Video Article

Eye-Tracking Control to Assess Cognitive Functions in Patients with Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder with pathological involvement of upper and lower motoneurons, subsequently leading to progressive loss of motor and speech abilities. In addition, cognitive functions are impaired in a subset of patients. To evaluate these potential deficits in severely physically impaired ALS patients, eye-tracking is a promising means to conduct cognitive tests. The present article focuses on how eye movements, an indirect means of communication for physically disabled patients, can be utilized to allow for detailed neuropsychological assessment. The requirements, in terms of oculomotor parameters that have to be met for sufficient eye-tracking in ALS patients are presented. The properties of stimuli, including type of neuropsychological tests and style of presentation, best suited to successfully assess cognitive functioning, are also described. Furthermore, recommendations regarding procedural requirements are provided. Overall, this methodology provides a reliable, easy to administer and fast approach for assessing cognitive deficits in patients who are unable to speak or write such as patients with severe ALS. The only confounding factor might be deficits in voluntary eye movement control in a subset of ALS patients.

Video Link

The video component of this article can be found at https://www.jove.com/video/54634/

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder usually leading to death within 3 to 5 years. In the course of the pathology, patients present with progressive loss of respiratory and bulbar functioning as well as impairments in movement abilities[1]. It shares some clinical, pathological, and genetic features with frontotemporal dementia[2] and it is well documented that about 30% of ALS patients exhibit cognitive deficits[3]. These deficits are most prominent in the domains of executive function, verbal fluency and language[4] and have an influence on survival[5], compliance[6] and carer burden[7]. Thus, reliable neuropsychological assessment is crucial in this disease.

Advancing impairments in motor and speech abilities are, however, a limiting factor for thorough evaluation of cognitive abilities in later stages of the disease[8]. Here, oculomotor based approaches seem to be very promising, as basic eye movement control remains intact for a comparably long time during the course of ALS for the majority of patients[9]. Eye-tracking parameters itself have been used to gain information about the cognitive status of patients with ALS[10] and also correlate with the sequential spreading pattern of ALS[11]. Eye movement as a means to control cognitive tests in the context of ALS has also been studied in previous works. One study has successfully demonstrated its usability in healthy controls using an oculomotor based version of the Trail-Making Test[12], whereas another found it suitable to distinguish between healthy controls and ALS patients based on cognitive performance and to discriminate between cognitively more and less impaired patients[13].

The research described here used an oculomotor based methodology to study cognitive impairments in ALS patients, specifically in the domain of executive functioning. Two well validated and commonly used neuropsychological tests were adapted to eye movement control: the Raven's coloured progressive matrices (CPM)[14] and the D2-test[15]. The CPM is a non-verbal instrument used to measure executive and visuospatial abilities as well as fluid intelligence. The D2-test is also a non-verbal tool used to uncover executive dysfunction in the domains of selective and sustained attention and visual processing speed. Both are widely used clinical tools which have been successfully employed in previous studies assessing potential cognitive decline during the course of the disease[16] and the neuropsychological status of ALS patients compared to healthy controls[17].

The goal of this work was to show the requirements for successful evaluation of cognitive deficits in ALS independent of movement and speech disabilities using a reliable, eye-tracking based version of the CPM and the D2-test. Importantly, the method described here has the potential to be expanded to study other populations of patients with severe motor impairments.

Protocol

The study was approved by the Ethics Committee of the University of Ulm (Statement No. 19/12) and the protocol described therefore follows their guidelines. All participants gave written informed consent.

1. Stimuli and Testing Environment

1. To keep distractions to a minimum perform the research in a dark or a very dimly lit and quiet room.
2. Use an appropriate eye tracking device.
   NOTE: There are a wide variety of devices available to perform eye movement studies. In the present research a portable eye movement recording device with goggles was used, which synchronously measure binocular eye positions, using two integrated cameras with an infrared light emitting diode (IR LEDs), one for each eye[18].
   1. To ensure optimal eye-tracking, adjust the cameras manually by tilting them in all 6 degrees of freedom (3 translational, 3 rotational) until eye movement detection is optimal.
      NOTE: The measurements of the system are displayed in real-time on an experimenter's screen to monitor recording quality and participants' response behavior. The key features of the system are described below and detailed specifications are given in **Table 1**.
3. Implement a standardized oculomotor testing paradigm, which is able to detect deficits in eye movement control.
   NOTE: This can be a series of tasks like smooth pursuit or saccade tasks, in which participants with impaired eye movement control perform badly (*e.g.,* the methods described by Gorges *et al.* 2015[11]). These participants have to be excluded from further testing.
4. Present tasks using appropriate software that projects the stimuli on a hemi-cylindrical screen via a projector mounted above the subject's head[11]. Additionally, ensure that a red laser spot (diameter: 0.3°, position: 10° vertical) is present for the D2-test.
5. Seat the participants on an elevated chair with an adjustable chin rest, so that eye-to-screen distance is approximately 150 cm.
6. Use set A and B of the CPM (12 stimuli for each set) for the first part of the experiment. Show these stimuli as 22° long/15° high matrices with six possible alternatives depicted below, which might fit in a 6° wide and 5° high blank space cut out from the matrix.
7. For the D2-test, use the five blocks with 47 stimuli, corresponding to line 2 - 6 of the standard D2-test[15], and depict them one stimulus after another in the middle of the screen with a height of 11° and a width of 2.5°. Make sure each stimulus lasts for 2,000 msec.

2. Running the Experiment

1. Before the experiment starts, ask participants to fill out a written informed consent form to ensure the study is in accordance with ethical standards.
2. Give general instructions concerning the purpose and procedure of the experiment and control for CNS-active drugs, *i.e.,* ask the participant if he/she is currently taking any medication which affects alertness and therefore cognitive performance.
3. Turn off all devices which might be a potential disturbance, such as mobile phones or pagers.
4. Seat participants comfortably with the chin rest in optimal position. Ensure that the whole screen is visible and ask the participant to maintain posture during the whole experiment.
5. Ask participants to place their head on the chin rest and place the videooculography goggles onto their head. Adjust them to individual head size/shape.
   NOTE: Thereby, the best possible compromise between comfort for the participant and minimal risk of unwanted slipping during measurement must be made.
6. Make sure that both eyes are visible on the experimenter's screen, where the images of the two eye movement recording cameras within the goggles are displayed and then focus the cameras to center the images on the screen.
   NOTE: This is important for optimal detection and tracking of the pupil as an improper acuity can lead to a disturbed signal.
7. To ensure continuous recording of eye movements at all times, start calibration of the system by instructing the participant to look in each corner of the hemi-cylindrical screen. In case the signal is lost, change the angle of the camera tracking the respective pupil of the eye to resolve the problem.
8. Start the standardized oculomotor testing paradigm described above and exclude all patients with substantial visual impairments as these will cause corrupted task performance.
9. Instruct the participant to track a single spot on the screen, oscillating horizontally (± 20°) and then vertically (± 15°) with a frequency of 0.125 Hz to map the non-calibrated orthogonalized 'raw' data from the eye movement recording device with respect to the 'true' orthogonalized eye position for calibration of the system.
10. Check if calibration is acceptable, *i.e.,* if the 'true' eye movement and the 'raw' data are spatially and temporally synchronized and then instruct the participant to not move the head as this might result in bad data quality.
    NOTE: Position of the videooculography device and the subject is expected to be stationary during the course of the experiment, so that there is no need for re-calibration.
11. Explain the procedure of the training session for the CPM:
    1. Instruct the subjects to identify the missing pieces below the upcoming matrices displayed on the hemi-cylindrical screen for which they have infinite time. After making a choice, have the subject close their eyes for at least 250 msec to start off a green frame outlining all of the possible alternatives of missing pieces for 1,500 msec each.
    2. Have the participant choose the alternative they think is correct by closing their eyes for at least 250 msec while their choice is enframed.
    3. Project the choice separately on the hemi-cylindrical screen. Ask the participants to confirm. If the participant confirms, instruct them to close their eyes again for at least 250 msec.
    4. Instruct the participants that the next stimulus (matrix with 6 alternatives of missing pieces) will automatically (again, presented by the software described in step 2) appear and that this will be done four times with training stimuli taken from set AB of the CPM[14].

12. Answer any questions subjects might have about the procedure. Then, instruct the participants to choose the missing piece of the matrix, as they have learned during the training session and start the CPM (**Figure 1**).
13. Explain the procedure of the training session for the D2-test:
    1. Instruct participants to direct their gaze to the center of the screen and observe 47 stimuli separately (47 d's corresponding to line 1 of the standard D2-test).
    2. Instruct the participants to look at the red laser spot positioned above the stimuli whenever a "d" with two dashes is presented until the next stimulus appears. NOTE: If no target stimulus is presented the gaze needs to be focused at the center of the screen where the next stimulus will be presented.
14. Answer any questions subjects might have about the procedure. Then, instruct the participant to proceed for the following five blocks of 47 stimuli, similar to the training session and start the D2-test.
15. For quality control, inspect the data obtained from each session for each subject carefully (visually by a trained experimenter). Check if data quality is corrupted, for example due to technical difficulties, corrupted eye movements or misunderstandings.
16. Thank subjects for their participation and answer all questions during the experiment.

Representative Results

For the purpose of the research presented here, *i.e.,* the development of a reliable oculomotor based neuropsychological assessment for ALS patients, in-house developed software stores the subject's choices of the CPM in a separate file, allowing for manual computation of the percentage of correct answers. For the D2-test, a record of the vertical eye movements is manually analyzed using a threshold of + 5° for detection of a relevant response. Recordings are assigned to each stimulus presentation and percentage of correct answers can subsequently be computed. There are many options available of how data can be analyzed, either based on visual inspection of the eye movements or fully computerized, depending on the neuropsychological tasks used.

Figure 2 shows the good congruency between the oculomotor and the standard version (*i.e.,* applied according to standard protocol using paper versions to be marked with a pencil) of the CPM, in a sample of ALS patients ($R^2 = 0.712$; $p = 0.001$). **Figure 3** depicts the results from a comparison between cognitively more and less impaired ALS patients, indicating statistically significant group differences in the CPM ($p < 0.001$) and the D2-test ($p = 0.024$)[13]. This further confirms the usability of this technique as it reliably distinguishes between more and less cognitively impaired ALS patients.

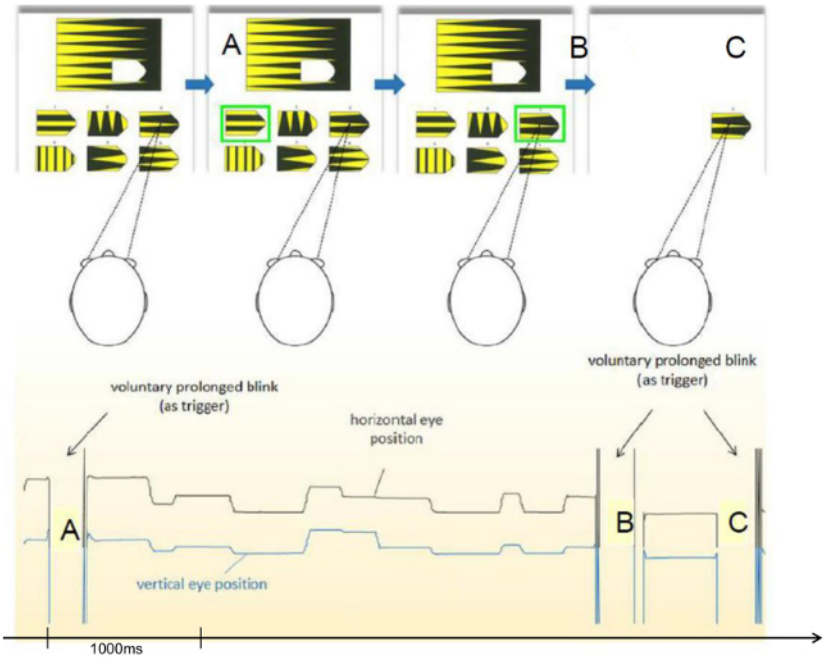


Figure 1. Illustration of Eye-tracking Based CPM. Example of the CPM selection procedure as displayed on the participants screen (upper panel) with its corresponding traces of horizontal (upper line) and vertical (lower line) eye positions (lower panel); a scale bar indicating time is given on the bottom of the Figure. When the subject has mentally decided for a choice, movement of a green frame along the presented alternatives of missing pieces which is triggered by a prolonged blink of the subject **(A)**. Selection of one alternative of a missing piece is performed by another prolonged blink of the subject **(B)**. Subsequently, presentation of subject's choice appears separately and confirmation of the choice is done via closing the subject's eyes for at least 250 msec **(C)**. Modified from Keller *et al.* 2015[13]. Please click here to view a larger version of this figure.

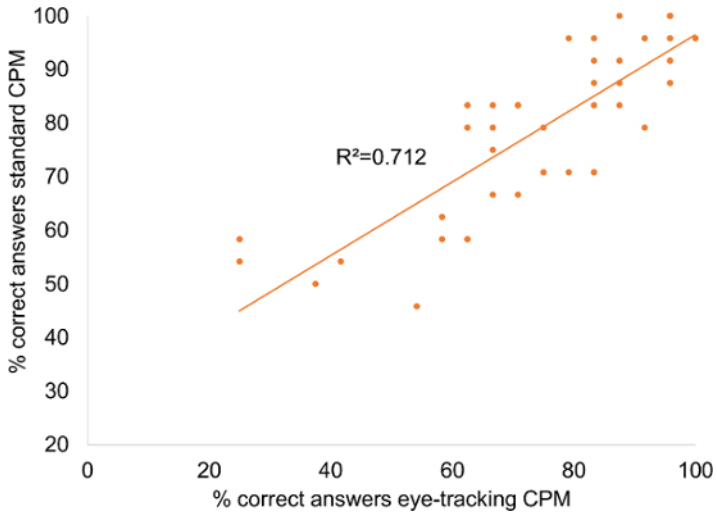
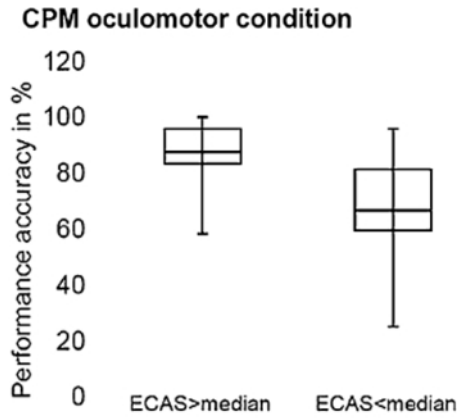


Figure 2:. Congruency between Oculomotor and Standard Version of the CPM. Correlation between results from the standard and the oculomotor condition of the CPM. Given is the percentage of correct answers in the oculomotor (x-axis) and the standard paper-pencil (y-axis) condition of the CPM in ALS patients ($R^2 = 0.712$; $p = 0.001$). Please click here to view a larger version of this figure.



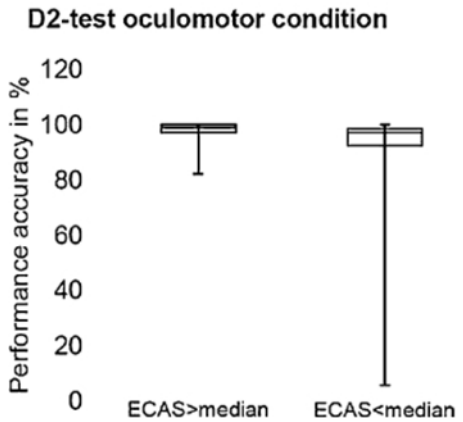


Figure 3. Comparison Between More and Less Cognitively Impaired Patients. Subjects were divided into more and less cognitively impaired according to a median split on their results in the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)[19], a standard tool for neuropsychological assessment in ALS patients. Shown are boxplots depicting the percentage of correct answers in the eye-tracking versions of the CPM and the D2-test for both groups. The error bars indicate the highest and lowest percentage scored. Modified from Keller *et al.* 2015[13]. Please click here to view a larger version of this figure.

PARAMETER	VALUE
Cameras	2
IR LED Wavelength	> 850 nm
Total Head Mount Weight	60 g
Sampling Rate	220 Hz
Spatial Resolution	0.05° - 0.1°
Noise Level	0.015°
Accuracy	1°
Distance Camera-Eye	~ 50 mm

Table 1: Specifications of the Videooculography System. Important parameters and their respective values of the system used.

Discussion

It is a challenging task to successfully assess the cognitive status of patients with ALS who are unable to speak and write. The use of videooculography systems provides a promising approach. The hereby presented technique is reliable in detecting cognitive deficits, which play a pivotal role in the context of carer burden and disease management[20] in ALS patients. Also, the oculomotor versions of the CPM and the D2-test correlate significantly with their respective standard paper-pencil versions, but further support is needed to claim the usefulness in a clinical context.

The researcher needs to make sure that eye movement recordings are as noise free as possible to allow for sufficient data quality. Therefore, it is important for researchers to select an eye movement recording device with an appropriate sampling rate. Usually, sampling rates range between 50 Hz and 1,000 Hz. In general, the more subtle oculomotor measurements are required for the task, the higher temporal resolution needs to be used. It needs to be yielded that higher sampling rates usually require a larger restriction of head movement. Also, to allow for a higher sampling rate, researchers may record the movement of just one eye. Another important parameter is spatial accuracy, which is expressed in degrees of visual angle and in this work is 0.05° - 0.1°, depending on pupil size. Again, the higher the demands on visual accuracy in the task the better spatial resolution needs to be. Furthermore, a major issue in quality of the obtained oculomotor data is head movement, which has to be restricted to a tolerable minimum. Most eye-tracking studies use a chin rest and/or a head mounted device. If possible, combine both options as this restricts head movement and its accompanying confounds most. However, this is not possible in all patients, *e.g.*, patients with very serious physical impairments, and might then be altered according to the subject's capacities. It should also be noted that newer devices, which calculate the eye position via a small stationary camera placed in front of the subject underneath the screen on which stimuli are presented, do not require goggles or a chin rest, while also sufficiently correcting for head movements.

The cognitive tests are interchangeable with other standard neuropsychological tests, depending on the cognitive domain one is interested in. To use other tests in ALS patients, they just need to be adapted to a format in which answers can be given using eye movements. Especially given the rapid technological advance in the field of eye-tracking, further increasing acuity, flexibility and handiness, this methodology might also be suited for a large variety of cognitive research questions in different clinical samples.

Some patients might be too impaired in their cognitive abilities to correctly understand the instructions of the tasks used in this study. One other serious limitation for the use of eye-tracking technologies in ALS patients are potential oculomotor abnormalities, or even complete loss of eye movement control, previously reported in patients with the disease[21,22]. These abnormalities are very subtle in early stages of the disease and sequentially impact more basic oculomotor functions in the progress of ALS pathology[11].

The protocol presented here is therefore only suited for those ALS patients unable to speak and write but still able to control their eye movements. This however encompasses a comparably large group, for which reliable information about cognitive status is crucial[23]. For patients with no satisfactory eye movement control or ability to blink, this protocol is not suited. However, another hand and speech-motor free way to assess cognitive function in these cases is brain-computer interface control, as has been done in recent work[24].

The technique presented here is fast, easy to administer, user-friendly and potentially allows clinicians and researchers to perform neuropsychological assessments with patients who are severely physically impaired and therefore not able to undergo paper-pencil based testing anymore, such as - but not necessarily limited to - patients with ALS, using an eye-tracking device.

It provides an opportunity to gain information about potential cognitive deficits in patients with complete paralysis, *i.e.*, information which then plays a critical role in the context of life prolonging therapeutic treatments and end-of-life decision making in ALS[6,25].

In the future, mobile devices with high acuity and head movement tolerability which can be handled more flexibly might be used to comfortably assess cognition in immobile patients at their bedside, eliminating the need for a special testing environment. Also, the use of other, possibly more sophisticated eye-tracking controlled experimental procedures is needed to assess more subtle cognitive deficits in severely impaired patients.

Disclosures

The authors declare that they have no competing financial interests.

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References

1. Kiernan, M.C., *et al.* Amyotrophic lateral sclerosis. *Lancet.* **377** (9769), 942-955 (2011).
2. Neumann, M., *et al.* Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science.* **314** (5796), 130-133 (2006).
3. Beeldman, E., Raaphorst, J., Klein Twennaar, M., de Visser, M., Schmand, B.A., de Haan, R.J. The cognitive profile of ALS: a systematic review and meta-analysis update. *J. Neurol. Neurosurg. Psychiatry.* pii:jnnp-2015-310734 (2015).
4. Phukan, J., *et al.* The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *J. Neurol. Neurosurg. Psychiatry.* **83** (1), 102-108 (2012).
5. Elamin, M., *et al.* Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. *Neurology.* **76** (14), 1263-1269 (2011).
6. Martin, N.A., *et al.* Psychological as well as illness factors influence acceptance of non-invasive ventilation (NIV) and gastrostomy in amyotrophic lateral sclerosis (ALS): a prospective population study. *Amyotroph. Lateral. Scler. Frontotemporal. Degener.* **15** (5-6), 376-387 (2014).
7. Chiò, A., *et al*. Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life. *Eur. J. Neurol.* **17** (10), 1298-1303 (2010).
8. Lakerveld, J., Kotchoubey, B., Kübler, A. Cognitive function in patients with late stage amyotrophic lateral sclerosis. *J. Neurol. Neurosurg. Psychiatry.* **79** (1), 25-29 (2008).
9. Sharma, R., Hicks, S., Berna, C.M., Kennard, C., Talbot, K., Turner, M.R. Oculomotor dysfunction in amyotrophic lateral sclerosis: a comprehensive review. *Arch. Neurol.* **68** (7), 857-861 (2011).
10. Witiuk, K., Fernandez-Ruiz, J., McKee, R. Cognitive Deterioration and Functional Compensation in ALS Measured with fMRI Using an InhibitoryTask. *J. Neurosci.* **34** (43), 14260-14271 (2014).
11. Gorges, M., *et al.* Eye Movement Deficits Are Consistent with a Staging Model of pTDP-43 Pathology in Amyotrophic Lateral Sclerosis. *PLoS One.* **10** (11), e0142546 (2015).
12. Hicks, S.L., *et al.* An eye-tracking version of the trail-making test. *PLoS One.* **8**(12), e84061 (2013).
13. Keller, J., *et al.* Eye-tracking controlled cognitive function tests in patients with amyotrophic lateral sclerosis: a controlled proof-of-principle study. *J. Neurol.* **262** (8), 1918-1926 (2015).
14. Raven, J.C., Court, J.H., Raven, J. *Manual for Raven's progressive matrices and vocabulary scales.* Section 2, the coloured progressive matrices. Oxford Psychologists Press, Oxford (1998).
15. Brickenkamp, R. *Aufmerksamkeits-Belastungs-Test (Test d2), 8th edn.* Hogrefe, Göttingen (1994).
16. Elamin, M., *et al.* Cognitive changes predict functional decline in ALS. *Neurology.* **80** (17), 1590-1597 (2013).
17. Ludolph, A.C., *et al.* Frontal lobe function in amyotrophic lateral sclerosis: a neuropsychologic and positron emission tomography study. *Acta. Neurol. Scand.* **85** (2), 81-89 (1992).
18. Schneider, E., *et al.* Eye-SeeCam: an eye movement-driven head camera for the examination of natural visual exploration. *Ann. N. Y. Acad. Sci.* **1164**, 461-467 (2009).
19. Lulé, D. et al. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen: a cross-sectional comparison of established screening tools in a German-Swiss population. *Amyotroph. Lateral. Scler. Frontotemporal.* Degener. **16** (1-2), 16-23 (2015).
20. Olney, R.K., *et al.* The effects of executive and behavioral dysfunction in the course of ALS. *Neurology.* **65** (11), 1774-1777 (2005).
21. Donaghy, C., Thurtell, M.J., Pioro, E.P., Gibson, J.M., Leigh, R.J. Eye movements in amyotrophic lateral sclerosis and its mimics: a review with illustrative cases. *J. Neurol. Neurosurg. Psychiatry.* **82** (1), 110-116 (2011).
22. Mizutani, T., *et al.* Development of ophthalmoplegia in amyotrophic lateral sclerosis during long-term use of respirators. *J. Neurol. Sci.* **99** (2-3), 311-319 (1990).
23. Khin Khin, E., Minor D., Holloway, A., Pelleg, A. Decisional Capacity in Amyotrophic Lateral Sclerosis. *J. Am. Acad. Psychiatry Law.* **43** (2), 210-217 (2015).
24. Kübler, A., et al. Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. *Neurology.* **64** (10), 1775-1777 (2005).
25. Connolly, S., Galvin, M., Hardiman, O. End-of-life management in patients with amyotrophic lateral sclerosis. *Lancet Neurol.* **14** (4), 435-442 (2015).

