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What is This?
Covert Visuospacial Attention Orienting in a Brain-Computer Interface for Amyotrophic Lateral Sclerosis Patients

Mauro Marchetti, PhD¹, Francesco Piccione, MD², Stefano Silvoni², Luciano Gamberini, PhD¹, and Konstantinos Priftis, PhD¹, ²

Abstract

Background. Brain-computer interfaces (BCIs) allow people to control devices by translating brain signals into commands. BCIs represent a concrete solution with regard to communication and motor control disabilities of patients with amyotrophic lateral sclerosis (ALS). Most of the BCIs rely on visual interfaces in which patients must move their eyes to achieve efficient BCI control. This fact represents a limitation of BCI use in ALS patients who are in the final stages of the disease. Objective. We aimed to improve visual interfaces for ALS patients to control the movement of a cursor on a monitor by orienting their covert visuospatial attention (ie, orienting without eye movements). Methods. A total of 10 ALS patients with different levels of impairment used 2 new visual interfaces in an event-related potential (ERP)–based BCI. In the first interface, they were required to use exogenous visuospatial attention orienting (VAO), whereas in the second interface, they were required to use endogenous VAO. Results. ALS patients were able to use the 2 interfaces for controlling the ERP-based BCI system in real time. Nevertheless, better target classification and information transfer rate were associated with the interface that was based on endogenous VAO. Conclusions. ALS patients can exploit their covert VAO to control a BCI that does not require eye movements. The implementation of endogenous VAO in the design of covert visuospatial attention-based interfaces seems to be suitable for designing more ergonomic and efficient BCIs for ALS patients with impaired eye movements.

Keywords

brain-computer interface, amyotrophic lateral sclerosis, endogenous visuospatial attention orienting, exogenous visuospatial attention orienting, P300, late negative component

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that leads affected patients to paralysis and death typically within 2 to 5 years from the initial diagnosis.¹ ALS patients progressively enter into a condition in which eye muscle control and/or external sphincter control are usually the only spared movements (ie, locked-in state² [LIS]). In the later stages of the illness, however, muscle control becomes impossible. In this case, ALS patients enter into the so-called complete locked-in state (CLIS).

By using brain-computer interfaces (BCIs), ALS patients can communicate and interact with their environment.³ BCIs, indeed, allow users to control external devices such as computers or prostheses without the aid of the users’ peripheral nerves and muscles. ALS patients constitute the most investigated clinical population in BCI studies.⁴ Most of the BCIs tested with ALS patients rely on EEG signals (ie, event-related potentials [ERP], slow cortical potentials [SCPs], and sensorimotor rhythms) and on visual interfaces. ALS patients with minor, moderate, or major impairment⁵ are able to control online visual BCIs through ERPs,⁶,⁷ SCPs,⁸,⁹ and sensorimotor rhythms.¹⁰,¹¹ Birbaumer et al¹² first described 2 ALS-LIS patients who successfully used the SCPs for communicating through a word spelling system. Efficient control has been reached by other ALS-LIS patients.⁶,⁹,¹⁰,¹³-¹⁷ In a remarkable longitudinal study,¹⁸ an ALS-LIS patient was described who, for more than 2 years, was able to control the most investigated BCI (ie, the P300-speller¹⁹). Nevertheless, in some other studies, ALS-LIS patients were unable to use a BCI.¹⁵,²⁰

Less encouraging are the findings of studies on ALS-CLIS patients. Only a few cases have been described in the literature, and none of them was able to reach an acceptable level of BCI control.⁸,²¹,²² In their meta-analysis, Kübler

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and Birbaumer\(^5\) have hypothesized that the reason for this failure might be the extinction of goal-directed thinking in ALS-CLIS patients. An alternative explanation might be that visual BCIs are not suitable for ALS-CLIS patients. The use of auditory\(^{23-27}\) or tactile\(^{28}\) BCIs can be the solution, but these BCIs have never been tested on ALS-CLIS patients. In summary, visual BCIs for communication seem to be suitable for ALS patients with minor, moderate, and major impairment but not for those who are in the CLIS condition.

Visual BCIs have been successfully used by ALS-LIS patients in some cases\(^{6,9,10,13-17}\) but not in others.\(^{15,20}\) It is clear that the evolution of the illness leads ALS-LIS patients to progressively lose their eye movement control.\(^{29}\) Recent studies, however, have shown that successful use of the P300-speller requires participants to be able to move their gaze.\(^{30,31}\) Thus, the development of gaze-independent visual BCIs is required for use with ALS-LIS patients before they enter the CLIS condition.

Recently, we have designed and implemented new visual interfaces\(^{32,33}\) in which healthy participants used their covert visuospatial attention orienting (VAO; ie, shift of the focus of spatial attention without eye movements) to control a virtual cursor on a monitor by means of their ERPs (ie, P300 and late negative component [LNC])\(^{33}\). In the aforementioned studies,\(^{2,33}\) our aim was to investigate whether there was an advantage in implementing the principles of covert VAO\(^{34}\) in our interfaces. Many studies (for review\(^{35}\)) have suggested that covert VAO can be oriented by 2 types of cues: peripheral cues, which elicit an exogenous VAO (ExVAO), and central cues, which activate endogenous VAO (EnVAO). The results confirmed that healthy participants can use a BCI in a covert VAO condition.\(^{36,37}\) Moreover, healthy participants reached higher performance with the interface that required EnVAO than with the interfaces that required ExVAO. To date, however, no one has tested covert VAO with ALS patients to investigate whether these patients are able to use visual BCIs, even when their eye movements are impaired.

In the present study, we tested a group of ALS patients who showed different levels of motor impairment. We tested their ability to control a visual BCI without performing eye movements. In addition, we hypothesized that ALS patients, like healthy participants,\(^32\) would control the BCI better by means of EnVAO than by means of ExVAO. Finally, we investigated whether there was an effect of pathology level (measured through the revised ALS functional rating scale: ALSFRS-R\(^{38}\)) on participants’ performance.\(^{5,7}\)

### Methods

#### Participants

In all, 10 ALS patients gave their informed consent to participate in the study. Their demographic and clinical data are reported in Table 1. Participants were recruited from ALS patients who were in clinical treatment at the IRCCS San Camillo Hospital, Venice-Lido. The study was approved by the ethical committee of the hospital.

#### Apparatus, Stimuli, and Procedure

Participants sat in front of a monitor (HP L1906T Flat Panel LCD Screen; dimensions: 38 × 30.5 cm; refresh frequency:...
60 Hz; resolution: 1024 × 768). The apparatus of the present
study was identical to that we had previously used with
healthy participants, except for the use of a chin rest.
Patient P01 was tracheotomized, and patients P04, P08,
P09, and P10 sat in a wheelchair; for these reasons, it was
impossible for them to use the chin rest. The monitor was
placed at a distance of about 60 cm in front of each partici-
pant’s eyes. This experimental setting allowed us to test the
use of our BCI system in a more natural situation.

Two interfaces were presented to the participants: the
“Auto” interface (Figure 1B) and the “Vol” interface (Figure
1C). Both interfaces were designed for controlling the
movement of a virtual cursor on a monitor. The cursor’s
control was used for reaching target icons displayed on the
monitor. The icons showed everyday activities that might
be used by the patients for communicating their needs (eg,
the icon of a doctor for requiring his or her assistance; Figure 1A).

In the “Auto” interface, the principle of ExVAO was imple-
mented. In this, 4 icons were placed in the periphery of the
monitor. All icons were presented at a distance of 7 cm from the
central cross. During the sessions, the icons disappeared for 75
ms and reappeared at the same spatial position. The offset/onset
order of the icons was semirandom. Each participant was asked
to pay attention to the icon that was in the target spatial position
(ie, the to-be-reached icon that was indicated by the experi-
menter at the beginning of each session) to guide the cursor
toward the target spatial position. Moreover, participants were
required to keep their gaze on the cross and ignore the offset of
the icons in the nontarget spatial positions.

In the “Vol” interface, the principle of EnVAO was
implemented. The 4 icons remained always displayed on
the monitor. Four capital letters were presented on the cross,
1 at a time, for 900 ms, in a sequential semirandom order,
and then they disappeared. Each one was the initial letter of
an Italian directional word and indicated the spatial position
of 1 of the icons. Participants were required to pay attention
to the letter indicating the direction of the target spatial
position (ie, the to-be-reached icon that was indicated by the
experimenter at the beginning of each session) and to
ignore the others. Moreover, participants were required to
keep their gaze fixed on the cross.

Participants’ EEG was recorded during the presentation
of the trials with both the interfaces (ie, “Auto”: the offset
of an icon for 75 ms; “Vol”: the onset of a letter for 900 ms).
The ERPs related to each trial were processed online by an
ad hoc classifier (see next paragraph for a description of the
online classification procedure). If participants per-
formed the task correctly, different ERPs were elicited by
the target trials than by the nontarget trials. The classifier
was trained for detecting the difference between the fea-
tures in the ERPs related to the target trials and those related
to the nontarget trials. When the classifier detected the fea-
tures of the ERPs related to a target trial, the cursor was
moved 1 step toward the cued spatial position (ie, true posi-
tive). Otherwise, the cursor was not moved. To reach an
icon, participants needed to perform at least 4 steps with the
cursor toward the direction of the icon. Note that also when
the classifier detected a target ERP following a nontarget
cue, the cursor moved 1 step toward the nontarget direc-
ponent analysis decomposition, fixed features extraction, and person through a 3-step procedure: independent com-

The present study took place during 9 consecutive days. On the first day, each participant performed 8 training sessions with each interface. The training sessions were characterized by the automatic movement of the cursor after each target trial occurred. The training sessions were performed to collect a sample of EEG epochs for training the classifier that was used on the first day of the experimental sessions. In the following 8 days, each participant performed 4 testing sessions per day. On each day, each participant used either the “Vol” or the “Auto” interface. For half of the participants, the order of interface presentation during the 8 days was: “Vol”->“Auto”->“Auto”->“Vol”->“Auto”->“Vol”->“Vol”->“Auto.” For the other half of the participants, the order of interface presentation on the 8 days was “Auto”->“Vol”->“Vol”->“Vol”->“Auto”->“Vol”->“Auto”. The target spatial position was different in each of the 4 testing sessions. The order of the target positions was counterbalanced across the 8 days.

Electrophysiological Data Acquisition and Online Processing

The montage of the electrodes was performed according to the International 10-20 System at Fz, Cz, Pz, and Oz. The electro-oculogram was recorded from a pair of electrodes below and laterally to the left eye. All electrodes were referenced to the left earlobe, and the ground was on Fpz. Impedance was lower than 5 kΩ. The 5 channels were amplified, band-pass filtered between 0.15 and 30 Hz, and digitized at 200 Hz sampling rate. Each ERP epoch was synchronized with each trial. The output of the support vector machine classifier was used to control the movements of the cursor. The average number of trials added after each day of testing sessions was 254 (standard deviation [SD] = 72) and 224 (SD = 59) for the “Auto” and “Vol” interfaces, respectively. The variability between the interfaces and among the ALS patients depended on the classification accuracy that was reached by the participants during the online sessions.

Electrophysiological Data and Offline Processing

ALS patients were required to maintain their gaze fixed on the cross while they were performing the BCI sessions. In this way, we aimed to virtually simulate the condition of ALS-LIS patients, who cannot move their eyes voluntarily while using a visual BCI. Moreover, epochs containing eye movement artifacts were excluded from the statistical analyses. The criterion of ±75 µV was chosen to detect the artifacts that were caused by eye blinks and to detect gaze shifts greater than 5° of visual angle. In fact, a bipolar electro-oculogram recording permits us to detect deflections of about 16 µV for each degree of eye movement. The distance between the fixation point and the center of each icon (ie, “Auto” and “Vol” interfaces) measured 7° of visual angle. The cutoff level of ±75 µV permitted us to detect whether there were artifacts in the epochs because of gaze shifts from the center toward one of the icons displayed in the periphery of the screen (or vice versa). On average, 6.42% of trials were rejected for each participant (ie, “Auto” interface: M = 6.02%; “Vol” interface: M = 6.84%).

Design

Efficiency. The independent variables for testing the effects of VAO on the efficiency of the BCI were the following: interface (“Auto,” “Vol”) and day (Day 1, Day 2, Day 3, Day 4). The dependent variables were the accuracy (correctly classified trials in percentage), the percentage of error in the classification in the target trials, and the information transfer rate (ITR) measured in bit/min.

Event-related potentials. The independent variables for testing the effects of VAO on the ERPs were the following: interface (“Auto,” “Vol”), channel (Fz, Cz, Pz, and Oz), and trial class (target, nontarget). The dependent variables were the amplitude of the P300 and the amplitude of the LNC, taken from the epoch grand average of all the experimental sessions for each ALS patient after having excluded the epochs affected by eye movements (ie, epochs exceeding ±50 µV). The amplitude of the P300 was defined as the average ERP amplitude from 300 to 600 ms. The amplitude of the LNC was defined as the average ERP amplitude from 600 to 995 ms. The time windows used for defining the amplitude were identified through visual inspection of the grand average ERPs.

Disease level. To test whether there was any influence of disease level on the efficiency of BCIs, we performed, for each interface, a linear regression by means of the ALS-FRS-R score as predictor of the performance indexes.
Results

We ran analyses of variance (ANOVAs) for repeated measures. The Greenhouse-Geisser correction coefficient is reported when the assumption of sphericity was violated.

Accuracy

There was an improvement in the accuracy (Figure 2A) as a function of Day (day 1: mean [M] = 64.89%, SD = 6.1; day 2: M = 68.64%, SD = 4.9; day 3: M = 70.77%, SD = 5.1; day 4: M = 71.39%, SD = 6.4; \( F(3, 27) = 12.15, P < .001, \eta^2_p = 0.57 \)). In contrast, neither the main effect of the Interface nor the Interface × Session interaction were significant: \( F(1, 9) < 1 \) and \( F(3, 27) < 1 \), respectively.

Classification Errors on Target Trials

The analysis of the classification errors on target trials (Figure 2B) revealed that there were fewer classification errors on target trials in the “Vol” interface (M = 60.39%; SD = 17.7) than in the “Auto” interface (M = 67.24%; SD = 16.9); \( F(1, 9) = 3.83, P < .05 \), 1-tailed, \( \eta^2_p = 0.3 \). Moreover, the number of incorrectly classified target trials diminished as a function of Day: \( F(3, 27) = 10.53, P < .001, \eta^2_p = 0.54 \). Post hoc comparisons, with Bonferroni corrections, revealed a significant difference in the percentage of incorrectly classified target trials between day 4 (M = 51.75%; SD = 19.9) and both day 1 (M = 73.76%; SD = 10.7; \( P < .001 \)) and day 2 (M = 68.89%; SD = 14.5; \( P < .05 \)). Instead, there was no difference between day 4 and day 3 (M = 60.86%; SD = 16.2; \( P > .05 \)). The Interface × Session interaction was not significant: \( F(3, 27) < 1 \).

Information Transfer Rate

The analysis of the communication speed data (Figure 2C) showed that patients reached a higher ITR using the “Vol” interface (M = 5.11 bit/min, SD = 2.34) than using the “Auto” interface (M = 4.13 bit/min, SD = 2.28); \( F(1, 9) = 5.32, P < .05 \), 1-tailed, \( \eta^2_p = 0.37 \). The ITR improved as a function of Day (day 1: M = 3.3 bit/min, SD = 1.6; day 2: M = 3.8 bit/min, SD = 1.7; day 3: M = 4.9 bit/min, SD = 2.1; day 4: M = 6.3 bit/min, SD = 3.1); \( F(3, 27) = 11.98, P < .001, \eta^2_p = 0.57 \). Post hoc comparisons, with Bonferroni corrections, revealed a significant difference in the ITR between day 4 and both day 1 (\( P < .001 \)) and day 2 (\( P < .05 \)). In contrast, there was no difference between day 4 and day 3 (\( P > .05 \)). The Interface × Session interaction was not significant: \( F(3, 27) < 1 \).

P300 Amplitude

The ANOVA results for the mean amplitude of the P300 are shown in Table 2. For reasons of clarity, only the results that were relevant for our hypotheses are extensively reported within the text below, with particular regard to the Trial Class factor. The P300 amplitude was not differently modulated by the target (M = 1.07 µV, SD = 0.91) and the nontarget trials (M = 1.02 µV, SD = 0.95); \( F(1, 9) = 2.67, P > .05 \). This was true for both the interfaces (Interface × Trial Class interaction, \( F(3, 27) < 1 \)) and for all the channels (Channel × Trial Class, \( F(3, 27) = 2.59, P > .05 \)). Moreover, the Interface × Channel × Trial Class interaction was not significant: \( F(3, 27) < 1 \).

LNC Amplitude

The ANOVA results for the mean amplitude are reported in Table 2. As for the P300 amplitude, only the results concerning the modulation of the LNC because of the Trial Class factor are described in detail.
There was a larger negativity in the LNC epoch window on the target (M = −0.44 µV; SD = 0.68) than on the nontarget trials (M = −0.04 µV, SD = 0.59); \( F(1, 9) = 84.21, P < .001, \eta^2 = 0.9 \). The Interface × Channel × Trial Class interaction was also significant: \( F(3, 27) = 3.97, P < .05, \eta^2 = 0.31 \). Indeed, the LNC amplitude on target and nontarget trials was differently modulated in the “Auto” and in the “V ol” interfaces: \( F(3, 27) = 10.18, P < .05, \eta^2 = 0.53 \). To further investigate this interaction effect, pairwise comparisons between the LNC amplitude in the “Auto” and “V ol” interfaces were performed, separately for the target and the nontarget trials. There was a significant difference between the LNC amplitude in the “Auto” and “V ol” interfaces, elicited by the nontarget trials: \( t(9) = 2.89, P < .05 \) (“Auto”: \( M = −0.28 \mu V, \ SD = 0.32 \); “V ol”: \( M = 0.18 \mu V, \ SD = 0.51 \)) but a nonsignificant difference between the LNC amplitude in the “Auto” and “V ol” interfaces, elicited by target trials: \( t(9) = 0.68, P > .05 \) (“Auto”: \( M = −0.53 \mu V, \ SD = 0.44 \); “V ol”: \( M = 0.41 \mu V, \ SD = 0.58 \)). Moreover, the LNC amplitude was affected by Channel. That is, there was a larger difference in amplitude between target and nontarget trials in the fronto-central sites, which decreased in the parieto-occipital sites: \( \text{Channel} \times \text{Trial Class} \) interaction, \( F(3, 27) = 7.41, P < .001, \eta^2_p = 0.45 \).

### Disease Level

The effect of disease level on BCI use was tested by means of linear regression. The ALSFRS-R score was used as the predictor for each of the following dependent variables in both the interfaces: accuracy, classification errors on target trials, and ITR. The disease level measured with the ALSFRS-R scale did not predict ALS patients’ ability to control the BCI. The parameters of the statistical analyses are reported in Table 3.

Furthermore, we investigated whether there was a relation between the disease level of ALS patients and the amplitude of the ERPs elicited by the 2 interfaces (Figure 3). We performed a Pearson correlation between the ALSFRS-R score and the amplitude of both the P300 and the LNC for target and nontarget trials of the “Auto” and “V ol” interfaces and for all the recorded channels (ie, Fz, Cz, Pz, and Oz). There were no significant correlations (all \( P > .05 \)), even without using any correction for the multiple correlations performed.

### Discussion

We tested the effects of 2 visual interfaces, each based on different principles of covert attention orienting (ie, exog-
enous and endogenous\textsuperscript{34}, with ALS patients. Participants reached good performance in controlling a cursor with both the interfaces. Even if the mean accuracy of ALS patients was lower than 75\% (about 70\%), it has to be taken into account that this result might have been affected by our experimental procedures, which were mainly designed for comparing the 2 interfaces and not for ameliorating the overall efficiency of the system. ALS patients were better at using the “Vol” interface than the “Auto” interface. That is, higher ITR and fewer errors in target classification were associated with the use of the “Vol” interface. The better results obtained with the “Vol” interface might be a result of a different effect of the “Vol” interface on the ERPs. In fact, a lower LNC amplitude on nontarget trials was associated with the “Vol” interface. This resulted in a larger difference between target and nontarget trials with the “Vol” interface, which in turn might explain the advantages of ALS patients while using the “Vol” interface. Then, we tested whether there was an effect of ALS patients’ disease level on BCI use (ie, accuracy [in percentage], error in targets classification [in percentage], and ITR [in bit/min]). There was no significant relation between ALS patients’ level of impairment and the results obtained using the 2 interfaces. This finding is in line with previous results.\textsuperscript{5,7}

Visual BCIs are the most used devices for improving communication in ALS patients. Performance with the most used visual BCI (ie, the P300-speller) depends on the possibility of the users to move their gaze.\textsuperscript{30,31} This makes it difficult for patients with impaired eye muscle control to use the BCIs, such as ALS patients in the final stages of the illness. Thus, new interfaces that do not depend on eye movements might be required. Our results, however, support the idea that ALS patients who have impaired eye movements can use the covert VAO to avoid the problems related to BCIs that require eye movements. Note that our ALS patients were neither in the LIS nor in the CLIS condition. Nevertheless, both our findings and those from other studies\textsuperscript{5,7} have suggested that there is no relation between disease level and BCI performance, at least after CLIS patients are excluded. This allows us to hypothesize that our new interfaces might be efficient also with ALS-LIS patients. This hypothesis, however, can be definitively tested only by means of a study on ALS-LIS patients.

Other systems for communication with ALS patients in the final stages of their illness (eg, eye-tracking systems and alternative augmentative communication devices) cannot be easily used because these patients’ eye movement control gets progressively worse. We suggest that an efficient BCI system based on a covert VAO interface guided by endogenous orienting might be suitable for permitting ALS patients to communicate their needs, even in the advanced stages of their illness.

Declaration of Conflicting Interests
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