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Brain–computer interfaces in amyotrophic lateral sclerosis: A metanalysis

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HIGHLIGHTS

- Amyotrophic lateral sclerosis (ALS) patients might communicate through brain–computer interfaces (BCI).
- We metanalyzed all relevant studies on BCI efficacy.
- There is limited evidence of BCI efficacy in ALS patients.

ABSTRACT

Objective: Despite recent groundbreaking findings on the genetic causes of amyotrophic lateral sclerosis (ALS), and improvements on neuroimaging techniques for ALS diagnosis have been reported, the main clinical intervention in ALS remains palliative care. Brain–computer interfaces (BCIs) have been proposed as a channel of communication and control for ALS patients. The present metanalysis was performed to test the evidence of BCI effectiveness in ALS, and to investigate whether the promising aims emerged from the first studies have been reached.
Methods: Studies on ALS patients tested with BCIs, until June 2013, were searched in PubMed and PsychInfo. The random-effect approach was used to compute the pooled effectiveness of BCI in ALS. A meta-regression was performed to test whether there was a BCI performance improvement as a function of time. Finally, BCI effectiveness for complete paralyzed ALS patients was tested. Twenty-seven studies were eligible for metanalysis.
Results: The pooled classification accuracy (C.A.) of ALS patients with BCI was about 70%, but this estimation was affected by significant heterogeneity and inconsistency. C.A. did not significantly increase as a function of time. C.A. of completely paralyzed ALS patients with BCI did not differ from that obtained by chance.
Conclusions: After 15 years of studies, it is as yet not possible to reliably establish the effectiveness of BCIs.
Significance: Methodological issues among the retrieved studies should be addressed and new well-powered studies should be conducted to confirm BCI effectiveness for ALS patients.

1. Introduction

In the second half of the 19th century, Jean-Martin Charcot described a new "*progressive atrophy invading the muscles*" (Goetz, 2000). Thanks to his "*method anatomoclinique*", Charcot associated the signs of the abovementioned neuromuscular disease with distinct, white and grey matter lesions, in specific sites of the central nervous system. Indeed, Charcot was the first to diagnose a case of amyotrophic lateral sclerosis (ALS; Charcot and Joffroy, 1869). Progressively, ALS brings the affected patients to lose the ability of voluntarily initiating and controlling their movements. ALS results in death, on average, within 2–5 years from onset, with some exceptions of patients that can survive for more than 10 years (Testa et al., 2004). The first cause of death in ALS is respiratory failure (Radunovic et al., 2013). Those patients who decide for respiratory

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support (i.e., tracheotomy or long-term mechanical ventilation), and for the feeding tube, can live longer (Dreyer et al., 2014). Despite the promising improvements in neuroimaging techniques for diagnosis (Foerster et al., 2013), and the recent breakthrough on the genetic causes of the pathology (Turner et al., 2013), ALS remains a fatal disease. As a consequence of the current limited possibility of therapies, ALS patients must face a continuous loss of functions and everyday independence because of disease progression. Even the possibility of ALS patients to communicate and interact with the environment is progressively reduced. Palliative care practices are the main clinical intervention with ALS patients (Mitsumoto and Rabking, 2007). The progressive reduction of autonomy and the perspective of complete paralysis, impacts patients' end-of-life decisions (Eisen and Krieger, 2013). In western countries the choice of being administered with long-term ventilation is rare (<5%), whereas in eastern countries that percentage is somewhat higher (e.g., ~30% in Japan; Furukawa et al., 2012). Nonetheless, the advent of more ergonomic and less invasive ventilators, followed by improved education of clinicians in this practice, is resulting in a growing number of patients who opt for long-term ventilation even in western societies (Bourke et al., 2012). Thus, the population of ALS patients who reach a state of disease, close-to or of complete paralysis, is intended to increase. While waiting for an effective therapy, there is urgency for solutions to offer devices to ALS patients, which would permit them to interact with their physical, technological, and social environment. By directly translating brain signals into commands, the Brain–Computer Interface (BCI) systems allow users to control devices without the involvement of the peripheral nerves and muscles (Daly and Wolpaw, 2008). The bioengineer J.J. Vidal coined the term BCI and elaborated on how to control a computer by means of the electroencephalogram (EEG; Vidal, 1973). Only 15 years later, Farwell and Donchin described and tested a method for "talking off the top of your head" (Farwell and Donchin, 1988) which became a milestone in the literature regarding BCIs. They designed a 6×6 matrix of characters (named "P300-speller"), which permitted users to type on a monitor, by means of correctly classified event-related potentials (ERPs). Since that seminal publication, the research on BCIs has exploded. Indeed, the number of articles on the topic has been exponentially grown, with hundreds of studies published in the last years (Shih et al., 2012). BCIs have been depicted as the best candidate for offering a new communication and motor control channel for severely paralyzed patients (Wolpaw et al., 2002). With this aim, ALS patients have been the first (McFarland et al., 1997; Kübler et al., 1998) and most studied clinical population by means of BCIs (Moghimi et al., 2013). The initial results were very promising. For instance, Birbaumer and colleagues described two patients with advanced ALS (Birbaumer et al., 1999) who successfully modulated their slow cortical potentials (SCPs) for controlling a word-typing software. This result posed substantial hope in the possibility of communication even with ALS patients in completely locked-in state (CLIS), in which the voluntary control of any muscle is impossible (Smith and Delargy, 2005). ALS patients can significantly control BCIs using different EEG signals (mainly ERPs, SCPs, and sensorimotor rhythms [SMRs]; Moghimi et al., 2013; Kübler and Birbaumer, 2008).

After fifteen years of research on BCIs for ALS patients, now is time to empirically address three main questions. First, what is the effectiveness, to date, of the BCIs tested with ALS patients? Second, is there any improvement in BCI effectiveness with ALS patients, from the first studies to date? Third, is there any evidence of communication, by means of BCIs, with ALS–CLIS patients? Through the present metanalysis we tried to answer these questions, in order to assess whether the initial "promises" have been kept and to offer clinicians and caregivers a clearer picture of the state-of-the-art in the field.

2. Methods

2.1. Searching strategies, selecting criteria, and data extraction

In June 2013, a systematic search with PubMed and PsychInfo databases was performed (Fig. 1). We searched for the terms "brain–computer interface(s)", or "BCI", or "brain–machines interface(s)", or "BMI", or "man–machines interface(s)", or "direct brain interface(s)", or "mental prosthesis/-es", in combination with each of the following terms: "amyotrophic lateral sclerosis", or "ALS", or "motor neuron disease", or "MND". No language restriction was used. Duplicated manuscripts were excluded, and original studies reporting tests of ALS patients with BCI systems were retrieved. The reference list of the retrieved papers was further checked to identify additional relevant articles. Selection criteria for inclusion in the systematic review (descriptive analysis) and metanalysis (quantitative analysis) were: ALS patients should have tested with a BCI system, and measures of classification accuracy of ALS patients' performance should have been reported. Exclusion criteria were: no measures of classification accuracy were reported – or measures of BCI effectiveness other than the classification accuracy measure were reported, or the performance of ALS patients had been already described in other articles.

The following data were systematically extracted from each selected study: publication's year, sample size, signal used for BCI control (i.e., SCP, SMR, ERP, or steady-state visual evoked potentials [SSVEP]), sensory modality used for BCI control (i.e., visual or acoustic), type of interface (defined as the number of possible classification choices), the percentage of classification accuracy, and the level of chance (L.C.) performance (i.e., the level of classification accuracy that can be reached just by chance, in percentage: L.C. = 100/number of targets). The same data were extracted from studies in which single cases of ALS–CLIS patients were tested with BCIs. Whenever a single case or a group of ALS patients had been tested with different interfaces within the same study, the best classification accuracy among the employed BCIs was selected for the present systematic review and metanalysis.

2.2. Endpoints

The classification accuracy (C.A.), defined as the percentage of correct classifications with the BCI, was extracted from each study as endpoint for addressing the first question (i.e., what is the effectiveness, to date, of the BCIs tested with ALS patients?). The reported measures of variability around the averaged C.A. of each study (i.e., standard error and standard deviation) were used to compute the 95% confidence intervals (i.e., mean ± [1.96 × standard error of the mean]) around the effect size measure (i.e., the row C.A.). The pooled C.A. was computed separately for SCP-based, SMR-based, and ERP-based BCIs, to estimate the effectiveness of the different BCIs.

To address the second question (i.e., whether there has been a BCI improvement in the last fifteen years), we performed a transformation of the row C.A. This transformation was performed to account for the different level of chance among the included studies to directly combine the C.A. obtained with different BCI systems. The equation used to calculate the corrected C.A. (i.e., percentage of above chance C.A.) was:

$$\text{Corr.C.A.} = (\text{C.A.} - \text{L.C.}) * 100/(100 - \text{L.C.})$$

The corrected C.A. cannot be interpreted as a measure of absolute BCI effectiveness. Instead, it must be considered as a proportional measure of above-chance C.A. Finally, the corrected C.A. was used to address whether there was evidence of above-chance, BCI control in ALS–CLIS patients (i.e., the third question).