The combined use of Brain Computer Interface and Eye-Tracking technology for cognitive assessment in Amyotrophic Lateral Sclerosis

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***Abstract* — Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease. Cognitive deficits are known to be present in some ALS patients. Recently, it has been hypothesized that most ALS patients show cognitive impairments of one sort or the other. In this study we explore the capability of a combined use of Brain Computer Interface and Eye-Tracking technology to assess such deficits and as augmentative and alternative communication tools. In particular, we propose a setup based on both technologies in order to realize a neuropsychological battery for cognitive assessment in ALS.**

Keywords - ALS, BCI, Eye-tracking, Cognitive Assessment, AAC

I. INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease involving motor neurons in the cerebral cortex, corticospinal tracts, brainstem and spinal cord. Although ALS has been traditionally described as a pure motor disease, it is now known to involve also a range of cognitive deficits in most patients, with a small proportion (5%) presenting clinical features of frontotemporal dementia (FTD).

The most consistently reported cognitive changes regards frontal executive functions, i.e. verbal fluency, attention, working memory, planning and abstract reasoning. However, the assessment of cognitive impairment in ALS still remains a problematic issue, because of the severe physical disabilities of patients, including movement impairment, paralysis in the advanced stages and dysarthria, which interfere with the outcome of traditional neuropsychological testing. In fact, all standard assessment tools involve a motor response although corrections for time and adjustments to control for motor speed are employed [1,2].

New technologies to enable communication have been recently used in several studies; however, a comprehensive battery for cognitive assessment has never been implemented with these promising methodologies. Among these methods, Brain Computer Interface (BCI) and Eye Tracking (ET) are the most promising technologies. BCI uses neurophysiological signals as input commands to control external devices, while ET allows the measurement of eye position and movements. Of all movements eye movements are preserved the longest in ALS.

The purpose of the eBrain project is to evaluate the use of a BCI P300 methodology and an eye-tracking system, both as Augmentative and Alternative Communication (AAC) device and cognitive assessment tool with ALS patients.

II. ALS ASSESSMENT

Although ALS has been traditionally thought to spare cognitive functions, the presence of cognitive and behavioral symptoms in such patients has been reported for over a century [1]. Mild cognitive impairment, mainly involving executive functions, have been described in 10-50% of ALS patients, while a small proportion of patients (5%) present clinical evidence of frontotemporal dementia (FTD). In particular, an association between ALS and FTD has been postulated, with increasing evidence of clinical, radiological, pathological and genetic overlap between the two diseases.

The most common impairment reported in ALS patients regards dysfunctions in subcomponents of the executive system, such as attention and verbal fluency [3], together with behavioral aspects such as personality change, irritability, obsessions and poor insight [4]; deficient performances in memory and language have been less consistently reported. Cognitive and behavioral deficits in ALS may appear along a clinical continuum, ranging from mild-to-moderate impairment to FTD [5]. More recently, Strong and colleagues [6] proposed the ALSci (ALS with cognitive impairment) and ALSbi (ALS with behavioral impairment) acronyms which refer to patients with cognitive limitations or changes in cognition, affect and social behavior that do not meet the criteria for dementia. The terms ALSci, ALSbi and ALS-FTD (amyotrophic lateral

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sclerosis-frontotemporal dementia) and ALS non-FTD dementia, are concepts that aim to capture the key differences among the various clinical phenotypes. Zago and colleagues recently reviewed the possible continuum characterizing the whole spectrum of ALS cognitive impairment , highlighting the need of a multidisciplinary approach [7].

The observation, and possible quantitative evaluation, of cognitive impairments in patients with ALS have relevant clinical and practical implications; in fact, such impairments may affect the capacity to make decisions about health care, to properly manage financial situations, and may even reduce compliance with therapies.

In recent years, such cognitive effects in ALS have been extensively discussed as an unsolved matter, due to methodological problems mainly resulting from the limitations of traditional neuropsychological tests. The evaluation of cognitive abilities, especially in patients at the advanced stage of paralysis, such as for ALS patients, still represents a challenge, since all standard assessment tools for both verbal and non-verbal cognitive abilities usually involve motor control capabilities [8]. Even tests relying on some form of rudimentary motor function such as blinking, nodding, or pointing, cannot be administered to totally locked-in patients [9]. New methods for supporting communication in ALS patients have been recently introduced. Among these methods, Brain Computer Interface (BCI) is a promising technology, using neurophysiological signals as input commands to control external devices [10]. Iversen and colleagues [11] developed a brain-computer interface tool, based on slow-cortical potentials (SCP) of electroencephalogram (EEG). It aims to asses some cognitive functions in completely paralyzed ALS patients. During a training period, patients learned to control certain components of their EEG to direct the movement of a visual symbol on a monitor. Following, a series of two-choice cognitive tasks were administered to two severely paralyzed ALS patients. In a successive study, Iversen and colleagues [12] employed the same SCP-EEG control in order to administer a conditional-associative learning task to a late-stage ALS patient, testing the ability to learn arbitrary associations among visual stimuli. In both studies, a good level of accuracy was observed in detecting patient performances. In addition, patients were able to understand the verbal instructions and to respond in the successive tasks accordingly. However, this method requires an extensive pre-training in order to learn to control the EEG, and it cannot be used for tasks based on recall or where a choice must be made among more than two stimuli. Contrary to all other existing BCIs, learning self-regulation of the brain response and feedback is not necessary in P300-based BCIs. Despite the advantages provided, to date this approach has not yet been employed in order to develop tools allowing the cognitive assessment of locked-in patients.

Another available technology for cognitive assessment in ALS is the eye tracker (ET) technology. One approach is the analysis of saccadic eye movements which may provide a useful tool for investigating neurological or psychiatric disorders in which the frontal lobe is impaired [13]. Involvement of frontal function has recently been studied exploring ocular fixation with the aid of eye-tracking technology. Eye movements investigated with the anti-saccade paradigm is ideal to explore frontal cognitive functions. In the anti-saccade paradigm, subjects are instructed not to make a reflexive saccade to an appearing lateral target but to make an intentional saccade to the opposite side. This ability depends on the integrity of the dorsolateral prefrontal cortex (DLPFC) and involves attention and inhibition capacities.

Overall, the Eye-tracking technology has the capacity to measure voluntarily ocular movement control of ALS patients, thus generating an Augmentative and Alternative Communication Systems (AAC). To date, no applications have been developed, using ET as a communication device in order to administer cognitive tasks to ALS patients.

The main disadvantage in the use of ET systems is that they require full ocular mobility, and the absence of important visual deficits; the former may be lost or altered in the final stages of ALS, and the latter may be present in ALS patients of advanced age, thus forbidding the use of this device.

III. Advanced Computer Interfaces for ALS: Eye-tracking and BCI

Eye-tracking systems are used to assess several neurological and psychiatric disorders, including schizophrenia, pervasive developmental disorders (autism, Asperger's syndrome, etc.), ADHD and neurodegenerative diseases (Parkinson's, Alzheimer's, Huntington's, motor neuron disease, frontal-temporal dementia, etc.). There are several paradigms which might be applicable to assess cognitive functions in ALS. Ocular fixation, anti-saccade and smooth pursuit paradigms allow the assessment of frontal involvement characterizing the ALS cognitive pattern. Despite it has been reported in late stage ALS a range of ocular motor disorders, including slowed saccades [14,15], increased saccadic latencies [16], decreased smooth pursuit gain [17-19], and saccadic interruptions of smooth pursuit [20], in early to mid-stage, Eye-tracking might still be proficiently used.

In the most comprehensive study to date [21], patients showed increased error rates and latencies in the anti-saccade and remembered saccade paradigms, with preservation of reflexive saccades and smooth pursuit. Disturbances of fixation were also found, with patients showing an increased frequency of small saccadic intrusions. This pattern of eye movement disorder suggests a prefrontal lobe dysfunction. Evdokimidis and colleagues [22] also investigated the involvement of frontal lobe impairment in ALS using ocular motor paradigms and neuropsychological testing. One-third of 51 patients showed high distractibility which correlated with lower performance in neuropsychological tests assessing frontal functioning (WSCT and Stroop Test). Moreover, patients exhibited longer latencies to eye movement than controls. According to Donaghy and colleagues [23] ALS patients show abnormalities in ocular fixation. These instabilities can be considered as a marker of sub-clinical frontal lobe dysfunction in ALS.

As previously described, however, ET may not be proficiently used in case of poor or lack of eye-motor control, such as in late stage ALS patients. In this case there is the need of a more direct interface between voluntary cortex activity and the computer. BCI may offer an interesting answer to this issue with a growing number of different paradigms proposed. The most frequently used is the P300, a positive deflection of the

EEG that occurs 200-700 ms after stimulus onset of a deviant stimulus; it is typically recorded over central-parietal scalp locations [24-26]. P300 may represent a robust way to directly interface a computer, since the generation of P300 does not depend on the exact orientation of the eyes and on the activity of peripheral nerves and muscles, but mainly depends on the user's intent to pay attention to one stimulus. It is even present if no attention is paid. This permits its use with patients suffering from complete paralysis and impairment in oculo-motor dysfunctions, such as ALS and locked-in patients. In addition, a P300-based BCI does not strictly require initial user training in order to generate a P300 in response to the desired target.

Such a phenomenon has been observed across different BCI approaches, with 20% of subjects being not proficient in using BCI called "BCI illiteracy" [27]. This is due to the fact that not every person can generate the brain activity necessary to control a specific BCI. In fact, even if all individual's brains shared (more or less) the same functional properties and subdivisions, some difference in brain structure can be present, i.e. some users produce brain activity not detectable at the scalp level. About 10% of healthy subjects do not produce a robust P300. With regard to ALS patients, some studies have shown that some of those persons produce less typical ERPs than healthy matched subjects [28,29]. A previous ERP study in patients with sporadic ALS found that P3a and P3b amplitudes of ALS patients were lower and P3a latencies were significantly longer compared with the controls [30]; ERP recordings in non-demented patients with sporadic ALS also showed prolonged N200 and P300 latencies compared to healthy controls [31]. Ogawa and colleagues [32], by employing neuropsychological measures, event-related potentials (ERPs) and clinical scales, studied a sample of patients with early-stage sporadic amyotrophic lateral sclerosis (ALS). They found that patients with the bulbar-onset type showed marked prolongation of P3 latency compared to patients with the limb-onset type and controls. Furthermore, bulbar functional rating scale correlated with prolonged P3 latency and low P3 amplitude. Additionally, patients with bulbar-onset ALS had consistently poorer cognitive test performance than those with limb-onset ALS [33]. A significant correlation was found between the respiratory function tests and P3 amplitude, suggesting that ventilatory impairment interacts with P3 performance overriding P3 alterations due to cognitive impairment. These results represent a challenge for the use of P300 as an input signal in BCIs. Kübler and Birbaumer [8] investigated the relationship between the level of motor and physical impairment and the ability to use brain computer interface by comparing three different BCI systems (P300, SCP and sensorimotor rhythms (SMRs). They found no continuous decrement in BCI performance with physical decline, even in the completed locked-in state (CLIS) where no communication was possible. The major challenge remains the use of BCI-based systems with CLIS patients, who have the greatest needs for a BCI in order to communicate. Some issues must be considered while planning to use a P300-BCI system.

Two important criteria in order to evaluate the feasibility of a BCI system are speed and accuracy [34]. The former is related to the fact that the more rapidly a BCI can be controlled, the greater quantity of information can be produced by the user and the greater the chance for communication. Obviously, compared to verbal speech production, communication rate is severely reduced with BCI. With regard to accuracy, it consists of the percentage of correct selections per time interval. A wrong selection could turn into an error in communication, with both practical and psychological consequences for the user. In order to avoid this, the BCI system must be equipped with options that allow the user to correct wrong selections. A balance between speed and accuracy should be identified.

Moreover, technical challenges are related to the recording quality in an environment different from the laboratory setting, such as the user's home, when different sources of electromagnetic noise can disturb the EEG recording [26]. In addition, the patient's ventilators may induce electrical or mechanical artifacts. Perceptual and cognitive abilities, in particular the capacity to pay selective and sustained attention to the target stimuli must be considered when employing P300. It is necessary to determine whether a user is able not only to see the computer display, but also to focus on a particular stimulus on the display. Alternatively, auditory P300 BCI can be used which might be more convenient in late stage ALS patients with poor eye control. Furthermore, P300-BCI requires attention and counting the number of flashes of the matrix cell might interfere with focusing on the characters to be selected. Accordingly, the user should not be distracted. Overall, it may be difficult to use a P300 BCI in everyday life [34].

IV. The eBrain project

A recently funded project, "eBrain: BCI-ET for ALS," proposed to evaluate BCI P300 technique with the eye-tracking technology such as AAC systems. Administration of cognitive tests, in particular the ones to test frontal function, is anticipated in ALS patients.

Patients fulfilling El Escorial Criteria [35] for ALS and controls will be enrolled and undergo a neuropsychological computerized battery. All patients will receive the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). Patients will receive a standard protocol for AAC with both systems. The AAC protocol will focus on feasibility, user-friendliness, and pleasantness. Regarding cognitive assessment different cognitive domains will be investigated with both methods with special focus on executive and frontal abilities. In order to collect such neuropsychological measures, an ad hoc computerized battery will be created; patients will perform the cognitive tasks by means of both the adapted P300 Spelling System and the eye tracking system. A training phase will be conducted for both methods in patients and controls. The training length will vary depending on the subjects' ability. The recruitment of a small sample of patients at late stage of the disease (locked-in syndrome like) will help to evaluate the feasibility of a P300 protocol and the effectiveness as a communicative aid in this particular ALS population.

V. Test Setup

In the eBrain project, test architecture will consist of an eye-tracking system, and a BCI device connected to a laptop PC. From figure 1 it is possible to understand the test setup we

propose. The BCI device module will be based on the g.USBAmp (7) biosignal amplifier (Guger Technologies, Graz, Austria), connected to an active electrode head cuff (5) (g.GammaCap, Guger Technologies). The biosignal amplifier will be connected to a (6) portable laptop (HP DV3-4101SL, Hewlett Packard, USA), running Windows 7 64 bit. This laptop will be connected to an external monitor (2), where the stimuli will be presented to the user. For the eye-tracker the Eyelink-1000 will be used (SR Research Ltd., Mississauga, Ontario, Canada), consisting of a high-speed infrared camera and the related illuminator (3), positioned just below the Display Monitor. The eye-tracker host computer (1) is to acquire eye-head information via the camera and process them in real time. The two computers will be connected by Ethernet, for fast communications in order to synchronize the different acquisitions performed by the BCI and the eye-tracking. This will allow us to extract interesting features from combined use of both technologies, e.g. the screen eye-gaze patterns during the BCI tests.

On the Display PC a suitable custom software, developed within the project, will provide information of the general management of the eBrain tests and the sequence of the stimuli for the eye-tracking tests, while for the BCI, we will use an adapted version of the widespread used BCI2000 (http://www.bci2000.org/BCI2000/Home.html).

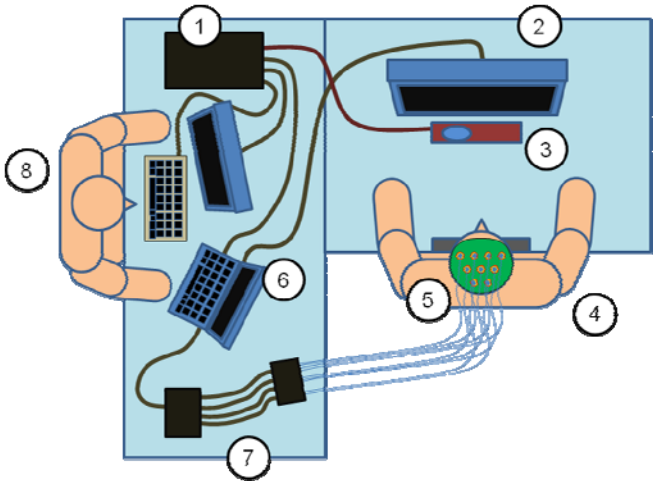

Figure 1. Setup Example: (1) Eye-tracker Host Computer, (2) Eye-tracker Display Monitor, (3) Eye-tracker sensing device, (4) User, (5) EEG Head Cuff, (6) Display PC, (7) EEG Amplifier, (8) Operator

VI. Conclusions and Future Work

Since no studies have been performed so far to evaluate BCI and the eye-tracking system for AAC and cognitive assessment in ALS, we aim to provide evidence for the specific value of these techniques. In addition, the BCI/computerized assessment of ALS patients could provide new insight into the understanding of cognitive deficits in ALS, as a result of the integration of multidisciplinary data (above all neurophysiological, neuropsychological, behavioural and psychological).

The proposed study is characterized by the presence of several innovative aspects: (1) Comparison between two promising technologies, one extensively investigated (ET), the other a very promising candidate (P300 BCI), (2) realization of a computerized cognitive battery, aiming at the neuropsychological assessment of higher order cognitive functions in ALS patients and (3) synergic evaluation of clinical, experimental and laboratory data will provide a more comprehensive perspective about the disease.

Finally, these results will have implications for both clinical practice (the availability of an effective tool for neuropsychological evaluation of ALS patients) and ethical issues, the last arising from the importance of cognitive ability preservation with regard to taking end-life decisions.

References

[1] Phukan J, Pender NP, Hardiman O. (2007). Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol, 6(11):994-1003.

[2] Kübler A, Birbaumer N. (2008). Brain-Computer interfaces and communication in paralysis: extinction of goal directed thinking in completely paralysed patients? Clinical Neurophysiology, 119:2658-2666.

[3] Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grisé D, Goldstein LH. (2000). Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). Neuropsychologia, 38(6):734-47.

[4] Bak TH, Hodges JR. (2001). Motor neurone disease, dementia and aphasia: coincidence, co-occurrence or continuum? J Neurol, 248(4):260-70.

[5] Strong MJ, Lomen-Hoerth C, Caselli RJ, et al. (2003). Cognitive impeirment, frontotemporal dementia, and the motor neuron diseases. Ann Neurol, 54:S20-23.

[6] 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. (2009). Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler, 10(3):131-46.

[7] Zago S, Poletti B, Morelli C, Doretti A, Silani V. (2011). Amyotrophic lateral sclerosis and frontotemporal dementia (ALS_FTD). Archives Italiennes de Biologie, 149: 39-56.

[8] Kübler A, Birbaumer N. (2008). Brain-Computer interfaces and communication in paralysis: extinction of goal directed thinking in completely paralysed patients? Clinical Neurophysiology,119:2658-2666.

[9] Anastasia A, Urbina S. (1997). Psychological testing. Upper Saddle River, NJ: Prentice Hall.

[10] Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. (2002). Brain–computer interfaces for communication and control. Clinical Neurophysiology, 113:767–791.

[11] Iversen IH, Ghanayim N, Kübler A, et al. (2008). A brain-computer interface tool to assess cognitive functions in completely paralyzed patients with amyotrophic lateral sclerosis. Clinical Neurophysiology, 119:2214-2223.

[12] Iversen IH, Ghanayim N, Kübler A, et al. (2008). Conditional associative learning examined in a paralyzed patient with amyotrophic lateral sclerosis using brain-computer interface technology. Behavioral and brain functions, 4(53).

[13] Donaghy C, Pinnock R, Abrahams S, Cardwell C, Hardimann O, Patterson V, McGivern RC, Gibson JM. (2010). Slow saccades in bulbar-onset motor neurone disease. J Neurol, 257:1134–1140.

[14] Averbuch-Heller L, Helmchen C, Horn AK, Leigh RJ, Büttner-Ennerver JA. (1998) Slow vertical saccades in motor neuron disease: correlation of structure and function. Ann Neurol, 44(4):641-8.

[15] Okuda B, Yamamoto T, Yamasaki M, Maya K, Imai T. (1992). Motor neuron disease with slow eye movements and vertical gaze palsy. Acta Neurol Scand, 85:71–76.

[16] Marti-Fabregas J, Roig C. (1993). Oculomotor abnormalities in motor neuron disease. J Neurol, 240:475–478.

[17] Abel LA, Williams IM, Gibson KL, Levi L. (1995). Effects of stimulus velocity and acceleration on smooth pursuit in motor neuron disease. J Neurol, 242:419–424.

[18] Leveille A, Kiernan J, Goodwin JA, Antel J. (1982). Eye movements in amyotrophic lateral sclerosis. Arch Neurol, 39:684–686.

[19] Ohki M, Kanayama R, Nakamura T, Okuyama T, Kimura Y, Koike Y. (1994). Ocular abnormalities in amyotrophic lateral sclerosis. Acta Otolaryngol Suppl, 511:138–142.

[20] Jacobs L, Bozian D, Heffner RR Jr, Barron SA. (1981). An eye movement disorder in amyotrophic lateral sclerosis. Neurology, 31:1282–1287.

[21] Shaunak S, Orrell RW, O'Sullivan E, Hawken MB, Lane RJ, Henderson L, Kennard C. (1995). Oculomotor function in amyotrophic lateral sclerosis: evidence for frontal impairment. Ann Neurol, 38:38–44.

[22] Evdokimidis I, Constantinidis TS, Gourtzelidis P, Smyrnis N, Zalonis I, Zis PV, Andreadou E, Papageorgiou C. (2002). Frontal lobe dysfunction in amyotrophic lateral sclerosis. Journal of the Neurological Sciences, 195:25– 33.

[23] Donaghy C, Pinnock R, Abrahams S, Cardwell C, Hardiman O, Patterson V, McGivern RC, Gibson JM. (2009). Ocular fixation instabilities in motor neurone disease. A marker of frontal lobe dysfunction? J Neurol, 256(3):420-6.

[24] Fabiani M, Gratton G, Karis D, Donchin E. (1987). Definition, identification and reliability of the P300 component of the event-related brain potential. Ackles, P.K., Jennings, J.R., Coles, M.G.H. (Eds.). Advances in psychophysiology, 2. New York, NY: JAI Press, 1-78.

[25] Sellers EW, Donchin E. (2006). A P300-based brain–computer interface: Initial tests by ALS patients. Clin Neurophysiol,117:538-548.

[26] Sellers EW, Kübler A, Donchin E. (2006). Brain-computer interface research at the University of South Florida Cognitive Psychophysiology Laboratory: the P300. Speller. IEEE Trans Neural Syst Rehabil Eng, 14(2):221-4.

[27] Dickhaus T, Sannelli C, Muller KR, Curio G, Blankertz B. (2009). Predicting BCI performance to study BCI illiteracy. BMC Neuroscience, 10.

[28] 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. (2008). A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. Clin Neurophysiol, 119(8):1909-16.

[29] Paulus KS, Magnano I, Piras MR, et al. (2002). Visual and auditory event-related potentials in sporadic amyotrophic lateral sclerosis. Clin Neurophysiol, 113:853–61.

[30] Hanagasi HA, Gurvit IH, Ermutlu N, et al. (2002). Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials. Cognitive Brain Research, 14:234-244.

[31] Gil R, Neau JP, Dary-Auriol M, et al. (1995). Event-related auditory evoked potentials and amyotrophic lateral sclerosis. Arch Neurol, 52: 890-896.

[32] Ogawa T, Tanaka H, Hirata K. (2009). Cognitive deficits in amyotrophic lateral sclerosis evaluated by event-related potentials. Clinical Neurophysiology, 120:659-664.

[33] Schreiber H, Gaigalat T, Wiedemuth-Catrinescu U, Graf M, Uttner I, Muche R, Ludolph AC. (2005). Cognitive function in bulbar- and spinal-onset amyotrophic lateral sclerosis. A longitudinal study in 52 patients. J Neurol, 252(7):772-81.

[34] Kübler A, Kotchoubey B, Kaiser J, et al. (2001). Brain-Computer Communication: unlocking the locked in. Psychological Bullettin, 127(3): 358-375.

[35] Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. (2000). El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord, 1(5):293-9.