Running head: **BCIs in ALS: a meta-analysis**

Title: **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.

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 support (i.e., tracheotomy or long-term mechanical ventilation), and for the feeding tube, can live longer (Dreyer et al., 2013). 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 et al., 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 x 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., 1997). 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.

Methods

Searching strategies, selecting criteria, and data extraction

In June 2013, a systematic search with Pubmed and PsychINFO databases was performed (Figure 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.

Figure 1 about here

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.

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 X 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:

$$Corr.C.A. = (C.A. – L.C.) * 100 / (100 – L.C.)$$

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).

Statistical analyses

Because of differences in the experimental procedures used in the included studies, there might be more than one effect size influencing the abovementioned studies. Thus, in the metanalysis, a

random-effects approach was used, following the assumption that the effect sizes of the studies represented a random sample of the real ones (Cumming, 2012; Borenstein et al., 2009).

First, the mean C.A. of each study and the respective confidence intervals (C.I.) were used to separately estimate the pooled C.A., for SCP-based, SMR-based, and ERP-based BCIs. Heterogeneity and inconsistency among studies were assessed by means of Cochran's Q and I2 tests (Higgins et al., 2003). To address the possible publication bias, we computed the Kendall's tau rank correlation with continuity correction and the Egger's regression tests (Rothstein et al., 2003). Second, publication year was used as a moderator variable to test the effect of time on BCI performance. Third, we tested whether there was evidence of above-chance BCI performance with ALS-CLIS patients, by performing a t-test versus zero of C.A. We performed analyses by using Comprehensive Metanalysis (v. 2.2.064) and the "metafor" package (Viechtbauer, 2010) of R statistic software (v. 3.0.1).

Results

Once the selection procedure was performed, 41 studies resulted eligible for descriptive analysis (Figure 2). Of the 41 studies, 14 studies were single cases not describing ALS-CLIS patients, and, thus, could not be included in the metanalysis. Twenty-seven studies were selected for the metanalysis.

Figure 2 about here

In the majority of the studies included in the metanalysis (90.24%), BCIs using the visual modality were used. In two studies, instead, BCIs using the acoustic and the visual modality

together were tested. Finally, in two studies BCIs based on acoustic interfaces were used. Most of the abovementioned BCIs were guided by ERPs (56.1%), followed by SCPs (24.4%), by SMRs (17.1%), and by SSVEPs (one study).

The pooled effect size of BCIs based on the visual modality was estimated separately for SCPs, SMRs, and ERPs. Six studies were eligible for SCP-based, BCIs metanalysis (Figure 3.A). The estimated C.A. was 72.94% (C.I. 95%: 67.32 to 83.36). This estimation, however, was limited by the significant heterogeneity among the considered studies ($Q = 23.83$, $p < 0.001$; $I2 = 97.75$). Analyses for testing the publication bias were either significant (Egger's test, $t(4) = -2.82$, p(2-tailed) = 0.048) or non-significant (Kendall's $\tau = 0$, p(2-tailed) = 1). Four studies were eligible for SMR-based BCIs metanalysis (Figure 3.B). The estimated C.A. was 70.04% (C.I. 95%: 52.22 to 87.85). The estimation was limited by significant, huge heterogeneity among the considered studies ($Q = 696.58$, $p < 0.001$; $I2 = 99.57\%$). The analyses performed for testing the publication bias were both non-significant (Egger's test, $t(2) = 1.86$, p(2-tailed) = 0.2; Kendall's $\tau = 0$, p(2-tailed) = 1). Fifteen studies were considered with reference to ERP-based BCIs metanalysis (Figure 3.C). The pooled C.A. was 72.94% (C.I. 95%: 64.26 to 81.62). Like in the previous analyses, the estimation was limited by a significantly large heterogeneity and inconsistency among the considered studies ($Q = 505.55$, $p < 0.001$; $I2 = 97.23\%$). The analyses performed for testing the publication bias were both non-significant (Egger's test, $t(13) = 0.12$, p(2-tailed) = 0.9; Kendall's $\tau = 0.89$, p(2-tailed) = 0.37).

Figure 3 about here

A meta-regression, with publication year as moderator, was performed on all 27 eligible studies. The C.A. did not increase significantly as a function of time (i.e., publication year; B = 1.676, C.I. 95%: -1.602 to 4.954; Qmodel = 1.005, p = 0.316).

Finally, in our systematic search eight single cases of ALS-CLIS patients tested with BCIs were found (Figure 4). The C.A. of each ALS-CLIS patient was computed, and we tested whether there were significant differences with respect to the L.C. (i.e., zero). The C.A. reached by the ALS-CLIS patients was not significantly different from zero ($t(7) = 1.402$, $p = 0.203$, Cohen's $d = 0.496$).

Figure 4 about here

Discussion

The present metanalysis represents the first attempt to verify the evidence of BCI effectiveness with ALS patients reported to date. Pooled measures of BCI effectiveness (i.e., C.A.) were computed from the retrieved studies. These pooled measures were all above 70%, independently of the brain signal used (i.e., SCP-, SMR-, and ERP-based, BCIs). The estimations, however, cannot be safely considered as depicting the real effect, because they were affected by huge heterogeneity and inconsistency. Thus, after 15 years of research in which there were no signs of classification accuracy improvement (i.e., no effect of publication year), it is as yet not possible to reliably establish the effectiveness of BCIs for communication and control with ALS patients. In the following paragraphs we shall elaborate more on some crucial points regarding BCIs and the present metanalysis.

High heterogeneity among studies

The heterogeneity in C.A. that emerged from the analysis could be due to several factors: the small ALS samples' size, the different procedures implemented among the retrieved studies and the complex requirements of several technologies (both hardware and software) implemented in the development of a BCI system among the various laboratories. These issues represent relevant limits for the estimation performed in the present metanalysis, but at the same time they may give precious indications for designing future more informative studies.

Laboratory vs. ecological settings

A further point is that the estimation of BCI effectiveness, in most of the studies, is restricted to few sessions in laboratory settings. In contrast, for effective clinical practice, it is necessary to demonstrate BCI effectiveness at patients' bedsides, in their homes, or in the clinics. To reach this aim, significant effort by both researchers and clinicians is needed. The potential usefulness of testing patients at bedside is supported, to date, by only one single-case study, in which the successful BCI use at home, by an ALS patient for more than two years, was described (Sellers et al., 2010). Note, however, that the patient was not in CLIS, but in LIS (Smith and Delargy, 2005) and he could still use the BCI.

BCI illiteracy

It has been reported that even a variable portion of the healthy participants (estimated from 15 to 30%) is not able to control a BCI system, an issue referred to with the term "BCI illiteracy" (Vidaurre and Blankertz, 2010). In the present metanalysis the question of ALS patients who were not able to control a BCI has not been addressed. It can be pointed out that this could represent a bias. Indeed, some cases of unsuccessful BCI control by ALS patients have been reported in the

literature (Kübler and Birbaumer, 2008; Murguialday et al, 2011; Mak et al., 2012; Nijboer et al., 2008).

Publication bias

Most of the tests for controlling publication bias in our meta-analyses were negative. Nonetheless, we consider more plausible the fact that the cases of successful BCI control with ALS patients would have been more likely to be published than vice versa. Thus, whether a publication bias might have affected the effectiveness estimations in the present metanalysis, is irrelevant for two reasons. The first reason is that there is huge heterogeneity in the estimated BCI performances, and the addition of unsuccessful cases (i.e., C.A. equal or close to the C.L.) would have only lowered the value estimated for BCI effectiveness. The second reason is that, even if considering the BCI performance computed as being accurate, it is uncertain whether the level of 70% C.A. can be considered as a satisfactory level of BCI effectiveness for ALS patients. Indeed, according to Kübler and Birbaumer (2008) the 70% accuracy level can be considered a general threshold for defining the "criterion level" (i.e., the minimum necessary classification accuracy level for communication). Nonetheless, it must be underlined that this estimation (i.e., 70%) has been obtained by testing ALS patients who retained at least some muscle control. Before reaching the LIS condition, effective assistive devices, for meeting patients' communication needs, are available (Spataro et al., 2013).

BCIs in CLIS

Even in the LIS condition, when at least one movement can be reliably present under the voluntary control of the patient, this is sufficient to permit a rudimental but essential level of communication (e.g., binary communication: yes or no; Murguialday et al., 2011). BCIs, instead,

have been indicated as the most promising device for communication in CLIS patients, when no other forms of communication are available. In our metanalysis we considered eight cases of ALS patients described as CLIS who were tested with BCIs. Their performances were not significantly different from those that can be obtained just by chance.

BCIs and cognitive impairment in ALS

It has been proposed that the condition of complete paralysis "might be responsible for the cessation of voluntary cognitive activity, goal direct thinking, and imaging" (Murguialday et al., 2011), a condition that might impair the possibility of learning to control a BCI. It is important to consider the possibility that some patients usually defined as being in LIS or in CLIS might not have all of their cognitive abilities preserved. This is even more relevant for the case of ALS patients who can be affected by frontotemporal lobar degeneration (FTLD), whose presence has been increasingly supported by genetic, behavioral, and neuroimaging evidence (Turner et al., 2013; Kuruvilla et al., 2013; Robberecht et al., 2013). In future trials, with BCIs in ALS patients, this issue must be taken into account. Hence, results about neuroimaging and neuropsychological assessment must be reported and related to the measures of BCI performances.

BCIs and different sensory modalities

At present, it is already clear that BCIs based on the visual modality, which represent the majority of the cases described in the literature, might not be suitable for ALS-CLIS patients (Murguialday et al., 2011). BCI systems using other sensory modalities or BCIs not based on external stimulation are necessary for "giving a voice" to ALS-CLIS patients (and even to non-ALS but completely-paralyzed patients).

When start training with BCIs?

One further observation derived from the attempts of teaching ALS-CLIS patients to control a BCI is that, in all the reported studies, the training was initiated when the patients had already been in the latest stages of the illness. On the basis of this observation, it can be hypothesized that the adoption of a longitudinal approach, which contemplates training ALS patients with a BCI prior to entering the LIS condition, could augment the possibilities of successful BCI control in CLIS condition.

With regard to the three questions directly investigated through the present metanalysis, we can conclude that there isn't as yet clear evidence of BCI effectiveness with ALS patients, and the studies with ALS in CLIS have been unsuccessful. Our results are in accordance with those of a recent specific metanalysis, which was focused on the efficacy of the P3-speller (Marchetti and Priftis, 2014). Furthermore, there is no evidence of a positive trend in BCI performance as a function of time (i.e., publication year). Should we conclude that the BCIs for communication in ALS have failed to reach their aim? The answer is no! Nonetheless, more improvements are needed, and now it is time to redefine the priorities in BCI research with ALS patients.

It can be suggested that in future studies:

1. Larger ALS patients' samples should be recruited for reaching excellent statistical power (i.e., .95);
2. Patients' categorization should be improved (e.g., not only by reporting their motor impairment level, but also by describing their sensory and cognitive status);
3. Longitudinal approaches in ecological settings should be adopted (i.e., patients' home).
4. Well defined experimental paradigms from cognitive (neuro)psychology should be used to

better controlling all cognitive parameters necessary for eliciting robust and clear brain signals (e.g., Marchetti et al., 2012, 2013b).

5. Distinct sensory modalities (e.g., visual, acoustic, etc.) should be directly compared, within the same sample of ALS patients, to identify which sensory modality, and under what conditions, can be the most suitable for effective BCI use.
6. Different EEG signals (e.g., P300, SCP, SMR, etc.) should be directly tested, within the same sample of ALS patients, to verify the best signal(s) for guiding BCIs.
7. Different mathematical methods and algorithms for processing EEG signals should be tested, within the same sample of ALS patients, to increase signal recognition and improve successful classification (e.g., Marchetti et al., 2013a).

For addressing the abovementioned points 1-7, wherever required, pilot studies on healthy participants are necessary before testing ALS patients (e.g., Marchetti et al., 2012, 2013b). Some of the issues that emerged in the present metanalysis are being addressed, at least in part, by ongoing independent studies in US and Europe (i.e., three registered clinical trials: http://clinicaltrials.gov/show/NCT00718458 [accessed the 07/01/2013]; http://clinicaltrials.gov/ct2/show/study/NCT00786032 [accessed the 07/01/2013]; http://clinicaltrials.gov/ct2/show/NCT01897818 [accessed the 07/01/2013]), and a multicenter EU research project (http://www.backhome-fp7.eu/ [accessed the 07/01/2013], all to studies to be concluded in the next two years).

The successful control of a BCI, even by only one ALS-CLIS patient could have the groundbreaking theoretical impact of demonstrating the presence of preserved cognitive functions despite complete paralysis, thus confuting the “extinction of goal thinking theory” (Kübler and Birbaumer, 2008). Effective BCI control by ALS-CLIS patients would further have the enormous

ethical impact of "giving a voice" to completely paralyzed patients, offering them the possibility of communicating their decisions; even those decisions regarding the end-of-life issues.

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Figure captions

FIGURE 1: Flaw diagram of how the reported studies were selected.

FIGURE 2: Studies retrieved for descriptive analysis. Dots and bars represent the mean classification accuracy and the 95% confidence intervals, respectively, extracted from each listed study. In the columns are listed (from left to right): ID = identification number of the study in reference list, Study (Year) = study abbreviation (year of publication), Signal = brain signal used for BCI control, N. = sample size, Mod. = sensory modality used, Clas. = whether the classification was performed in real time (online) or not (offline), and Interface = the type of device.

FIGURE 3: Forest plots for SCP-based BCIs (A), SMR-based BCIs (B), and ERP-based BCIs (C).

FIGURE 4: Studies of ALS-CLIS patients tested with BCI. Dots represent the classification accuracy for each ALS-CLIS patient using a BCI extracted from the listed studies. In the columns are listed (from left to right): ID = identification number of the study in reference list, Study (Year) = study abbreviation (year of publication), ± = whether the patient presented (+) or not (-) any sign of minimal muscle control reported in the study, Sex = gender of the patient, Age = age of the patient, Signal = brain signal used for BCI control, Clas. = whether the classification was performed in real time (online) or not (offline).

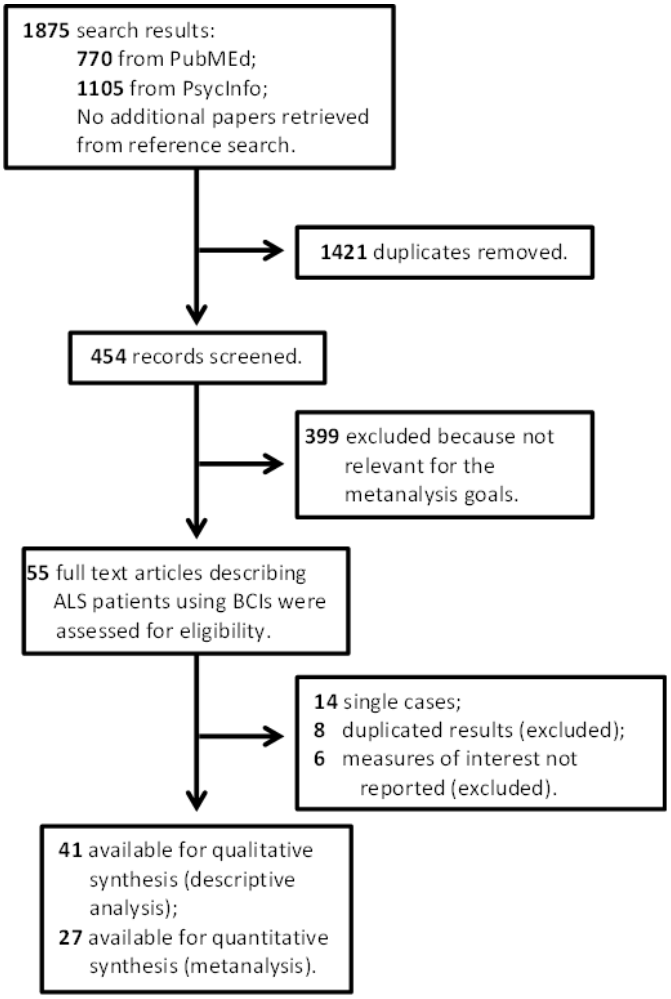
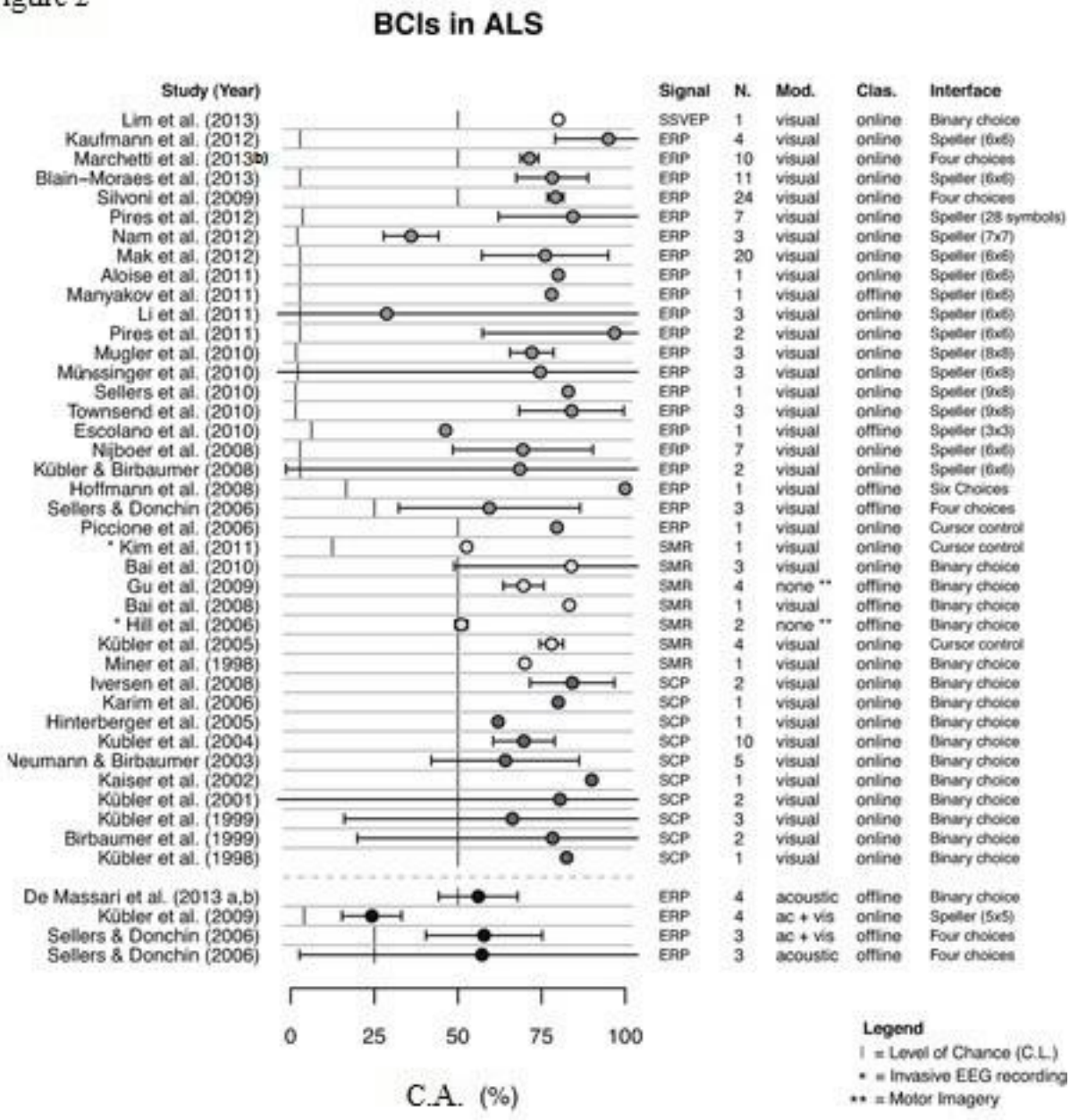

1875 search results:
770 from PubMEd;
1105 from PsycInfo;
No additional papers retrieved from reference search.
1421 duplicates removed.
454 records screened.
399 excluded because not relevant for the metanalysis goals.
55 full text articles describing ALS patients using BCIs were assessed for eligibility.
14 single cases;
8 duplicated results (excluded);
6 measures of interest not reported (excluded).
41 available for qualitative synthesis (descriptive analysis);
27 available for quantitative synthesis (metanalysis).

Figure 1

Figure 2


BCIs in ALS
Study (Year)
Signal
N.
Mod.
Clas.
Interface
Lim et al. (2013) SSVEP 1 visual online Binary choice
Kaufmann et al. (2012) ERP 4 visual online Speller (6x6)
Marchetti et al. (2013b) ERP 10 visual online Four choices
Blain-Moraes et al. (2013) ERP 11 visual online Speller (6x6)
Silvoni et al. (2009) ERP 24 visual online Four choices
Pires et al. (2012) ERP 7 visual online Speller (28 symbols)
Nam et al. (2012) ERP 3 visual online Speller (7x7)
Mak et al. (2012) ERP 20 visual online Speller (6x6)
Aloise et al. (2011) ERP 1 visual online Speller (6x6)
Manyakov et al. (2011) ERP 1 visual offline Speller (6x6)
Li et al. (2011) ERP 3 visual online Speller (6x6)
Pires et al. (2011) ERP 2 visual online Speller (6x6)
Mugler et al. (2010) ERP 3 visual online Speller (8x8)
Münssinger et al. (2010) ERP 3 visual online Speller (6x8)
Sellers et al. (2010) ERP 1 visual online Speller (9x8)
Townsend et al. (2010) ERP 3 visual online Speller (9x8)
Escolano et al. (2010) ERP 1 visual offline Speller (3x3)
Nijboer et al. (2008) ERP 7 visual online Speller (6x6)
Kübler & Birbaumer (2008) ERP 2 visual online Speller (6x6)
Hoffmann et al. (2008) ERP 1 visual offline Six Choices
Sellers & Donchin (2006) ERP 3 visual offline Four choices
Piccione et al. (2006) ERP 1 visual online Cursor control
* Kim et al. (2011) SMR 1 visual online Cursor control
Bai et al. (2010) SMR 3 visual online Binary choice
Gu et al. (2009) SMR 4 none ** offline Binary choice
Bai et al. (2008) SMR 1 visual offline Binary choice
* Hill et al. (2006) SMR 2 none ** offline Binary choice
Kübler et al. (2005) SMR 4 visual online Cursor control
Miner et al. (1998) SMR 1 visual online Binary choice
Iversen et al. (2008) SCP 2 visual online Binary choice
Karim et al. (2006) SCP 1 visual online Binary choice
Hinterberger et al. (2005) SCP 1 visual online Binary choice
Kubler et al. (2004) SCP 10 visual online Binary choice
Neumann & Birbaumer (2003) SCP 5 visual online Binary choice
Kaiser et al. (2002) SCP 1 visual online Binary choice
Kübler et al. (2001) SCP 2 visual online Binary choice
Kübler et al. (1999) SCP 3 visual online Binary choice
Birbaumer et al. (1999) SCP 2 visual online Binary choice
Kübler et al. (1998) SCP 1 visual online Binary choice
De Massari et al. (2013 a,b) ERP 4 acoustic offline Binary choice
Kübler et al. (2009) ERP 4 ac + vis online Speller (5x5)
Sellers & Donchin (2006) ERP 3 ac + vis offline Four choices
Sellers & Donchin (2006) ERP 3 acoustic offline Four choices
0
25
50
75
100
C.A. (%)
Legend
| = Level of Chance (C.L.)
* = Invasive EEG recording
** = Motor Imagery

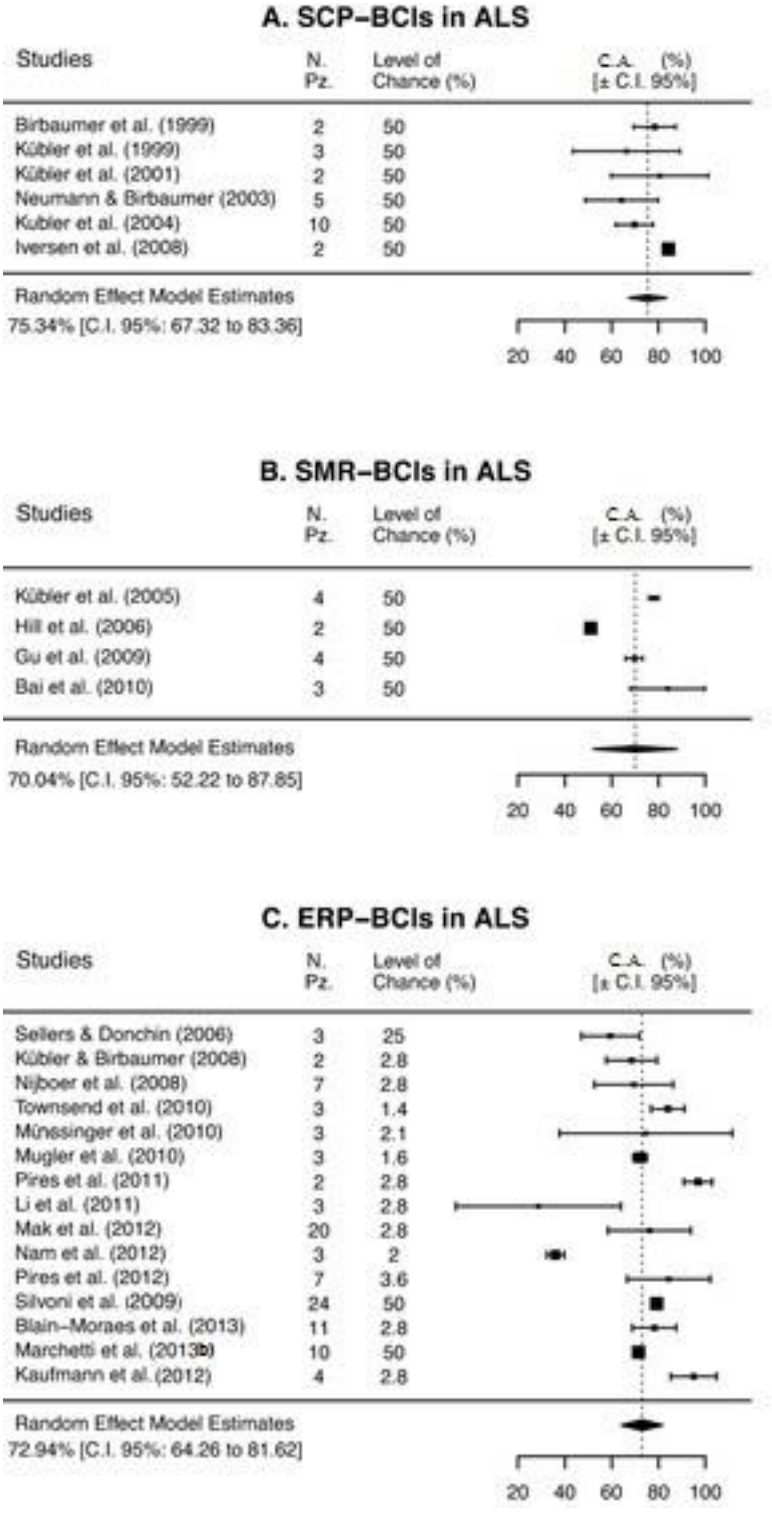

A. SCP–BCIs in ALS
Studies
N. Pz.
Level of Chance (%)
C.A. (%) [± C.I. 95%]
Birbaumer et al. (1999) 2 50
Kübler et al. (1999) 3 50
Kübler et al. (2001) 2 50
Neumann & Birbaumer (2003) 5 50
Kubler et al. (2004) 10 50
Iversen et al. (2008) 2 50
Random Effect Model Estimates
75.34% [C.I. 95%: 67.32 to 83.36]
20 40 60 80 100
B. SMR–BCIs in ALS
Studies
N. Pz.
Level of Chance (%)
C.A. (%) [± C.I. 95%]
Kübler et al. (2005) 4 50
Hill et al. (2006) 2 50
Gu et al. (2009) 4 50
Bai et al. (2010) 3 50
Random Effect Model Estimates
70.04% [C.I. 95%: 52.22 to 87.85]
20 40 60 80 100
C. ERP–BCIs in ALS
Studies
N. Pz.
Level of Chance (%)
C.A. (%) [± C.I. 95%]
Sellers & Donchin (2006) 3 25
Kübler & Birbaumer (2008) 2 2.8
Nijboer et al. (2008) 7 2.8
Townsend et al. (2010) 3 1.4
Münssinger et al. (2010) 3 2.1
Mugler et al. (2010) 3 1.6
Pires et al. (2011) 2 2.8
Li et al. (2011) 3 2.8
Mak et al. (2012) 20 2.8
Nam et al. (2012) 3 2
Pires et al. (2012) 7 3.6
Silvoni et al. (2009) 24 50
Blain-Moraes et al. (2013) 11 2.8
Marchetti et al. (2013b) 10 50
Kaufmann et al. (2012) 4 2.8
Random Effect Model Estimates
72.94% [C.I. 95%: 64.26 to 81.62]
20 40 60 80 100

Figure 3

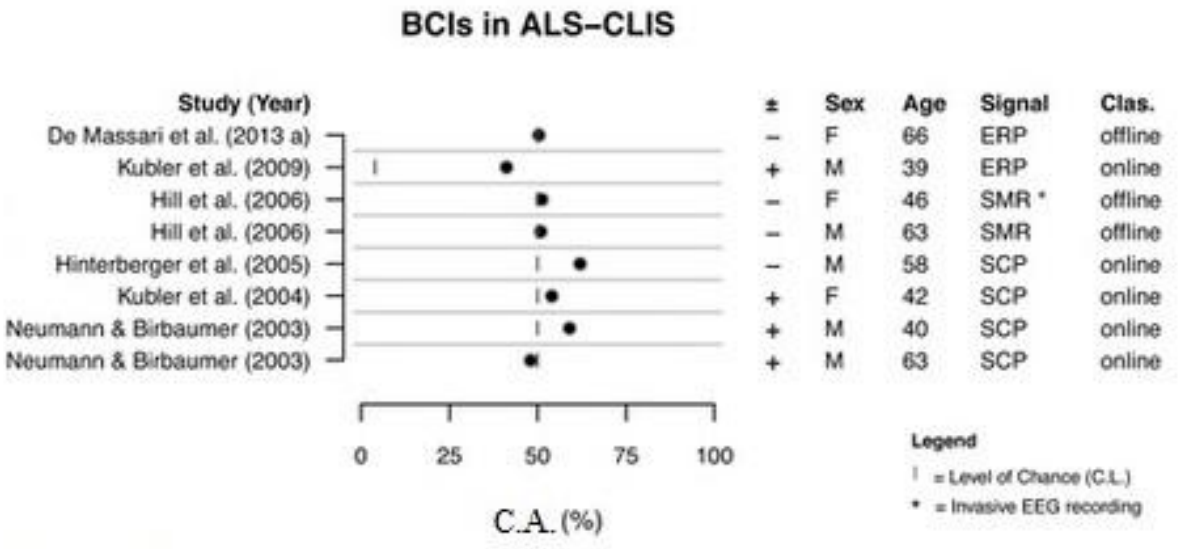

BCIs in ALS–CLIS
Study (Year)
De Massari et al. (2013 a)
Kubler et al. (2009)
Hill et al. (2006)
Hill et al. (2006)
Hinterberger et al. (2005)
Kubler et al. (2004)
Neumann & Birbaumer (2003)
Neumann & Birbaumer (2003)
±
Sex
Age
Signal
Clas.
– F 66 ERP offline
+ M 39 ERP online
– F 46 SMR * offline
– M 63 SMR offline
– M 58 SCP online
+ F 42 SCP online
+ M 40 SCP online
+ M 63 SCP online
0
25
50
75
100
C.A. (%)
Legend
| = Level of Chance (C.L.)
* = Invasive EEG recording

Figure 4