resources' demand were provided.

Summarizing, short-term BCI tests (of whatever BCI type) are usually characterized by very good and successful results in advanced ALS patients including LIS (classification accuracy rates are higher than 85% and sometimes close to 100%), whereas in medium-term and long-term BCI tests (any BCI type) the outcome measured by communication performance in advanced ALS patients is sub-optimal (roughly in the range of 60% to 85%, or below the chance level in worst cases), even though some single cases represent an exception. Table 1 describes in chronological order the main arguments proposed to explain the diffuse sub-optimal BCI performance in advanced and LIS ALS patients from late nineties up to now.

In our view, the main and most convincing reasons accounting for non-optimal performance in advanced ALS patients (including LIS, but excluding CLIS) may be: (i) the strong and sustained demand of cognitive-attentional system which leads to local and time restricted worsening of cognitive performance (i.e. during BCI task only), (ii) users' motivation which can boost or hamper the cognitive functioning, (iii) possible cognitive deficits (which are treated in two of the following paragraphs, *Mild and sub-clinical cognitive impairment in ALS* and *Cognitive changes in severely impaired, LIS and CLIS ALS patients*), (iv) hyperreflexia which leads to artefacts and (v) functional impairment of the sensory domain used as channel to stimulate the user or to provide feedback/reinforcement in the operant learning BCI task.

The single effect's estimation of the five above mentioned factors is difficult to measure quantitatively without a well defined BCI experiment design. However, these factors are likely to prevent the achievement of the optimal BCI outcome, which corresponds to the communication accuracy theoretical limit of 100%.

2.3 BCI and motivational aspects

Motivational aspects were not systematically investigated in BCI clinical trials. Motivation in BCI settings can be intrinsic, i.e. an endogenous factor (a personal motivation), or extrinsic, i.e. an exogenous factor such as monetary reward (Kleih et al., 2010) or specific engagement strategies (for instance, virtual reality) aimed to reinforce users' results (Leeb et al., 2007). Findings on association between BCI performance and users' motivation included mainly healthy participants (Nijboer et al., 2008a; Kleih et al., 2010; Baykara et al., 2016); these reports proved significant effects of motivation on both BCI classification accuracy and neurophysiological signals. Differently, one report showed no influence of motivation on BCI performance and the P300 amplitude (Kleih & Kübler, 2013).

In one study, including ten healthy participants and three ALS patients, depression, mood and motivation were assessed before a short-term BCI web browsing task (Mugler et al., 2010). Classification accuracy was high (around 90%) for healthy participants and above the 70% performance-threshold in the three patients. Additionally, neither symptoms of depression nor negative scores of mood and motivation were found.

Concerning ALS patients, in their meta-analysis Kübler & Birbaumer (2008) proposed a higher motivation in patients more in need for a BCI (without data confirming such intuitively plausible assumption). Later, in a follow-up study investigating ageing/clinical effects on BCI use, a positive correlation between BCI classification accuracy and patients' age was found (Silvoni et al., 2009; Silvoni et al., 2013) possibly due to the awareness of the late stage disease's implications in patients. Successively, significant relationships between motivational factors and BCI performance in three patients (challenge/mastery confidence in two patients and incompetence fear in one patient) were found, clearly indicating that the intrinsic motivational factor can play a relevant role determining BCI communication outcome variability (Nijboer et al., 2010).

Concluding, further investigations are necessary to elucidate the role of intrinsic and extrinsic motivation in BCI experiments. Nevertheless, intrinsic motivation seems to be important, at least at an individual level in ALS patients.

Table 1. Sub-optimal BCI performance in moderate, advanced, LIS and CLIS ALS patients only, excluding healthy individuals. Cells of the table with white background colour refer to studies with moderate, advanced and severely impaired ALS patients. Cells with light-gray background colour refer to studies with severely impaired ALS patients including LIS patients. Cells with middle-gray background colour refer to studies including CLIS ALS patients. Cells with thick border refer to the meta-analysis of Kübler & Birbaumer 2008.

BCI type	**Participants (ALS stands for 'ALS patients')**	**Study's length** [(1)]	**Classification accuracy range of ALS patients only (%)**	**Main arguments to explain sub-optimal performance**	**Reference**
SCP	2 LIS ALS	long	78.0 ÷ 81.0 (estimated limit from plots, free spelling)	altered SCPs during letter selection leading to false negative and false positive errors	Birbaumer et al., 1999
SCP	5 severely impaired ALS (including LIS)	long	77.0 ÷ 91.0 (estimated upper limit from plots, 2 ALS free spelling, 1 ALS copy-spelling)	change of cognitive strategy for self SCP control, unwillingness to continue the training	Birbaumer et al., 2000
SCP	5 severely impaired ALS (including LIS)	medium	47.6 ÷ 94.3	strong demand of cognitive-attentional system, users' motivation, possible cognitive deficits	Neumann & Birbaumer, 2003
SCP	10 healthy subjects, 10 moderate to severely impaired ALS	long	54.0 ÷ 79.0	low frequency of weekly training	Kübler et al., 2004
SMR	4 advanced ALS	long	76.0 ÷ 81.0	hyperreflexia	Kübler et al., 2005
averaged visual and auditory ERP	3 healthy subjects, 3 moderate ALS	long	auditory (1 run): 59.1 ÷ 73.2 visual (1 run): 53.9 ÷ 76.8 auditory + visual (1 run): 61.6 ÷ 68.9	task's complexity, abnormal ERPs, co-presence of fronto-temporal dementia, mild habituation effects, memory load	Sellers & Donchin, 2006
single-trial visual ERP	7 healthy subjects, 5 tetraplegic patients (1 advanced ALS)	medium	79.6 (1 advanced ALS)	limited spatial and sustained attention resources, head/eye movement artefacts (likely due to hyperreflexia)	Piccione et al., 2006
SMR	9 healthy subjects, 1 stroke patient, 1 moderate ALS	short	83.3 (1 ALS, motor imagery)	easily developed fatigue to sustain long-term effort	Bai et al., 2008
averaged visual ERP	8 severely impaired ALS (4 ALS completed Phase II)	long	69.6 ÷ 91.6 (Phase II, 4 ALS patients only, copy-spelling)	---	Nijboer et al., 2008b

(1) Study's length: short (days, within one week), medium (weeks), long (months), follow-up (with follow-up assessments)

Table 1. (continued)

BCI type	**Participants (ALS stands for 'ALS patients')**	**Study's length** [1]	**Classification accuracy range of ALS patients only (%)**	**Main arguments to explain sub-optimal performance**	**Reference**
meta-analysis (SCP, SMR, ERP)	29 severely impaired ALS (including LIS and CLIS), 6 patient with a severe neurological disease	---	SCP: 48.0 ÷ 94.0 SMR: 43.0 ÷ 81.0 ERP: 32.0 ÷ 87.0	users' motivation, possible training length effects, possible carry-over learning effects (patients who were tested with two BCI types), waking EEG slowing due to possible episodes of anoxia (inadequate artificial respiration), deterioration of cognitive function, "extinction-of-goal-directed-thought" hypothesis	Kübler & Birbaumer 2008
averaged auditory ERP	4 severely impaired ALS (3 of them LIS)	medium	25.0 ÷ 58.3	difficult decoding of the auditory stimuli (associated to a visual speller matrix), strong demand to the short-memory system	Kübler et al., 2009
single-trial visual ERP	9 healthy subjects, 21 moderate ALS	medium, follow-up	test: 67.9 ÷ 85.8 follow-up: 74.9 ÷ 87.4	enhanced complexity of the BCI task (quality and number of stimuli), sustained processing and attentive resources demand, eye movement artefacts	Silvoni et al., 2009
SMR and averaged visual ERP	7 severely impaired ALS (2 of them LIS)	long	SMR: 63.9 ÷ 67.8 (4 ALS patients) ERP: 46.0 ÷ 87.8 (6 ALS patients)	user's motivation (challenge/mastery confidence, incompetence fear), abnormal ERPs, sustained attentive resources demand, BCI sessions' interruptions (EMG artefacts, likely due to hyperreflexia)	Nijboer et al., 2010
averaged visual ERP	1 LIS ALS	long (years)	83.0	---	Sellers et al., 2010
averaged visual ERP	20 advanced ALS (14 ALS severely impaired, LIS)	short	0.0 ÷ 100.0 (30% and 48.8% of runs respectively)	abnormal ERPs, decreased alertness during BCI operations (vigilance level, drowsiness)	Mak et al., 2012
SSVEP	11 healthy subjects, 1 LIS ALS	short	80 (1 LIS ALS)	---	Lim et al., 2013
single-trial visual ERP	10 moderate ALS	medium	64.9 ÷ 71.4 (minimum and maximum mean values across days)	---	Marchetti et al., 2013
EEG reflexive conditioning	1 CLIS and 2 LIS ALS	medium		rapid fade of attention span and vigilance, "extinction-of-goal-directed-thought" hypothesis effect, aversive stimulus anticipation blocking effect, possible wrong selection of the pre-processing procedure	De Massari et al., 2013

[1] Study's length: short (days, within one week), medium (weeks), long (months), follow-up (with follow-up assessments)

Table 1. (continued)

BCI type	**Participants (ALS stands for 'ALS patients')**	**Study's length** [(1)]	**Classification accuracy range of ALS patients only (%)**	**Main arguments to explain sub-optimal performance**	**Reference**
single-trial visual ERP	24 moderate ALS (9 ALS follow-up 1; 5 ALS follow-up 2; 3 ALS follow-up 3)	medium, follow-up	1st test: 69.6 ÷ 91.0 f-up 1: 67.4 ÷ 87.4 f-up 2: 68.0 ÷ 83.6 f-up 3: 70.7 ÷ 78.6	---	Silvoni et al., 2013
averaged visual ERP	11 moderate to advanced ALS (1 LIS)	short	72.6 (mean) 58.4 ÷ 95.7 (estimated range)	decreased attention and worse filtering mechanisms of target vs. non-target stimuli	Halder et al., 2013
averaged visual ERP	8 moderate to advanced ALS	short	95.0 ÷ 100.0	deficits on the ability to keep the attentional filter active during target selection	Riccio et al., 2013
fNIRS reflexive conditioning	1 CLIS ALS	medium, follow-up	period 1: 71.7 period 2: 75.7 period 3: 76.3	---	Gallegos-Ayala et al., 2014
averaged visual ERP	25 advanced and severely impaired ALS (including LIS)	short	71.0 ÷ 100.0 (high-performers) 0.0 ÷ 36.0 (low-performers)	ptosis, diplopia, nystagmus (reduced P300 amplitude and 'later negative peak' were explained by visual dysfunctions)	McCane et al., 2014
averaged visual ERP	1 LIS ALS	long	zero ÷ high [(2)] (subjective level of BCI control)	deficient setup of electrodes montage, personal factors (concentration, tiredness, distraction), medical treatments during BCI session (aspiration, artificial feeding)	Holz et al., 2015
averaged visual ERP	14 healthy subjects, 14 advanced and severely impaired ALS (including LIS)	short	95.7 (mean maximum accuracy)	---	McCane et al., 2015
averaged visual ERP	12 advanced and severely impaired ALS (including LIS)	short	8.7 bit/min [(3)]	higher cognitive workload and lower usability than eye-tracking technology, possible effortful and time-consuming BCI task	Pasqualotto et al., 2015
SMR and averaged visual ERP	15 healthy subjects, 25 moderate to severely impaired ALS (including LIS)	long	SMR: 45.0 ÷ 97.0 ERP: 0.0 ÷ 100.0	decreased signal-to-noise ratio of task-relevant EEG band power, behavioural and cognitive dysfunction (mainly the executive component), possible visual dysfunction, reduced P300 amplitude	Geronimo et al., 2016

(1) Study's length: short (days, within one week), medium (weeks), long (months), follow-up (with follow-up assessments)

(2) The authors assessed and reported the subjective level of BCI control with a four items scale (zero, low medium and high)

(3) The BCI performance was measured in bits per minute only

Table 1. (continued)

BCI type	**Participants (ALS stands for 'ALS patients')**	**Study's length** [(1)]	**Classification accuracy range of ALS patients only (%)**	**Main arguments to explain sub-optimal performance**	**Reference**
averaged auditory ERP	5 end users: 1 muscular dystrophy, 1 anoxic brain injury, 1 multiple sclerosis, 2 moderate ALS	medium	68.0 ÷ 93.0 (1 muscular dystrophy, 2 ALS) 0.0 ÷ 10.0 (2) (1 anoxic brain injury, 1 multiple sclerosis) (estimated ranges from plot)	1 anoxic brain injury: apparent inability to sufficiently discriminate the auditory stimuli, variable time period between sessions 1 multiple sclerosis: no stimulus locked responses visible, possible effect of the disease on ERP latency, possible impairment of the verbal working memory	Halder et al., 2016
SSVEP	16 healthy subjects, 7 severely impaired ALS (including LIS)	short	76.9 ÷ 83.3 (3 ALS patients only)	ageing factors, reduced SNR, loss of attention, cognitive dysfunction, emotional/social cognition impairment	Hsu et al., 2016
fNIRS reflexive conditioning and EEG	4 CLIS ALS	medium	67.5 ÷ 75.8	fragile (oscillating) vigilance and unpredictable circadian rhythms that result in spontaneous sleep and dozing during the day	Chaudhary et al., 2017

(1) Study's length: short (days, within one week), medium (weeks), long (months), follow-up (with follow-up assessments)

(2) Classification accuracy range of patients with other diagnosis than ALS was also reported

3. Results

3.1 Vision in CLIS

Drying of the cornea and compromised vision following reduced oculo-motor control and eyelid weakness has been frequently observed in late stages of ALS (Birbaumer, 2006a). In one CLIS ALS patient the vision was severely compromised by necrosis of the cornea due to insufficient fluid availability caused by paralysis and apparent lack of adequate nursing (Murguialday et al., 2011). Therefore, vision-based BCIs are highly unlikely to work in completely locked-in ALS patients (see Table 2, physiological studies), thus, eye-gaze independent communication systems have been explored since last six years (Riccio et al., 2012).

For this reason, recent BCI studies had been conducted mainly employing the auditory modality of stimuli presentation (Kübler et al., 2009; De Massari et al., 2013; Gallegos-Ayala et al., 2014; Halder et al., 2016). In addition, an increasing number of recent BCI reports harnessed the tactile stimulation to recognize binary or multi-class brain responses for communication purposes (van der Waal et al., 2012; Severens et al., 2014) or for studying neural correlates of cognitive processing by means of ERPs (Silvoni et al., 2016).

Nevertheless, tactile stimuli employed in ERP based BCI systems can not directly represent/convey characters or symbols if short vibrations lasting hundreds of milliseconds are used (which are provided by small precision micro-drivers, motors, or piezo-electric systems). Conversely, more complex tactile stimuli such as small pins activations representing Braille numbers or letters of the Braille alphabet (Braille, 1829) can directly convey lexical, symbolic or semantic information. For this reason the above mentioned tactile ERP based BCI systems (van der Waal et al., 2012; Severens et al., 2014), which employed short vibrations, needed the association of the delivered stimuli with a static visual map to explain the meaning of each stimulus itself.

An alternative solution to this kind of tactile-visual BCI can be the tactile-auditory BCI. In tactile-auditory BCIs the somatosensory stimulation (i.e. vibrations) can be used to elicit event-related potentials, while the auditory channel can be employed to explain the meaning of each tactile stimulus to the user (for instance, the correspondence of a specific vibration to a single character or symbol). A third alternative can be the explanation of the stimuli's meaning by the experimenter while auditory and tactile stimuli are delivered simultaneously to enhance the characteristics of the elicited ERPs. This could improve the classification accuracy of such kind of auditory-tactile BCIs. This approach provided good BCI classification accuracy results (range 78-96%) in a group of twelve young healthy participants (Yin et al., 2016).

3.2 Circadian rhythm, sleep and vigilance/attention in ALS

Sleep, vigilance and attention interrelated effects on behavioural and cognitive tasks' performance have been extensively studied in both healthy and pathological conditions.

For instance, studies exploring the wake-sleep cycle in healthy samples proved increased EEG low frequency bands power (delta and theta other way round) during the transition from alert wakefulness to sleep (Dement & Kleitman, 1957; Tanaka et al., 1997). Sleep disorders have been extensively studied even in ALS (Ahmed et al., 2016). Patients show documented wake-sleep cycle disturbances, including sleep fragmentation, and have a significant poorer quality of sleep which is correlated with the severity of ALS and daytime somnolence (Lo Coco et al., 2011). Investigating the transition from locked-in to the completely locked-in state in one ALS patient by electro-corticography (ECoG), a clear increased fragmentation of slow wave sleep across the day was found which might reflect progressive circadian system impairment in this pathological condition (Soekadar et al., 2013). The somewhat irregular wake-sleep cycle was confirmed later in the same patient, but the overall duration of slow wave sleep seemed to be normal (Martens et al., 2014).

Concerning the processing of incoming stimuli during cognitive and memory tasks, healthy subjects exhibit a tonic increase in the EEG theta power associated with decreased performance (Klimesch, 1999). Similarly, a significant negative relationship between the EEG theta power and the ERP based BCI performance, likely reflecting decreased alertness during BCI operation, was found in advanced ALS patients, including LIS (Mak et al., 2012); this negative relationship was supported by the significantly higher theta spectral power observed in low-accuracy sessions compared to that of high-accuracy sessions.

Fluctuations/oscillations/lapses of attention and failures of response inhibition were separately associated with errors during a sustained attention task (i.e. go/no-go) employing ERPs in healthy volunteers (O'Connell et al., 2009). Exactly the same observations (i.e. two different neuro-electric correlates of errors) were shown in one group of moderately impaired ALS patients compared with a group of healthy participants presented with a tactile oddball test (Silvoni et al., 2016). Attentive resources and error monitoring processes were separately associated with two different types of ERPs classification errors in both groups equally (i.e. target ERPs erroneously classified as non-target, and non-target ERPs classified as target, respectively). Interestingly, the percentage of automatic offline target and non-target ERPs classification errors (associated to attentional oscillations and error monitoring) was about 27% in the ALS group. This percentage could be further reduced (i.e. to 22%) taking sequential effects (Holm et al., 2006) of stimuli presentation into account (Silvoni et al., 2016).

During the experimental sessions of the first classical semantic conditioning BCI procedure applied to severely impaired ALS patients (see paragraph *BCI performance in completely locked-in ALS patients*), a rapid drop of vigilance was detected suggesting attentional variations or variations of circadian period (De Massari et al., 2013). These findings were reported after the BCI training over an extended time period (weeks) in one completely locked-in patient and two locked-in patients.

In a recent long-term BCI study involving four CLIS ALS patients only (Chaudhary et al., 2017) a significant negative correlation between EEG low frequency bands mean power and binary classification accuracy was found in three out of four patients; this finding strongly suggests altered vigilance (or attention) effects. In addition, two out of the three patients clearly showed a significantly higher low frequency band (delta and theta) mean power during BCI communication of unsuccessful days compared to that of successful days (where ‘unsuccessful days’ stands for days characterized by classification accuracy below chance level). In two patients decreased vigilance (or attention) was reflected in higher power of slow EEG frequencies, in line with results reported by Klimesch (1999) and Mak and colleagues (2012) and may have prevented accurate communication.

In the completely locked-in condition, the hypothesized (but highly probable) progressive circadian system impairment (Soekadar et al., 2013) and the decreased alertness and vigilance drops (De Massari et al., 2013; Martens et al., 2014) can be highly interrelated, despite the enhanced difficulty to constantly assess and monitor the wake-sleep cycle in this condition. Even in advanced and LIS ALS patients neuro-electric correlates of decreased vigilance were found (Mak et al., 2012). Therefore, it is reasonable to conclude that findings of slow EEG oscillations and BCI classification accuracy results in CLIS ALS patients are correlated and decreased vigilance (or attention) prevents higher BCI communication accuracy (see Table 2). In addition, even healthy people show less than 100% BCI response accuracy in a medium-term BCI training taking the 70% performance-threshold for meaningful communication into account (Kübler et al., 2004; Silvoni et al., 2009; Geronimo et al., 2016; Halder et al., 2016).

3.3 Mild and sub-clinical cognitive impairment in ALS

Neuropsychological deficits and cognitive dysfunctions in ALS can be roughly categorized in mild cognitive disorders covering 32% of sporadic ALS patients' sample and severe cognitive impairments covering around 19% (Ringholz et al., 2005; number of enrolled ALS patients: $N=279$). The remaining half of the patients' sample has intact cognitive capabilities. Similar (not significantly different) percentages can be observed in familial ALS (Wheaton et al., 2007). Cognitive deficits in ALS are usually linked/associated to: (i) executive functions (Paulus et al., 2002), (ii) the central executive component of working memory (Volpato et al., 2010), (iii) verbal fluency (Hanagasi et al., 2002) and (iv) selective attention (Pinkhardt et al., 2008; Volpato et al., 2016), overall indicating the involvement of extramotor functions in a subsample of patients. In some cases these deficits are classified as 'mild cognitive dysfunction' (i.e. sub-clinical) and often are accompanied by abnormal ERPs (small amplitudes and delayed latencies). The above enumeration of studies investigating cognition in ALS would not be exhaustive, it is just to touch the involved cognitive processing domains and to provide an idea of extent of impaired patients. The above numbers and clinical features suggest that BCI communication outcome observed in ALS patients' samples might be affected by cognitive impairments.

However, cognitive dysfunctions are sparsely assessed in BCI studies. In some reports psychometric and/or neurophysiological tests were administered before BCI evaluation (Silvoni et al., 2009), in others studies interrelations of BCI outcome and cognitive functions (Riccio et al., 2013; Geronimo et al., 2016), or cognitive workload (Pasqualotto et al., 2015), or cognitive profile (Pasqualotto et al., 2015; Jeunet et al., 2015; Poletti et al., 2016) were estimated and in the remaining ones cognitive aspects were discussed only (not measured or just neurophysiologically assessed, see, for instance, Neumann & Birbaumer, 2003; Mak et al., 2012; Halder et al., 2013) or very briefly mentioned (see, for instance, Kübler et al., 2004; McCane et al., 2014).

In a visual ERP based BCI study a large group of twenty-one moderate ALS patients and a group of nine healthy participants were assessed by a neuropsychological test battery resulting in scores within normal ranges, with some tests related to attentive and executive functions indicating a (mild) sub-clinical cognitive impairment in the ALS group (Silvoni et al., 2009). The sub-clinical deficit in ALS patients did not prevent a reliable BCI communication performance, even after one year follow-up, however, the effects on BCI classification accuracy were not reported.

In a similar visual ERP based BCI study a group of eight moderate ALS patients were assessed by cognitive tasks targeting attention and memory (Riccio et al., 2013). The selective attention component in the cognitive tasks was found to be a predictor of both the binary classification accuracy and the P300 amplitude elicited with the BCI task (significant Pearson's correlation of 0.79 and 0.84 respectively). The conclusion was that the ability to keep the attentional filter active during target selection influenced BCI performance. It can not be excluded, however, that the small BCI classification accuracy variance influenced the observations in some extent due to the ceiling effect in the achieved BCI results (mean ± std: 97.5 ± 3.8 %).

A complementary study, comparing BCI and eye-tracking technologies and carried out in a group of twelve advanced ALS patients (five of them LIS), investigated the cognitive workload after the short-term use of both technologies (Pasqualotto et al., 2015). The authors concluded that eye-tracking device is more usable and the workload demand is smaller compared to that required by BCI technology (no further investigation of cognitive workload impact on BCI outcome was performed).

The cognitive profile of healthy young BCI users was also reliably associated to BCI performance observed during the execution of (left-hand) motor imagery and mental tasks (i.e. rotation and subtraction). Specific personality traits and cognitive profile indexes (tension, abstractness, learning style and self-reliance), as well as mental rotation scores, were the relevant predictors of the model accounting for about 80% of the BCI performance variance (Jeunet et al., 2015). The extent to which these cognitive profile factors might affect the BCI communication outcome in healthy elderly people and ALS patients remains to be investigated.

A very interesting controlled BCI study shed light on the impact of cognitive impairment on neurophysiological signals quality in an extended group of twenty-five moderate to advanced ALS patients (including LIS) employing both an ERP based and an SMR based BCI (Geronimo et al., 2016). Cognitively impaired patients performed significantly worse than controls in the ERP based BCI and significantly worse than cognitively intact patients in the SMR based BCI. Functional, behavioural and cognitive function indexes (such as motor, bulbar and respiration sub-scores of the ALSFRS-R scale and behavioural and cognitive scores of the ALS Cognitive and Behavioral Screen, Woolley et al., 2010) were selected as predictors of the BCI signals' quality (i.e. a quantitative index of how accurately binary neuro-electric signals can be distinguished, regardless of classification accuracy). Behavioural and cognitive scores predictors only were retained in the final model: deficits in tasks of attention and tracking significantly accounted for 17.9% and 17.4% of the ERP based BCI signals' quality variance respectively, suggesting small effects of cognitive dysfunction on BCI outcome. Similarly, tasks involving attention explained 26% of the SMR based BCI signals' quality variance, suggesting a greater impact of cognitive deficits on the outcome of this type of BCI (Geronimo et al., 2016).

Recently, a preliminary validation study revealed the possibility to use an alternative BCI assisted motor-verbal free neuropsychological tool instead of traditional 'paper and pencil' tools for cognitive screening in ALS (Poletti et al., 2016). The validation was assessed involving one group of fifteen moderate ALS patients and an age-matched group of healthy participants. Convergent validity of the BCI neuropsychological test battery was proven with the Montreal Cognitive Assessment tool (Pirani et al., 2007), together with satisfactory levels of usability in ALS group and high sensitivity and specificity levels in discriminating patients from controls (mainly due to slowing of processing speed regarding executive functions in ALS group). As additional advantage (not tested in the study), this new tool can be used concurrently with neurphysiological assessment of the cognitive functions since the BCI is based on event-related potentials, and if validated in a larger and heterogeneous sample it might provide further insights into the impact of cognitive dysfunctions on BCI communication performance.

In others BCI studies information processing mechanisms were discussed only to explain the effect on outcome variables (such as BCI performance) associated with cognitive functions. These aspects were mainly related to executive and working memory dysfunction (Neumann & Birbaumer, 2003), early and late ERP components abnormalities, altered selective attention and filtering mechanisms during the execution of the BCI task (Halder et al., 2013).

Comprehensively, mild (and sub-clinical) cognitive impairment in advanced ALS has a small effect on BCI outcome (accounting for 17% to 26% of BCI signal's quality variance; Geronimo et al., 2016) or do not prevent reliable BCI communication at all. The extent to which more severe cognitive deficits alter BCI communication performance remains to be investigated.

3.4 Cognitive changes in severely impaired, LIS and CLIS ALS patients

Numerous cognitive and behavioural screening tools are available for early and intermediate stages of ALS (see, for instance: Pirani et al., 2007; Woolley et al., 2010; Abrahams et al., 2014), some of them requiring validation (Poletti et al., 2016). These cognitive assessment tools were used in ALS population samples with different degrees of functional impairment, such as mild, moderate and severe (nearly LIS).

Conversely, sparse studies investigated cognitive abilities dysfunction in the last stages of the disease (i.e. LIS and CLIS) and the patients' sample size was almost always limited, such as single cases or small cohorts (Kotchoubey et al., 2003; Neumann & Kotchoubey, 2004; Lakerveld et al., 2008; Fuchino et al., 2008; Bensch et al., 2014). One of the reasons is the complete lack of verbal, motor and behavioural response (in severely impaired and LIS patients), especially in CLIS condition where even residual eye movements are lost. Consequently, the lack of reliable motor expression in LIS and CLIS promoted the use of neurophysiological cognitive evaluation (Kotchoubey et al., 2003). This kind of assessment requires electronic equipment to record event-related potentials elicited during the cognitive tasks, instead of 'paper and pencil' tools.

Neurophysiological translation of neuropsychological/cognitive tests has been mainly used to record non-invasive neuroelectric signals, the shape and other parameters extracted from ERPs have been analyzed and compared to those recorded in control participants. Progressively increasing the complexity of the tests it is possible to establish intact or deficient cognitive processing based on the cortical activity and the comparison with normative data of healthy individuals.

In one study involving three CLIS ALS patients the oddball, prosody, learning, semantic and movement intention tasks were administered (Kotchoubey et al., 2003). Recorded ERPs data were remarkably similar to healthy controls with a few exceptions. Cortical activity indicating preserved cognitive abilities and adequate language comprehension was reliably found in the first patient. Complex cognitive functions were found intact to a high degree in the second patient with consistent abnormalities of some ERP components. In the third patient no cortical activity related or correlated to cognitive task-processing was present.

Similar results were found in two LIS ALS patients who underwent a comprehensive and systematic neuropsychological assessment test battery including, among others, tests of general intelligence, learning and memory, speech comprehension, intentional semantic analysis and movement intention (Neumann & Kotchoubey, 2004). The first patient showed average performance (according to age and education norms) in most of the tests, while the second one performed below average in all tests clearly indicating a cognitive decline or lack of attention.

The neuropsychological assessment of a group of eleven severely impaired ALS patients (including one LIS) revealed performance within normal range and comparable to those of a matched control group (Lakerveld et al., 2008), although slight deficits in some aspects of executive functioning, learning and memory were found in a few individual patients. Noteworthy, both learning and memory outcomes showed a significant negative correlation with the functional status of the patients (measured by ALSFRS-R scale) indicating a significant improvement of such preserved skills.

Neurometabolic signatures of preserved cognitive functions were found also in one CLIS ALS patient by means of a near-infrared spectroscopy based assessment which included tests of dichotic listening, covert singing, word fluency and motor imagery (Fuchino et al., 2008). Differential cortical activation profiles of the signal extracted from oxygenated haemoglobin were observed during each task, with consistent activations of the bilateral sensorimotor area across tasks.

Investigating another ALS case, in the verge from LIS to CLIS, at least partially intact attentive and cognitive functions were assessed with an electrophysiological cognitive test battery (Bensch et al., 2014). Invasive electro-corticography was used and cognitive capabilities were evaluated at four different time-points, two before and two after the patient's last communication. ERPs elicited by auditory stimuli were consistent across the evaluations, whereas those elicited by semantic stimuli were not, suggesting a decline of semantic processing in CLIS. Reproducible attention independent ERPs (mismatch negativity) were observed throughout the study, while attention dependent ERPs (oddball task) were present and normal in the first three evaluations only, not in the last one (weeks after entering CLIS). Spectral analysis revealed an increase of the low frequency band power (delta and theta) correlated with abnormal ERPs results.

The above results confirm that cases of cognitive decline can be observed in advanced and late stages of ALS disease. Sometimes the cognition deficits are limited to executive functions, learning, memory and semantic processing. Particularly in the CLIS condition an underestimation of the cognitive capacity, due to the difficulty to assess the wake-sleep cycle, is possible (Soekadar et al., 2013). Similarly, different wake-sleep cycle disturbances and sleep fragmentation (Lo Coco et al., 2011) might affect the ERP based evaluation because of fluctuations of arousal (Kotchoubey et al., 2003). Nevertheless, consistent cortical activity indicating preserved and intact cognitive abilities, semantic processing and adequate language comprehension is more frequent. In addition, such cases of cognitive intactness assessed by neurophysiological techniques are not false positive results since the ERP technique can underestimate, but not overestimate the cognitive abilities of locked-in patients (Onofrj et al., 1997; Kotchoubey et al., 2003; Neumann & Kotchoubey, 2004). All these aspects should to be taken into account when BCI based communication is tested in these critical conditions (LIS and CLIS; see Table 2, cognitive studies).

Table 2. List of studies investigating physiological, behavioural and cognitive severity aspects in advanced ALS patients (including LIS and CLIS), excluding early stage individuals. Physiological studies are related to vision and sleep. Behavioural studies sought evidences of preserved sleep stages and vigilance. Cognitive studies investigated the degree of preserved cognitive functions. Cells of the table with white background colour refer to studies with moderately impaired ALS patients. Cells with light-gray background colour refer to studies with severely impaired ALS patients including LIS patients. Cells with middle-gray background colour refer to studies with CLIS ALS patients. The abbreviation "pt." stands for "patient".

Evaluation type (1)	**Participants (ALS stands for 'ALS patients')**	**Study's length** (2)	**Investigated aspect(s)**	**Observations/results (pt. refers to single patients)**	**Reference**
NPHYSIO-cognitive (ERP)	3 CLIS ALS	medium (8-10 weeks)	cognitive: probabilistic responses, short-memory, learning, semantic and emotional language comprehension, motor preparation	pt.1: preserved cognitive abilities, adequate language comprehension pt.2: high degree of intactness of cognitive functions, some abnormal ERPs pt.3: non-significant ERPs relationships	Kotchoubey et al., 2003
NPSYCHO-cognitive ('paper and pencil')	2 LIS ALS (answers were signalled by blinking of eyes)	short (one week)	cognitive: general intelligence, learning and memory, speech comprehension, intentional semantic analysis and movement intention (plus others)	pt.1: average performance (according to age and education norms) pt.1: below average indicating cognitive decline	Neumann & Kotchoubey, 2004
REVIEW (perspective paper)	results on 17 severely impaired ALS including LIS and CLIS	---	physiological, behavioural, cognitive: overview on state-of-the-art of BCI applications in late ALS stages	lack of positive BCI results in CLIS ALS, compromised vision in late stages, first formulation of two hypotheses: (i) drop of cognitive abilities arousal and attention, (ii) "extinction-of-goal-directed-thought"	Birbaumer, 2006a
NPSYCHO-cognitive ('paper and pencil')	11 severely impaired ALS (1 LIS), 11 healthy matched controls	medium (two weeks)	cognitive: general intelligence, executive function, learning and memory, and speech comprehension	ALS group comparable to healthy control group, executive functions, learning and memory deficits in some patients, preserved learning and memory skills improved in late disease stages	Lakerveld et al., 2008
NMETAB-cognitive (NIRS)	1 CLIS ALS	short (one week)	cognitive: dichotic listening, covert singing, word fluency and motor imagery	signatures of preserved cognitive functions (selective attention, covert production, phonemic verbal fluency and motor imagery), consistent activations of the bilateral sensorimotor area	Fuchino et al., 2008

(1) Evaluation type: NPHYSIO-cognitive (neurophysiological/cognitive), NPSYCHO-cognitive (neuropsychological/cognitive), REVIEW (perspective paper), NMETAB-cognitive (neurometabolic/cognitive using near-infrared spectroscopy), E-physiol. (electro-physiological)

(2) Study's length: short (days, within one week), medium (weeks), long (months)

Table 2. (continued)

Evaluation type (1)	**Participants (ALS stands for ‘ALS patients’)**	**Study’s length (2)**	**Investigated aspect**	**Observations/results (pt. refers to patient)**	**Reference**
E-physiol. (ECoG)	1 CLIS ALS	long (nine months)	physiological and behavioral changes in the transition from LIS to CLIS	at the verge of LIS-CLIS no facial muscle activity, nor external anal sphincter but eye control, complete loss of eye movements in CLIS, clear but abnormal ERPs, necrosis of cornea	Murguialday et al., 2011
E-physiol. (ECoG)	1 CLIS ALS	long (one month)	physiological: circadian rhythm and wake-sleep cycle	at the verge of LIS-CLIS no circadian rhythm in heart rate and body temperature, increased fragmentation of slow wave sleep	Soekadar et al., 2013
NPHYSIO-cognitive (ECoG)	1 CLIS ALS	long (six months)	neurophysiological and cognitive: mismatch negativity, standard oddball, priming and the semantic oddball	at the verge of LIS-CLIS partially intact attention and cognitive function, reproducible attention independent ERPs, almost reproducible attention dependent ERPs, increased power of low frequency bands associated with cognitive pathologies	Bensch et al., 2014
E-physiol. (ECoG)	1 CLIS ALS	long (six months)	physiological: sleep/arousal in CLIS	irregular wake-sleep cycle, with normal time periods overall sleep stages, identification of three different levels of arousal by means of dominant frequencies (below 4 Hz, around 7 Hz and around 20 Hz)	Martens et al., 2014
NPHYSIO-cognitive (ERP based BCI)	15 moderate ALS, age-matched group of 15 healthy controls	short (less than one week)	preliminary validation of a cognitive assessment based on an ERP BCI and targeting phonemic verbal fluency, attention, executive function and verbal comprehension abilities	neuropsychological test battery convergent validity compared to Montreal Cognitive Assessment tool, satisfactory levels of usability in ALS group, high sensitivity and specificity levels in discriminating patients from controls	Poletti et al., 2016

(1) Evaluation type: NPHYSIO-cognitive (neurophysiological/cognitive), NPSYCHO-cognitive (neuropsychological/cognitive), EDITORIAL (editorial paper), NMETAB-cognitive (neurometabolic/cognitive using near-infrared spectroscopy), E-physiol. (electro-physiological)

(2) Study’s length: short (days, within one week), medium (weeks), long (months)

3.5 The ill-posed "BCI illiteracy" problem

Factors explaining the "BCI illiteracy" problem have been explored since the early years of 2000. "BCI illiterates" are defined those subjects unable to achieve a good BCI control, roughly estimated from 10% up to 30% of overall participants in BCI studies. The non standardized definition of "BCI illiteracy" relies mainly on the chance-level performance (calculated according to BCI settings, see Müller-Putz et al., 2008) or on the 70% performance-threshold diffusely accepted by BCI researchers to achieve a reliable BCI control (Perelmouter & Birbaumer, 2000; Kübler et al., 2004). Based only on these criteria it is easy to classify as "illiterate" one BCI study's participant as can be observed, for instance, in SMR, ERP and SSVEP based BCI studies involving large samples (respectively: Blankertz et al., 2010; Guger et al., 2009; Allison et al., 2010). Nonetheless, additional criteria should be taken into account to enhance the above "BCI illiteracy" definition, such as training frequency and length, physiological/functional constraints (such as compromised/altered vision) and motivational aspects.

A low SCP training frequency per week had slightly negative BCI learning effects in a group of advanced ALS patients trained over weeks (Kübler et al., 2004) compared to a similar study in advanced ALS including LIS where a higher weekly training frequency was used (Neumann & Birbaumer, 2003). The training length led to improved BCI learning effects in a group of motor impaired users trained over weeks by an auditory ERP based BCI system (Halder et al., 2016; Baykara et al., 2016). Thus, training frequency and especially training length play a relevant role on the observation of below and above chance-level BCI performance, even about results above the 70% performance-threshold.

Conversely, the above mentioned BCI studies with large samples rely basically on one-day session only (Blankertz et al., 2010; Guger et al., 2009; Allison et al., 2010), i.e. short-term BCI tests. In addition, partially impaired vision (ptosis, diplopia, nygstamus; see paragraph *Advanced and LIS ALS patients sub-optimal BCI performance*) can be quickly diagnosed before a visual BCI test or training, as described in a recent report (McCane et al., 2014) and severely compromised vision can be expected in CLIS ALS patients (Murguialday et al., 2011).

Hence, it may be argued that "BCI illiteracy" is a kind of ill-posed problem because the supposed inability to use a BCI system is mainly based on short-term tests and because no BCI systems harnessing a sensory domain (auditory, visual and tactile) input can work adequately in persons with deficits or impairments in the same sensory domain. Moreover, motivational factors such as challenge/mastery confidence and incompetence fear can boost, or conversely hamper, BCI performance over a long-term training (Nijboer et al, 2010) and in medium-term trainings motivation correlates with BCI performance and neurophysiological signals (Baykara et al., 2016). Finally, BCI signal's quality variance was also correlated with mild (i.e. sub-clinical) cognitive deficits (Geronimo et al., 2016).

Perhaps, extensive studies with long lasting testing periods are difficult to manage and to be granted, thus, BCI research groups tend to optimize the studies' outcome mainly with short-term tests. Nevertheless, as a consequence, poor and below chance level BCI results should not be categorized just with an inexplicable phenomenon.

3.6 The "extinction-of-goal-directed-thought" hypothesis

Functional impairment and BCI outcome are uncorrelated when measured in ALS patients till LIS condition (excluding CLIS) as proved by most of the studies involving medium-to-large groups (Nijboer et al., 2008b; Silvoni et al., 2009; Halder et al., 2013; Silvoni et al., 2013; McCane et al., 2014). Even single cases of long-term BCI recordings lasting years prove such assumption (Sellers et al., 2010; Holz et al., 2015). Such results are in line with findings showing that learning of BCI control, as any other procedural skill, involves the same brain systems and information processing mechanisms: the cortico-thalamic-striatal-loop and the neuroplastic NMDA-receptor dependent synaptic connections of this system (Hinterberger et al., 2005; Koralek et al., 2012). For unknown reasons, despite the widespread destruction of the central and spinal motor system, skill learning seems to remain intact in the course of the disease up to the CLIS where it turned out to be impossible to assess any type of communication (Birbaumer, 2006b; Kübler & Birbaumer, 2008). At the time of the meta-analysis (i.e. 2008 and even before, i.e. 2006) these considerations led to the formulation of the "extinction-of-goal-directed-thought" hypothesis in CLIS.

CLIS patients are laying in a bed twenty-four hours a day with a very few, or not at all, social interactions. Therefore, the "loss of the contingency" between any voluntary response and/or intention and its feedback due to a lack of immediate reinforcement might prevent operant conditioning in any context (Birbaumer et al., 2012), even though sensory afferent input and cognitive processing is preserved. In CLIS condition, the complete isolation might cause the extinction of intentions at the cognitive and physiological level because any intended response or desire has no contingent consequence. Similarly, a lack of contingencies in instrumental learning is likely to lead to the extinction of goal-directed thinking and imagery (Chaudhary et al., 2016).

The above mentioned hypothesis talking about the extinction of goal-directed thoughts was formulated performing a parallel between the CLIS condition of ALS patients and animals (curarized rats) whose similar condition had been described since the sixties (Miller, 1969). Experimental evidences of learned self-regulation of autonomous functions in artificially immobilized rats seemed to open a new road in visceral learning research at that time. However, the failure in the eighties to replicate initial positive results was repeatedly documented and attributed to the missing homeostatic effect of the reward (Dworkin & Miller, 1986).

The "extinction-of-goal-directed-thought" hypothesis might explain the incompatibility of the immobilized condition -maintained by artificial nutrition and ventilation, similar in rats and patients- with instrumental learning and the consequent unsuccessful rewarding by feedback because no alterations or imbalances of the homeostatic functions occur (Birbaumer et al., 2012).

The "extinction-of-goal-directed-thought" hypothesis appeared for the first time in a paper by Birbaumer in 2006. Successively, in their meta-analysis, Kübler and Birbaumer (2008) investigated the relationships between severity of patients involved in BCI studies and the level of success in BCI use. They distinctly reported the drop of level of success in BCI tasks after entering the CLIS condition. These results underlined the difficulty to use the proposed BCI technology in the last ALS stage.

Nevertheless, from the failure of visceral learning in curarized rats (Dworkin & Miller, 1986) and the positive evidences of intact event-related potentials in CLIS ALS patients (Kotchoubey et al., 2003) the same authors concluded that passive sensory information processing in completely locked-in patients is preserved, even at higher semantic level, and envisioned that "extinction-of-goal-directed-thought" can be prevented before entering such condition possibly transferring already acquired BCI communication skill to CLIS (Birbaumer, 2006b). Hence, the complete lack of motor control and feedback was believed to be responsible for the cessation of voluntary cognitive activity in line with the “motor theory of thinking” scientifically introduced by James (1890) and further developed by Washburn (1916) following Titchener (1909).

These observations led the authors to find a different way to explain the failure of communication in CLIS. They proposed as an alternative the classical conditioning theory (Pavlov, 1927) which requires no volition or cognitive effort. Experiments in curarized rats (which are completely paralized and require artificial vetilation, similar to patients with CLIS) demonstrated the preservation of classical conditioning when operant learning is lost. Successful classical learning of autonomic functions was observed in these rats, but they failed to learn operant control of physiological responses (Dworkin & Miller, 1986; Dworkin, 1993). Birbaumer’s group argued, therefore, that a classical conditioning paradigm could provide a suitable learning paradigm to enable patients with CLIS to communicate (Birbaumer et al., 2012; Chaudhary et al., 2016).

Initially, semantic reflexive BCI paradigms using different unconditioned stimuli (such as auditorily presented pleasant/unpleasant sounds) have been developed and tested on healthy participants (Furdea et al., 2012; Ruf et al., 2013). The results were promising but insufficient to achieve a reliable control over BCI. Substantially, the semantically conditioned cortical binary responses to false and true statements (measured by EEG) were quite clearly distinguishable separately compared to the baseline, but not compared each other, even if significant differences of the neuroelectric signatures were observed (Ruf et al., 2013).

Further results on CLIS patients are described in the following paragraph (*BCI performance in completely locked-in ALS patients*).

4. Discussion

4.1 BCI performance in completely locked-in ALS patients

The complete failure of communication in CLIS was documented several times after publication of the "extinction-of-goal-directed-thought" hypothesis (Birbaumer, 2006a, 2006b; Kübler & Birbaumer, 2008; Birbaumer et al., 2012) which led to the implementation of a new kind of BCI experiments based on classical (i.e. Pavlonian) conditioning.

The first-ever experiment in CLIS condition employing a classical semantic conditioning BCI procedure was conducted over an extended time period (many weeks) in one CLIS patient and two LIS patients (De Massari et al., 2013). During each BCI session, semantically conditioned neuroelectric brain responses to affirmative and negative statements were recorded with EEG. Unconditioned stimuli were electrical pulses delivered to the hand. A pre-post session auditory oddball test was performed to monitor patients' level of vigilance. The results were not reliable (around chance level for all three patients) due to the fluctuations of classification accuracy results related to both "close" (with known answer) and "open" (without known answer) statements. The latter modality was assessed presenting two semantically reversed versions of the same open statement (for instance, "Berlin is the capital of France" and "Berlin is the capital of Germany") and long-term stability of classification accuracy. Nonetheless, offline results obtained using a more complex pre-processing chains (i.e. employing wavelet coefficients) showed the possibility to increase the BCI outcome up to 70%. In addition, as explained earlier, a rapid drop of vigilance was detected classifying standard and deviant ERP responses of the pre-post oddball test. This suggested attentional variations or variations of circadian period.

Excluding cognitive decline, the main reasons argued by De Massari and colleagues (2013) to explain the unreliable results were: (i) rapid reduction of attention span and vigilance in LIS/CLIS, (ii) the "extinction-of-goal-directed-thought" hypothesis effect which prevents even semantic conditioning, (iii) aversive stimulus anticipation blocking effect and (iv) possible wrong selection of the pre-processing procedure (in terms of frequencies span). This BCI study underlined three really important aspects: the necessity to conduct long-term and repetitive BCI measurements in CLIS (otherwise no consistent and reliable results can be obtained), the vigilance fluctuations issue and the possibility to introduce a new metric to assess BCI outcome, that is the semantic concordance between semantically reversed versions of open statements.

Successively, due to the exciting BCI results obtained discriminating haemodynamic responses in healthy volunteers executing a motor imagery task (Sitaram et al., 2007), a new NIRS based BCI was developed to comply the semantic conditioning procedure and tested in one CLIS patient (Gallegos-Ayala et al., 2014). Three BCI assessment periods lasting two to four weeks yielded very interesting results with average classification accuracies of the neurometabolic signals correspondent to true/false statements ranging from 71% to 76%. Sessions with “close” and “open” sentences were compared resulting in robust and consistent observations derived from the replication of the same statements. However, this is only a case report and further investigations are necessary to confirm the simplicity, reliability and robustness of NIRS technology for binary communication purposes.

A recent report (Chaudhary et al., 2017) dealt with the replication of the above mentioned NIRS based BCI system assessment in four CLIS ALS patients. Differently from Gallegos-Ayala’s and colleagues study (2014) simultaneous functional neurometabolic (fNIRS) and neuroelectric (EEG) signals recording was implemented. An extensive BCI assessment lasting from few weeks (twenty sessions in one patient) to several weeks (forty-six sessions in remaining three patients) was carried out. The results are really exciting. Four CLIS ALS patients communicated using the fNIRS based BCI with an above-chance-level correct response rate over 70%. Decreased vigilance (or attention) during BCI sessions was reflected in higher power of slow EEG frequencies preventing accurate communication in some sessions. Differential cognitive processing occurred during the BCI task as proved by EEG spectral analysis of true/false sentences’ presentation intervals compared to the yes/no answering intervals. Semantic concordance rate, estimated to ascertain the consistency of the answers between semantically equivalent but contrasting true and false sentences, was close to 70% in three CLIS patients.

These results confirm the vigilance fluctuations issue previously reported by De Massari and colleagues (2013) and extend previous successful observations on BCI performance described by Gallegos-Ayala and colleagues (2014).

The ‘pragmatic’ optimal BCI outcome is below 100% in CLIS as in healthy individuals. Roughly speaking and taking several factors into account (such as wake-sleep cycle, cognitive problems, vigilance changes and semantic concordance rate values), this ‘pragmatic’ limit should be in the range 75-95%.

4.2 A simple algorithm for ‘pragmatic’ optimal BCI outcome estimation

The ‘pragmatic’ optimal BCI performance can be roughly estimated taking some factors of each BCI study into account. The proposed estimation is provided for studies involving ALS patients only. These factors are: (i) the number of ALS patients included in the study, (ii) the number of ALS patients with BCI classification accuracy below the chance-level upper limit and (iii) the study length (in terms of number of BCI sessions and trials).

The first factor (number of ALS patients) enhances the ‘pragmatic’ optimal performance, toward the theoretical limit, with decreasing number of patients included in the study (the less the number of ALS patients, the higher the possibility to reach the theoretical limit of 100%). The second factor (number of patients with BCI classification accuracy below the chance-level) reduces the ‘pragmatic’ optimal performance with increasing performers below chance-level (the more the performers below chance-level, the lower the possibility to reach the theoretical limit of 100%). The third factor enhances the ‘pragmatic’ optimal performance, toward the theoretical limit, with decreasing study length (the less the study length, the higher the possibility to reach the theoretical limit of 100%).

The chance-level confidence interval (and its upper limit) can be estimated by using the metric proposed by Müller-Putz and colleagues (2008). The number of ALS patients with performance below chance-level upper limit is derived by the comparison with such limit. Then, the ‘pragmatic’ optimal BCI performance can be estimated summing a constant term and three variable terms. The constant term corresponds to the conservative classification accuracy value computed as the maximum value between median classification accuracy and chance-level upper limit. The three variable terms are the weighted contributions derived from each of the three above mentioned factors (number of ALS patients, number of ALS patients with classification accuracy below chance-level and study length). The meaning of used symbols is the following:

CA:	classification accuracy
max_ALS_NP:	highest number of ALS patients ever included in all BCI studies
NP:	number of participants of each BCI study
NP_below_chance_level:	number of participants with classification accuracy below chance-level
max_TOT_NT:	highest study length among all BCI studies (n. of sessions x n. of trials)
TOT_NT:	total number of trials of each BCI study
starting_performance:	maximum value between median CA and chance-level upper limit
we:	1/3 (the contribution of each factor, equally distributed)
pragmatic_performance:	'pragmatic' optimal BCI performance
theoretical_performance_gap:	gap between theoretical limit and 'pragmatic' optimal BCI performance

The algorithm is the following:

$$\mathit{starting\_performance} = \max(\text{ median } \mathit{CA}, \text{ chance-level upper limit })$$

$$w_{1n} = \mathit{we} \cdot [(\mathit{max\_ALS\_NP} - \mathit{NP}) / \mathit{max\_ALS\_NP}]$$

$$w_{2n} = \mathit{we} \cdot [(\mathit{NP} - \mathit{NP\_below\_chance\_level}) / \mathit{NP}]$$

$$w_{3n} = \mathit{we} \cdot [(\mathit{max\_TOT\_NT} - \mathit{TOT\_NT}) / \mathit{max\_TOT\_NT}]$$

where w_{kn} is weight of each *k-th* factor,

$$\mathit{theoretical\_performance\_gap} = 100 - \mathit{starting\_performance}$$

$$c_1 = \mathit{theoretical\_performance\_gap} \cdot \mathit{we}$$

$$c_2 = \mathit{theoretical\_performance\_gap} \cdot \mathit{we}$$

$$c_3 = \mathit{theoretical\_performance\_gap} \cdot \mathit{we}$$

$$pragmatic\_performance = starting\_performance + (c_1 \cdot w_{1n} + c_2 \cdot w_{2n} + c_3 \cdot w_{3n})$$

where c_1, c_2 and c_3 are the equally distributed contributions of each factor to the 'pragmatic' optimal BCI performance.

Figure 1 depicts the theoretical and 'pragmatic' optimal BCI performance for BCI studies involving ALS patients.

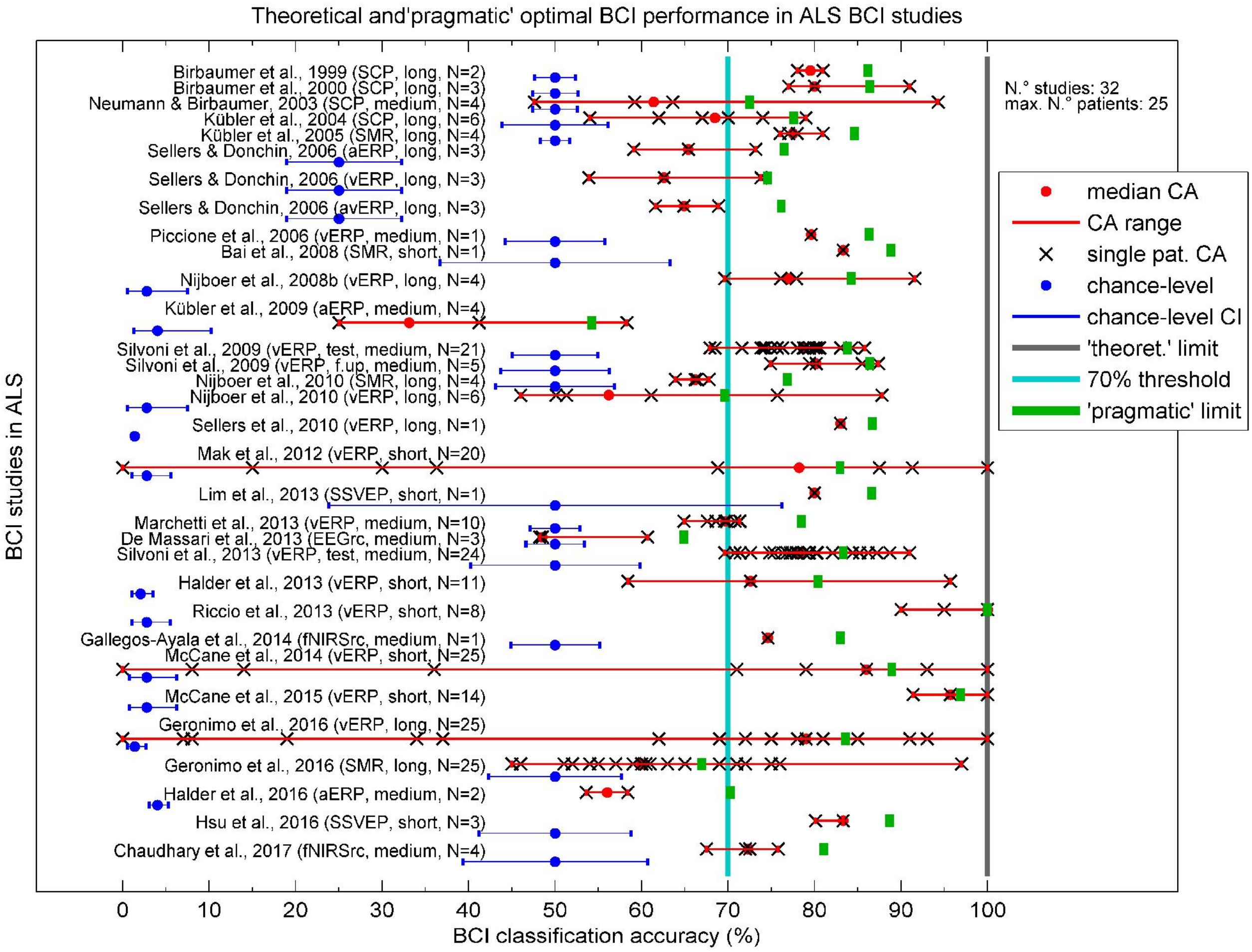

Figure 1. Theoretical and 'pragmatic' optimal BCI performance in ALS BCI studies. Median classification accuracy (i.e. 'CA') for each study is depicted in red, together with its range (horizontal line in red) and CA of single ALS patients (black 'x' symbol). Chance-level confidence interval (i.e. 'CI') and mean is symbolized by horizontal blue lines. Theoretical optimum (100%) and 70% performance-threshold are depicted as vertical gray and dark blue lines respectively. 'Pragmatic' optimal threshold for each study is plotted for each study in green (following the algorithm explained above). Chance-level confidence interval was calculated for each study separately (Müller-Putz et al., 2008), taking the most conservative values when ranges about number of trials and number of sessions were provided.

Figure 1. Extended legend:

- "SCP" stands for BCI based on slow cortical potentials;
- "SMR" stands for BCI based on sensorimotor rhythms;
- "aERP" stands for BCI based on auditory event-related potentials;
- "vERP" stands for BCI based on visual ERPs event-related potentials;
- "avERP" stands for BCI based on auditory and visual ERPs event-related potentials;
- "SSVEP" stands for BCI based on steady-state visual evoked potential;
- "EEGrc" stands for BCI based on electro-encephalograpic reflexive conditioning;
- "fNIRSrc" stands for BCI based on functional near infrared spectroscopy reflexive conditioning;
- "short" stands for BCI study lasting days (within one week);
- "medium" stands for BCI study lasting weeks (within one month);
- "long" stands for BCI study lasting months or years;
- "test" refers to testing sessions only;
- "f.up" refers to follow-up sessions only.

4.3 Conclusions

The complex picture of the problems concerning BCI communication in ALS, including the CLIS condition, ask for integration of instrumental learning principles (Skinner, 1953) and classical conditioning theory (Pavlov, 1927), advanced psycho-physiological technology such as fNIRS (Gallegos-Ayala et al., 2014), cognitive screening (Kotchoubey et al., 2003), circadian rhythm and sleep disorders assessment (Soekadar et al., 2013), vigilance detection (Martens et al., 2014) using low frequency bands (Klimesch, 1999; Mak et al., 2012), simultaneous neuroelectric and neurometabolic signal recording (fNIRS and EEG; Chaudhary et al., 2017) and attention monitoring using auditory (De Massari et al., 2013) or tactile (Silvoni et al., 2016) oddball procedures to solve the communication problem in advanced ALS stages and other disease states leading to LIS and CLIS.

The theoretical optimum of 100% BCI classification accuracy can be achieved using short-term experiments lasting one day to one week. However, reliability of clinical BCIs needs medium- and long-term assessments where the expected BCI outcome is lower than 100% (De Massari et al., 2013; Gallegos-Ayala et al., 2014; Chaudhary et al., 2017).

5. Summary

5.1 English summary

Amyotrophic Lateral Sclerosis (ALS) is a devastating condition which leads to the degeneration of motor neurons. It is a progressive disorder characterized by loss of mobility and verbal communication (Chaudhary et al., 2015). In 50% of the patients life expectancy estimates are 3-5 years after first symptoms' onset (Bensimon et al., 1994). However, if patients opt for artificial respiration and feeding life expectancy can be relatively healthy with optimal care. A percentage around 50% of patients present mild to severe cognitive impairment (Ringholz et al., 2005).

Since first attempts in the nineties (Birbaumer et al., 1999) brain-computer interface (BCI) systems have been successfully developed to secure communication with social environment in the late stages of the disease. However, BCI-systems in ALS do not reach 100% correct classification accuracy and in some case results are below chance level (McCane et al., 2014). The latter phenomenon is known as "BCI illiteracy" while the former one is generally ascribed to attentive issues, specific functional impairment, motivational factors and/or artefacts of the neurophysiological signals.

Our view relies on a more complex picture where many factors account for sub-optimal results, especially in the completely locked-in state (CLIS) when lack of communication is crucial. We will explore the critical factors determining sub-optimal BCI-performance, namely: (i) alteration of cognitive and/or emotional/behavioural states (Martens et al., 2014) such as vigilance/attention (Mak et al., 2012; De Massari et al., 2013), (ii) mild cognitive impairment (Volpato et al., 2016), (iii) the "extinction-of-goal-directed-thought" hypothesis (Kübler & Birbaumer, 2008), (iv) circadian rhythm and sleep disorders (Soekadar et al., 2013) and (v) visual sensory domain alterations (Murguialday et al., 2011).

These complementary factors suggest the integration of theoretical background on learning principles (Skinner, 1953), advanced technology (Gallegos-Ayala et al., 2014), multiple neural signals recording (Chaudhary et al., 2017) and vigilance/attention monitoring (De Massari et al., 2013; Silvoni et al., 2016) to reliably solve the communication problem in advanced ALS stages.

5.2 German summary

Leistungsfähigkeit der Gehirn-Computer Kommunikation bei der amyotrophen Lateralsklerose

Zusammenfassung

Die Amyotrophe Lateralsklerose (ALS) ist eine verheerende Erkrankung, die zur Degeneration der Motoneurone führt. Sie ist eine progrediente Störung, die durch den Verlust der Mobilität und verbalen Kommunikation charakterisiert ist. In 50% der Patienten die geschätzte Lebenserwartung 3-5 Jahrenach dem Beginn der erszten Symptome. Wenn sich die Patienten für eine künstliche Beatmung und Ernährung entscheiden, kann die Lebenserwartung relative lange sein, wenn eine optimale Versorgung gewährleistet ist. Bei etwas 50% der Patienten kommt es zu milder bis starker kognitiver Beeinträchtigung. Seit den ersten Versuchen in der 90er Jahren wurden Gehirn-Computer-Schnittstellen (brain computer interface, BCI) erfolgreich eingesetzt, um die Kommunikation mit der sozialen Umgebung in den späten Stadien der Erkrankung zu gewährleisten. Jedoch erreichen solche BCI Systeme keine 100% korrekte Klassifikation und in einigen Fällen sind sie unter der Zufallsgrenze. Dieses Phänomen hat man als BCI Analphabetentum bezeichnet, während Klassifikationsprobleme allgemein auf Aufmerksamkeitsprobleme, spezifische Funktionsbeeinträchtigungen, motivationale Faktoren und/oder Artefakte der neurophysiologischen Signale zurückgeführt wurden.

In unserer Sicht stellt sich das Problem komplexer dar, wobei viele Faktoren zu suboptimalen Ergebnissen führen, vor allem im Zustand des kompletten Eingeschlossenseins (completely locked-in state, CLIS), wo ein Mangel an Kommunikation entscheidend ist. Wir untersuchen die kritischen Faktoren, die suboptimale BCI-Leistungen bedingen, spezifisch: (i) Veränderungen kognitiver und/oder emotional/verhaltensbezogener Zustände wie Vigilanz oder Aufmerksamkeit , (ii) minimale kognitive Störungen, (iii) die Hypothese der Extinktion zielgerichteten Denkens (iv) circadiane Rhythmen und Schlafstörungen und (v) Veränderungen im visuellen System.

Diese komplementären Faktoren legen nahe, dass zur Lösung des Kommuniktionsproblems bei fortgeschrittener ALS der theoretische Hintergrund von

Lernprinzipien integriert werden sollte ebenso wie fortgeschrittene Technologien, die Aufzeichnung multipler neuraler Signale und das Monitoring von Vigilanz und Aufmerksamkeit.

Tübingen, _________________

Signed by Prof. Dr. Dr. h.c. mult. Niels Birbaumer _______________________

6. Bibliography

Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2014; 15(1-2): 9-14.

Ahmed RM, Newcombe RE, Piper AJ, Lewis SJ, Yee BJ, Kiernan MC, Grunstein RR. Sleep disorders and respiratory function in amyotrophic lateral sclerosis. Sleep Med Rev. 2016; 26:33-42.

Allison B, Luth T, Valbuena D, Teymourian A, Volosyak I, Graser A. BCI demographics: how many (and what kinds of) people can use an SSVEP BCI? IEEE Trans Neural Syst Rehabil Eng. 2010; 18(2): 107-16.

Appel SH, Zhao W, Beers DR, Henkel JS. The microglial-motoneuron dialogue in ALS. Acta Myol. 2011; 30(1): 4-8.

Bai O, Lin P, Vorbach S, Floeter MK, Hattori N, Hallett M. A high performance sensorimotor beta rhythm-based brain-computer interface associated with human natural motor behavior. J Neural Eng. 2008; 5(1):24-35.

Bauer G, Gerstenbrand F, Rumpl E. Varieties of the locked-in syndrome. J Neurol. 1979; 221(2): 77-91.

Baykara E, Ruf CA, Fioravanti C, Käthner I, Simon N, Kleih SC, Kübler A, Halder S. Effects of training and motivation on auditory P300 brain-computer interface performance. Clin Neurophysiol. 2016; 127(1): 379-87.

Bensch M, Martens S, Halder S, Hill J, Nijboer F, Ramos A, Birbaumer N, Bogdan M, Kotchoubey B, Rosenstiel W, Schölkopf B, Gharabaghi A. Assessing attention and cognitive function in completely locked-in state with event-related brain potentials and epidural electrocorticography. J Neural Eng. 2014; 11(2): 026006.

Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med. 1994; 330(9): 585-91.

Bernoulli J. Ars Conjectandi. Impensis Thurnisiorum Fratrum, Basilea, 1713.

Beukelman D, Fager S, Nordness A. Communication Support for People with ALS. Neurol Res Int. 2011; 2011:714693.

Birbaumer N, Ghanayim N, Hinterberger T, Iversen I, Kotchoubey B, Kübler A, Perelmouter J, Taub E, Flor H. A spelling device for the paralysed. Nature. 1999; 398(6725): 297-8.

Birbaumer N, Kübler A, Ghanayim N, Hinterberger T, Perelmouter J, Kaiser J, Iversen I, Kotchoubey B, Neumann N, Flor H. The thought translation device (TTD) for completely paralyzed patients. IEEE Trans Rehabil Eng. 2000; 8(2): 190-3.

Birbaumer N. Brain-computer-interface research: coming of age. Clin Neurophysiol. 2006a; 117(3): 479-483.

Birbaumer N. Breaking the silence: brain-computer interfaces (BCI) for communication and motor control. Psychophysiology. 2006b; 43(6): 517-32.

Birbaumer N, Murguialday AR, Cohen L. Brain-computer interface in paralysis. Curr Opin Neurol. 2008; 21(6): 634-638.

Birbaumer N, Piccione F, Silvoni S, Wildgruber M. Ideomotor silence: the case of complete paralysis and brain-computer interfaces (BCI). Psychol Res. 2012; 76(2): 183-91.

Birbaumer N, Gallegos-Ayala G, Wildgruber M, Silvoni S, Soekadar SR. Direct brain control and communication in paralysis. Brain Topogr. 2014; 27(1): 4-11.

Blankertz B, Losch F, Krauledat M, Dornhege G, Curio G, Müller KR. The Berlin Brain--Computer Interface: accurate performance from first-session in BCI-naïve subjects. IEEE Trans Biomed Eng. 2008; 55(10): 2452-62.

Blankertz B, Sannelli C, Halder S, Hammer EM, Kübler A, Müller KR, Curio G, Dickhaus T. Neurophysiological predictor of SMR-based BCI performance. Neuroimage. 2010; 51(4): 1303-9.

Braille L. Method of Writing Words, Music, and Plain Songs by Means of Dots, for Use by the Blind and Arranged for Them. Paris, France: National des Jeunes Aveugles [National Institute for Blind Children], 1829.

Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999; 169(1-2): 13-21.

Chaudhary U, Birbaumer N. Communication in locked-in state after brainstem stroke: a brain-computer-interface approach. Annals of Translational Medicine. 2015; 3(Suppl 1): S29.

Chaudhary U, Birbaumer N, Curado MR. Brain-machine interface (BMI) in paralysis. Ann Phys Rehabil Med. 2015; 58(1): 9-13.

Chaudhary U, Birbaumer N, Ramos-Murguialday A. Brain-computer interfaces for communication and rehabilitation. Nat Rev Neurol. 2016; 12(9): 513-25.

Chaudhary U, Xia B, Silvoni S, Cohen LG, Birbaumer N. Brain-Computer Interface-Based Communication in the Completely Locked-In State. PLoS Biol. 2017; 15(1): e1002593.

Connolly S, Galvin M, Hardiman O. End-of-life management in patients with amyotrophic lateral sclerosis. Lancet Neurol. 2015; 14(4): 435-42.

Coyle S, Ward T, Markham C, McDarby G. On the suitability of near-infrared (NIR) systems for next-generation brain-computer interfaces. Physiol Meas. 2004; 25(4): 815-22.

Daly JJ, Wolpaw JR. Brain-computer interfaces in neurological rehabilitation. Lancet Neurol. 2008; 7(11): 1032-1043.

De Massari D, Ruf CA, Furdea A, Matuz T, van der Heiden L, Halder S, Silvoni S, Birbaumer N. Brain communication in the locked-in state. Brain. 2013; 136(Pt 6): 1989-2000.

Dement W, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr Clin Neurophysiol. 1957; 9(4):673-90.

Dworkin BR. Learning and Physiological Regulation. University of Chicago Press, Chicago, 1993.

Dworkin BR, Miller NE. Failure to replicate visceral learning in the acute curarized rat preparation. Behav Neurosci. 1986;100(3):299-314.

Elbert T, Rockstroh B, Lutzenberger W, Birbaumer N, editors. Self-regulation of the brain and behavior. New York: Spinger; 1984.

Falkenstein M, Hohnsbein J, Hoormann J, Blanke L. Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. Electroencephalogr Clin Neurophysiol. 1991; 78(6): 447-55.

Fried-Oken M, Fox L, Rau MT, Tullman J, Baker G, Hindal M, Wile N, Lou JS. Purposes of AAC device use for persons with ALS as reported by caregivers. Augment Altern Commun. 2006; 22(3): 209-21.

Fuchino Y, Nagao M, Katura T, Bando M, Naito M, Maki A, Nakamura K, Hayashi H, Koizumi H, Yoro T. High cognitive function of an ALS patient in the totally locked-in state. Neurosci Lett. 2008; 435(2): 85-9.

Furdea A, Ruf CA, Halder S, De Massari D, Bogdan M, Rosenstiel W, Matuz T, Birbaumer N. A new (semantic) reflexive brain-computer interface: in search for a suitable classifier. J Neurosci Methods. 2012; 203(1): 233-40.

Gallegos-Ayala G, Furdea A, Takano K, Ruf CA, Flor H, Birbaumer N. Brain communication in a completely locked-in patient using bedside near-infrared spectroscopy. Neurology. 2014; 82(21): 1930-2.

Geronimo A, Simmons Z, Schiff SJ. Performance predictors of brain-computer interfaces in patients with amyotrophic lateral sclerosis. J Neural Eng. 2016; 13(2): 026002.

Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. Lancet Neurol. 2013; 12(4): 368-80.

Guger C, Daban S, Sellers E, Holzner C, Krausz G, Carabalona R, Gramatica F, Edlinger G. How many people are able to control a P300-based brain-computer interface (BCI)? Neurosci Lett. 2009; 462(1): 94-8.

Halder S, Ruf CA, Furdea A, Pasqualotto E, De Massari D, van der Heiden L, Bogdan M, Rosenstiel W, Birbaumer N, Kübler A, Matuz T. Prediction of P300 BCI Aptitude in Severe Motor Impairment. PLoS One. 2013; 8(10): e76148.

Halder S, Käthner I, Kübler A. Training leads to increased auditory brain-computer interface performance of end-users with motor impairments. Clin Neurophysiol. 2016; 127(2): 1288-96.

Hanagasi HA, Gurvit IH, Ermutlu N, Kaptanoglu G, Karamursel S, Idrisoglu HA, Emre M, Demiralp T. Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials. Brain Res Cogn Brain Res. 2002; 14(2): 234-44.

Hardiman O. Management of respiratory symptoms in ALS. J Neurol. 2011; 258(3): 359-65.

Hinterberger T, Veit R, Wilhelm B, Weiskopf N, Vatine JJ, Birbaumer N. Neuronal mechanisms underlying control of a brain-computer interface. Eur J Neurosci. 2005; 21(11): 3169-81.

Holm A, Ranta-aho PO, Sallinen M, Karjalainen PA, Müller K. Relationship of P300 single-trial responses with reaction time and preceding stimulus sequence. Int J Psychophysiol. 2006; 61(2): 244-52.

Holz EM, Botrel L, Kaufmann T, Kübler A. Long-term independent brain-computer interface home use improves quality of life of a patient in the locked-in state: a case study. Arch Phys Med Rehabil. 2015; 96 (3 Suppl): S16-26.

Hsu HT, Lee IH, Tsai HT, Chang HC, Shyu KK, Hsu CC, Chang HH, Yeh TK, Chang CY, Lee PL. Evaluate the Feasibility of Using Frontal SSVEP to Implement an SSVEP-Based BCI in Young, Elderly and ALS Groups. IEEE Trans Neural Syst Rehabil Eng. 2016; 24(5):603-15.

James W. The principles of psychology. Holt: NY. Reprint: Harvard University Press: Cambridge, Mass; 1983, 1890.

Jeunet C, N'Kaoua B, Subramanian S, Hachet M, Lotte F. Predicting Mental Imagery-Based BCI Performance from Personality, Cognitive Profile and Neurophysiological Patterns. PLoS One. 2015; 10(12): e0143962.

Kleih SC, Nijboer F, Halder S, Kübler A. Motivation modulates the P300 amplitude during brain-computer interface use. Clin Neurophysiol. 2010; 121(7): 1023-31.

Kleih SC, Kübler A. Empathy, motivation, and P300 BCI performance. Front Hum Neurosci. 2013; 7:642.

Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev. 1999; 29(2-3): 169-95.

Koralek AC, Jin X, Long JD 2nd, Costa RM, Carmena JM. Corticostriatal plasticity is necessary for learning intentional neuroprosthetic skills. Nature. 2012; 483(7389): 331-5.

Kotchoubey B, Lang S, Winter S, Birbaumer N. Cognitive processing in completely paralyzed patients with amyotrophic lateral sclerosis. Eur J Neurol. 2003; 10(5): 551-8.

Kübler A, Neumann N, Wilhelm B, Hinterberger T and Niels Birbaumer. Predictability of Brain-Computer Communication. Journal of Psychophysiology. 2004; 18: 121-129

Kübler A, Nijboer F, Mellinger J, Vaughan TM, Pawelzik H, Schalk G, McFarland DJ, Birbaumer N, Wolpaw JR. Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. Neurology. 2005; 64(10): 1775-7.

Kübler A, Birbaumer N. Brain-computer interfaces and communication in paralysis: Extinction of goal directed thinking in completely paralysed patients? Clin Neurophysiol. 2008; 119(11): 2658-2666.

Kübler A, Furdea A, Halder S, Hammer EM, Nijboer F, Kotchoubey B. A brain-computer interface controlled auditory event-related potential (p300) spelling system for locked-in patients. Ann N Y Acad Sci. 2009; 1157: 90-100.

Lakerveld J, Kotchoubey B, Kübler A. Cognitive function in patients with late stage amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2008; 79(1): 25-9.

Leeb R, Lee F, Keinrath C, Scherer R, Bischof H, Pfurtscheller G. Brain-computer communication: motivation, aim, and impact of exploring a virtual apartment. IEEE Trans Neural Syst Rehabil Eng. 2007; 15(4): 473-82.

Lim JH, Hwang HJ, Han CH, Jung KY, Im CH. Classification of binary intentions for individuals with impaired oculomotor function: 'eyes-closed' SSVEP-based brain-computer interface (BCI). J Neural Eng. 2013; 10(2): 026021.

Lo Coco D, Mattaliano P, Spataro R, Mattaliano A, La Bella V. Sleep-wake disturbances in patients with amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2011; 82(8): 839-42.

Lulé D, Diekmann V, Anders S, Kassubek J, Kübler A, Ludolph AC, Birbaumer N. Brain responses to emotional stimuli in patients with amyotrophic lateral sclerosis (ALS). J Neurol. 2007; 254(4): 519-27.

Lulé D, Zickler C, Häcker S, Bruno MA, Demertzi A, Pellas F, Laureys S, Kübler A. Life can be worth living in locked-in syndrome. Prog Brain Res. 2009; 177: 339-51.

Lulé D, Pauli S, Altintas E, Singer U, Merk T, Uttner I, Birbaumer N, Ludolph AC. Emotional adjustment in amyotrophic lateral sclerosis (ALS). J Neurol. 2012; 259(2): 334-41.

Lulé D, Burkhardt C, Abdulla S, Böhm S, Kollewe K, Uttner I, Abrahams S, Bak TH, Petri S, Weber M, Ludolph AC. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen: a cross-sectional comparison of established screening tools in a German-Swiss population. Amyotroph Lateral Scler Frontotemporal Degener. 2015 Mar;16(1-2):16-23.

Mak JN, McFarland DJ, Vaughan TM, McCane LM, Tsui PZ, Zeitlin DJ, Sellers EW, Wolpaw JR. EEG correlates of P300-based brain-computer interface (BCI) performance in people with amyotrophic lateral sclerosis. J Neural Eng. 2012; 9(2): 026014.

Marchetti M, Piccione F, Silvoni S, Gamberini L, Priftis K. Covert Visuospatial Attention Orienting in a Brain-Computer Interface for Amyotrophic Lateral Sclerosis Patients. Neurorehabil Neural Repair. 2013; 27(5): 430-8.

Martens S, Bensch M, Halder S, Hill J, Nijboer F, Ramos-Murguialday A, Schoelkopf B, Birbaumer N, Gharabaghi A. Epidural electrocorticography for monitoring of arousal in locked-in state. Front Hum Neurosci. 2014; 8: 861.

McCane LM, Sellers EW, McFarland DJ, Mak JN, Carmack CS, Zeitlin D, Wolpaw JR, Vaughan TM. Brain-computer interface (BCI) evaluation in people with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2014; 15(3-4): 207-15.

McCane LM, Heckman SM, McFarland DJ, Townsend G, Mak JN, Sellers EW, Zeitlin D, Tenteromano LM, Wolpaw JR, Vaughan TM. P300-based brain-computer interface (BCI) event-related potentials (ERPs): People with amyotrophic lateral sclerosis (ALS) vs. age-matched controls. Clin Neurophysiol. 2015; 126(11): 2124-31.

Miller N. Learning of visceral and glandular responses. Science. 1969; 163: 434-445.

Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. Lancet. 2007; 369(9578): 2031-41.

Mugler EM, Ruf CA, Halder S, Bensch M, Kubler A. Design and implementation of a P300-based brain-computer interface for controlling an internet browser. IEEE Trans Neural Syst Rehabil Eng. 2010; 18(6): 599-609.

Murguialday AR, Hill J, Bensch M, Martens S, Halder S, Nijboer F, Schoelkopf B, Birbaumer N, Gharabaghi A. Transition from the locked in to the completely locked-in state: a physiological analysis. Clin Neurophysiol. 2011; 122(5): 925-33.

Müller-Putz GR, Scherer R, Brauneis C, Pfurtscheller G. Steady-state visual evoked potential (SSVEP)-based communication: impact of harmonic frequency components. J Neural Eng. 2005; 2(4): 123-30.

Müller-Putz G, Scherer R, Brunner C, Leeb R, Pfurtscheller G. Better than random: a closer look on BCI results. International Journal of Bioelectromagnetism. 2008; 10(1): 52-55.

Neumann N, Birbaumer N. Predictors of successful self control during brain-computer communication. J Neurol Neurosurg Psychiatry. 2003; 74(8): 1117-21.

Neumann N, Kotchoubey B. Assessment of cognitive functions in severely paralysed and severely brain-damaged patients: neuropsychological and electrophysiological methods. Brain Res Brain Res Protoc. 2004; 14(1): 25-36.

Nijboer F, Furdea A, Gunst I, Mellinger J, McFarland DJ, Birbaumer N, Kübler A. An auditory brain-computer interface (BCI). J Neurosci Methods. 2008a; 167(1):43-50.

Nijboer F, Sellers EW, Mellinger J, Jordan MA, Matuz T, Furdea A, Halder S, Mochty U, Krusienski DJ, Vaughan TM, Wolpaw JR, Birbaumer N, Kübler A. A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. Clin Neurophysiol. 2008b; 119(8): 1909-16.

Nijboer F, Birbaumer N, Kübler A. The influence of psychological state and motivation on brain-computer interface performance in patients with amyotrophic lateral sclerosis - a longitudinal study. Front Neurosci. 2010; 4. pii: 55.

Ogawa T, Tanaka H, Hirata K. Cognitive deficits in amyotrophic lateral sclerosis evaluated by event-related potentials. Clin Neurophysiol. 2009; 120(4): 659-64.

O'Connell RG, Dockree PM, Bellgrove MA, Turin A, Ward S, Foxe JJ, Robertson IH. Two types of action error: electrophysiological evidence for separable inhibitory and sustained attention neural mechanisms producing error on go/no-go tasks. J Cogn Neurosci. 2009; 21(1): 93-104.

Onofrj M, Thomas A, Paci C, Scesi M, Tombari R. Event related potentials recorded in patients with locked-in syndrome. J Neurol Neurosurg Psychiatry. 1997; 63(6): 759-64.

Pasqualotto E, Matuz T, Federici S, Ruf CA, Bartl M, Olivetti Belardinelli M, Birbaumer N, Halder S. Usability and Workload of Access Technology for People With Severe Motor Impairment: A Comparison of Brain-Computer Interfacing and Eye Tracking. Neurorehabil Neural Repair. 2015; 29(10): 950-7.

Paulus KS, Magnano I, Piras MR, Solinas MA, Solinas G, Sau GF, Aiello I. Visual and auditory event-related potentials in sporadic amyotrophic lateral sclerosis. Clin Neurophysiol. 2002; 113(6): 853-61.

Pavlov IP. Conditioned Reflexes. Oxford University Press. 1927.

Perelmouter J, Birbaumer N. A binary spelling interface with random errors. IEEE Trans Rehabil Eng. 2000; 8(2): 227-32.

Piccione F, Giorgi F, Tonin P, Priftis K, Giove S, Silvoni S, Palmas G, Beverina F. P300-based brain computer interface: reliability and performance in healthy and paralysed participants. Clin Neurophysiol. 2006; 117(3): 531-7.

Piepers S, van den Berg JP, Kalmijn S, van der Pol WL, Wokke JH, Lindeman E, van den Berg LH. Effect of non-invasive ventilation on survival, quality of life, respiratory function and cognition: a review of the literature. Amyotroph Lateral Scler. 2006; 7(4):195-200.

Pinkhardt EH, Jürgens R, Becker W, Mölle M, Born J, Ludolph AC, Schreiber H. Signs of impaired selective attention in patients with amyotrophic lateral sclerosis. J Neurol. 2008; 255(4): 532-8.

Pirani A, Nasreddine ZS, Tulipani C, Neri M. Montreal Cognitive Assessment (MOCA): uno strumento rapido per lo screening del Mild Cognitive Impairment. Dati preliminari della versione italiana. Atti IV Congresso Regionale Associazione Italiana Psicogeriatria, Bologna, 2007.

Poletti B, Carelli L, Solca F, Lafronza A, Pedroli E, Faini A, Zago S, Ticozzi N, Meriggi P, Cipresso P, Lulé D, Ludolph AC, Riva G, Silani V. Cognitive assessment in Amyotrophic Lateral Sclerosis by means of P300-Brain Computer Interface: a preliminary study. Amyotroph Lateral Scler Frontotemporal Degener. 2016; 12: 1-9.

Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol. 2007; 118(10): 2128-48.

Posner MI. Orienting of attention. Q J Exp Psychol. 1980; 32(1): 3-25.

Radunovic A, Annane D, Rafiq MK, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2013; (3): CD004427.

Riccio A, Mattia D, Simione L, Olivetti M, Cincotti F. Eye-gaze independent EEG-based brain-computer interfaces for communication. J Neural Eng. 2012; 9(4): 045001.

Riccio A, Simione L, Schettini F, Pizzimenti A, Inghilleri M, Belardinelli MO, Mattia D, Cincotti F. Attention and P300-based BCI performance in people with amyotrophic lateral sclerosis. Front Hum Neurosci. 2013; 7: 732.

Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology. 2005; 65(4): 586-90.

Ruf CA, De Massari D, Furdea A, Matuz T, Fioravanti C, van der Heiden L, Halder S, Birbaumer N. Semantic classical conditioning and brain-computer interface control: encoding of affirmative and negative thinking. Front Neurosci. 2013 Mar 7;7:23.

Sellers EW, Donchin E. A P300-based brain-computer interface: initial tests by ALS patients. Clin Neurophysiol. 2006; 117(3): 538-48.

Sellers EW, Vaughan TM, Wolpaw JR. A brain-computer interface for long-term independent home use. Amyotroph Lateral Scler. 2010; 11(5): 449-55.

Severens M, Van der Waal M, Farquhar J, Desain P. Comparing tactile and visual gaze-independent brain-computer interfaces in patients with amyotrophic lateral sclerosis and healthy users. Clin Neurophysiol. 2014; pii: S1388-2457(14)00130-8.

Shih JJ, Krusienski DJ, Wolpaw JR. Brain-computer interfaces in medicine. Mayo Clin Proc. 2012; 87(3): 268-79.

Skinner, B. F. "Science and Human Behavior", 1953. New York: MacMillan.

Silvoni S, Volpato C, Cavinato M, Marchetti M, Priftis K, Merico A, Tonin P, Koutsikos K, Beverina F, Piccione F. P300-Based Brain-Computer Interface Communication: Evaluation and Follow-up in Amyotrophic Lateral Sclerosis. Front Neurosci. 2009 Jun 19;3:60.

Silvoni S, Cavinato M, Volpato C, Ruf CA, Birbaumer N, Piccione F. Amyotrophic lateral sclerosis progression and stability of brain-computer interface communication. Amyotroph Lateral Scler Frontotemporal Degener. 2013; 14(5-6): 390-6.

Silvoni S, Konicar L, Prats-Sedano MA, Garcia-Cossio E, Genna C, Volpato C, Cavinato M, Paggiaro A, Veser S, De Massari D, Birbaumer N. Tactile event-related potentials in amyotrophic lateral sclerosis (ALS): Implications for brain-computer interface. Clin Neurophysiol. 2016; 127(1): 936-45.

Sitaram R, Zhang H, Guan C, Thulasidas M, Hoshi Y, Ishikawa A, Shimizu K, Birbaumer N. Temporal classification of multichannel near-infrared spectroscopy signals of motor imagery for developing a brain-computer interface. Neuroimage. 2007; 34(4): 1416-27.

Soekadar SR, Born J, Birbaumer N, Bensch M, Halder S, Murguialday AR, Gharabaghi A, Nijboer F, Schölkopf B, Martens S. Fragmentation of slow wave sleep after onset of complete locked-in state. J Clin Sleep Med. 2013; 9(9): 951-3.

Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, Murphy J, Shoesmith C, Rosenfeld J, Leigh PN, Bruijn L, Ince P, Figlewicz D. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2009; 10(3): 131-46.

Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. Science. 1965; 150(700): 1187-1188.

Tanaka H, Hayashi M, Hori T. Topographical characteristics and principal component structure of the hypnagogic EEG. Sleep. 1997; 20(7): 523-34.

Titchener EB. Lectures on the experimental psychology of the thought processes. New York, The Macmillan Company, 1909.

van der Waal M, Severens M, Geuze J, Desain P. Introducing the tactile speller: an ERP-based brain-computer interface for communication. J Neural Eng. 2012; 9(4): 045002.

Vidal JJ. Toward direct brain-computer communication. Annu Rev Biophys Bioeng. 1973; 2: 157-80.

Volpato C, Piccione F, Silvoni S, Cavinato M, Palmieri A, Meneghello F, Birbaumer N. Working memory in amyotrophic lateral sclerosis: auditory event-related potentials and neuropsychological evidence. J Clin Neurophysiol. 2010; 27(3): 198-206.

Volpato C, Prats Sedano MA, Silvoni S, Segato N, Cavinato M, Merico A, Piccione F, Palmieri A, Birbaumer N. Selective attention impairment in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2016; 17(3-4): 236-44.

Walter WG. Slow potential waves in the human brain associated with expectancy, attention and decision. Arch Psychiatr Nervenkr. 1964; 206:309-22.

Wang Y, Gao X, Hong B, Jia C, Gao S. Brain-computer interfaces based on visual evoked potentials. IEEE Eng Med Biol Mag. 2008; 27(5): 64-71.

Washburn MF. Movement and mental imagery: outlines of a motor theory of the complexer mental processes. Boston and New York Ed. Houghton Mifflin Company. The Riverside Press Cambridge, 1916.

Westphal KP, Heinemann HA, Grözinger B, Kotchoubey BJ, Diekmann V, Becker W, Kornhuber HH. Bereitschaftspotential in amyotrophic lateral sclerosis (ALS): lower amplitudes in patients with hyperreflexia (spasticity). Acta Neurol Scand. 1998; 98(1): 15-21.

Wheaton MW, Salamone AR, Mosnik DM, McDonald RO, Appel SH, Schmolck HI, Ringholz GM, Schulz PE. Cognitive impairment in familial ALS. Neurology. 2007; 69(14): 1411-7.

Wolf J, Wöhrle JC, Palm F, Nix WA, Maschke M, Safer A, Becher H, Grau AJ. Incidence of Amyotrophic Lateral Sclerosis in Rhineland-Palatinate, Germany. Amyotroph Lateral Scler Frontotemporal Degener 2014; 15(3-4): 269-74.

Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. Clin Neurophysiol. 2002; 113(6): 767-91.

Woolley SC, York MK, Moore DH, Strutt AM, Murphy J, Schulz PE, Katz JS. Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive Behavioral Screen (ALS-CBS). Amyotroph Lateral Scler. 2010;11(3):303-11.

Yin E, Zeyl T, Saab R, Hu D, Zhou Z, Chau T. An Auditory-Tactile Visual Saccade-Independent P300 Brain-Computer Interface. Int J Neural Syst. 2016; 26(1):1650001.

7. Declaration of Contributions to the Dissertation

The dissertation work was carried out at the Institute for Medical Psychology and Behavioural Neurobiology, University Tübingen, under the supervision of the Prof. Dr. Dr. h.c. mult. Niels Birbaumer.

The research work was designed in collaboration with Prof. Dr. Dr. h.c. mult. Niels Birbaumer, co-head of the above mentioned Department.

I carried out the research work independently with the assistance of my supervisor Prof. Dr. Dr. h.c. mult. Niels Birbaumer. Computations and statistical analysis were carried out by myself under the supervision of Prof. Dr. Dr. h.c. mult. Niels Birbaumer.

I confirm that I wrote the manuscript myself under the supervision of Prof. Dr. Dr. h.c. mult. Niels Birbaumer and that any additional sources of information have been duly cited.

Signed by Stefano Silvoni ____________________________________

On ____________________ in Tübingen

Acknowledgements

First of all, I am really grateful to Prof. Niels Birbaumer for helping me in finding internal motivations for work, as well as the necessary criticism about the scientific approach and investigation, as he does with all persons.

I am particularly grateful to all ALS patients and relatives for their cordiality and willingness to support the research, especially to Alessandro and Davide.

I would like to thank Chiara for her coherence and her professional support about neuropsychological aspects of the patients. Similarly, thanks a lot to Ujwal who’s enthusiasm and passion for this work has been transmitted to me.

I am grateful to many colleagues of S.Camillo Neuro-rehabilitation Hospital in Venice where I grew up my research competences and worked in an inter- and multi-disciplinary team: Marianna, Flavio, Irene, Maria, Emanuela, Andrea T., Michela, Francesco, Maria Rosaria, Paolo, Antonio, Cristina and Andrea P. (and many others which I can not list here).

Similarly, thanks to all colleagues of the Institute for Medical Psychology and Behavioural Neurobiology, University Tübingen, for their precious comments on my work and for sharing valuable ideas: Ander, Daniele, Boris Kleber, Boris Kotchoubey, Azim and Aygul (impossible here to list everyone).

Thanks a lot to Herta who offered me the great opportunity of a research work and her support in finalizing the dissertation. Thanks a lot to Dieter for his deep expertise and knowledge in neuroscience which inspired me.

Finally I am really grateful to Stefania for her patience and her far-sightedness.