TITLE

Brain communication in a completely locked-in patient using bedside near- infrared spectroscopy.

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SUPPLEMENT

CONTENT

table e-1

Medical data and time line of the disease development

Diagnosis Amyotrophic lateral sclerosis	May 2007
Artificial ventilation	Since September 2007
Artificial feeding system (percutaneous endoscopic gastrostomy). At this point in time she could still move.	Since October 2007
Use of a home eye tracking communication system	12.2007 until 12.2008
Use of a home sensor based device for book and magazine reading	First months of 2009
Use of a home sensor based system sensitive to minimal head movement to communicate basic needs	2009 until 05.2009
Locked-in-state	05.2009
Completely locked-in state diagnosis	21.05.2010

e-patient

Patient description

When the patient still had eye movements, she communicated with the help of an eye tracking system, which was available at her home. This system enabled the patient to select words or phrases (through blinks) that could be expressed via a voice synthesizer. The patient also used a page turning system based on a sensor to read books and magazines. When neither this, nor the use of the eye tracking system was any longer possible, she communicated basic needs through an alarm system, sensitive to small head movements.
Apart from sporadic hospitalizations the patient lived at her home with the husband and caregivers (not at any care facility).
A medical report from a neurologist dated 21.05.2010 confirmed the completely locked-in state In the completely locked-in state the husband, caregivers, and authors of the paper interacted with the patient.

The husband, the caregivers and the authors believe that the patient is conscious and has awareness. Certainly, we interact with her as such.

e-assessment

Neuropsychological and neurophysiological assessment of the patient

The completely locked-in state has to be defined by the absence of any detectable vertical or horizontal eye movements. Eye movements were measured on several occasions using electrooculography in combination with EEG, electrodes were placed at the outer canthi of the eyes and above and below the eyes. The patient was instructed to move her eyes. These recordings resulted in a straight line (see also video1).

The patient also underwent an electrophysiological assessment which consisted of 4 daily measurements comprising 5 different experimental paradigms as described in Neumann and Kotchoubey.[1] The EEG was recorded using 16 Ag/AgCl electrodes attached at F3, Fz, F4, T7, C3, Cz, C4, T8, Cp3, Cp4, P3, Pz, P4, Po7, Po8, Oz according to the international 10-20 system mounted on a 64-channel cap (Easycap GmbH, Munich, Germany). The electrodes were referenced to an electrode positioned at the top of the nose and grounded to an electrode placed over the left mastoid. The impedances were kept below 5 KΩ throughout all the experiment. The EEG signals were acquired using a multi-channel EEG amplifier (Brain Amp DC, Brain Products, Munich, Germany) and sampled at 500 Hz.

Each session comprised 5 paradigms: mismatch negativity, oddball without instruction, oddball with instruction, word pairs and semantically incongruent and congruent sentences. All the paradigms were based on the presentation of auditory stimuli through pneumatic earphones inserted in the patient's ears. Mismatch negativity consisted of 1000 stimuli (100 deviants, 900 standards) with an inter-stimulus interval of 400 ms. The deviants and the standards had a duration of 30 ms and 70 ms, respectively. The auditory oddball paradigm comprised the presentation of 360 stimuli (60 deviants, 300 standards), the inter-stimulus interval was set to 900 ms and all the tones had a duration of 100 ms. Two auditory oddball paradigms were performed and only before the second one the patient was instructed to pay attention to the deviants (e.g. to count the deviants). In the word pairs paradigm, 100 pairs of words were presented, 50 of which consisted of two highly related words (e.g. sun-moon) and 50 consisted of two semantically unrelated words (e.g. dog-moon). Similarly, the sentence paradigm comprised 100 sentences, 50 of which end with a semantically congruent word and the remaining 50 sentences end with a semantically incongruent word. From the second session the sentence paradigm was repeated three times within each daily session in order to increase the number of trials recorded.

figure e-1

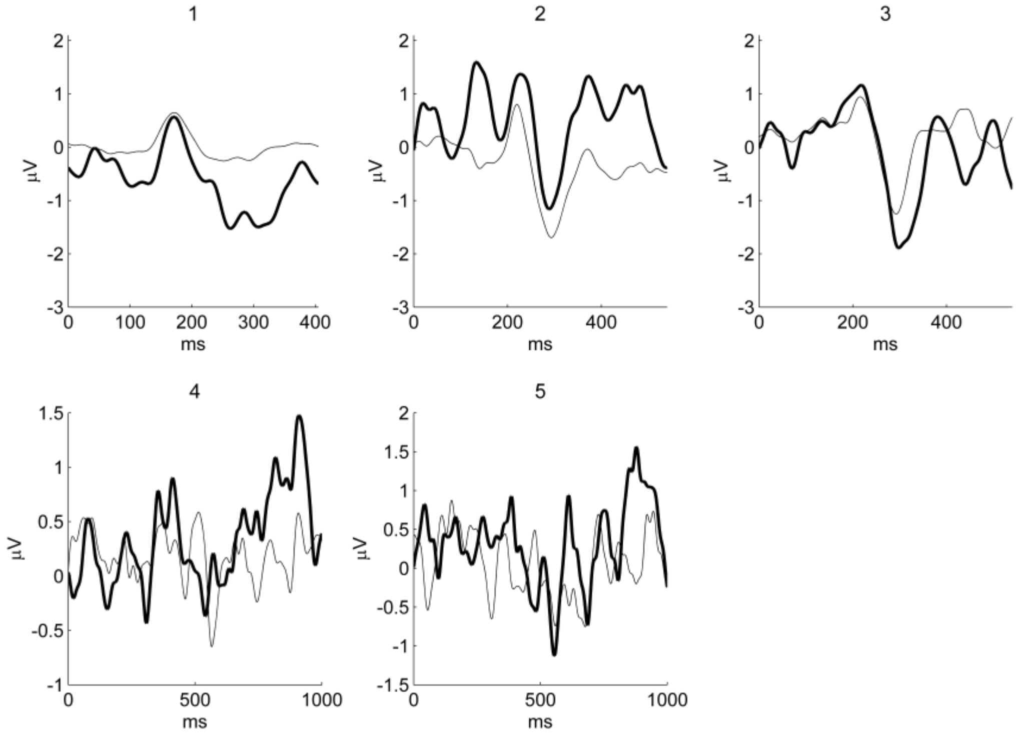

figure e-1: Cognitive event-related potentials (ERP) of the patient
Average event-related potentials (across all four daily measurements) for the patient during the electrophysiological assessment (channel Pz).
1: Mismatch negativity. Bold line: deviants (400 trials); thin line: standards (3203 trials).
2: Auditory oddball without instructions. Bold line: deviants (240 trials); thin line: standards (969 trials).
3: Auditory oddball with instructions. Bold line: deviants (240 trials); thin line: standards (968 trials).
4: Sentences, ERP to the last word. Bold line: semantically related words (475 trials); thin line: unrelated words (475 trials).
5: word pairs, ERP to the second word. Bold line: semantically related words (200 trials); thin line: unrelated words (200 trials). The differences found between the two different cognitive conditions investigated in each paradigm indicated intact cognitive processing this patient.

Reference:

1 Neumann N, Kotchoubey B. Assessment of cognitive functions in severely paralysed and severely brain-damaged patients: neuropsychological and electrophysiological methods. Brain Res Brain Res Protoc 2004;14:25-36.

e-SVM

Description of the Support Vector Machine classification method

We used support vector machines[1,2] to classify changes in deoxyhemogloblin concentrations from the intersentence intervals as corresponding to the patterns of either true or false sentences.

The training data for the classifier consisted of an initial subset of 300 sentences (150 true, and 150 false sentences). The parameters of several models were learned from different subsets of data (with at least 100 sentences), based on radial basis functions and sigmoid kernels. Models were validated on an additional subset of 6 sessions, and the model with the highest performance was selected for the future online sessions with feedback.

For learning and validation of models we used LibSVM, freely available online.[3]

References:

1 Vapnik V. The Nature of Statistical Learning Theory. New York: Springer-Verlag; 1995.

2 Rasmussen C, Williams C. Gaussian Processes for Machine Learning, MIT Press; 2006. ISBN-10 0-262-18253-X

3 Chang CC, Lin C-J. LIBSVM: a library for support vector machines. ACM Transactions on Intelligent Systems and Technology, 2:27:1-27:27, 2011. Software available at www.csie.ntu.edu.tw/~cjlin/libsvm. Version 3.17, April 2013. Accessed November 07, 2013.

figure e-2

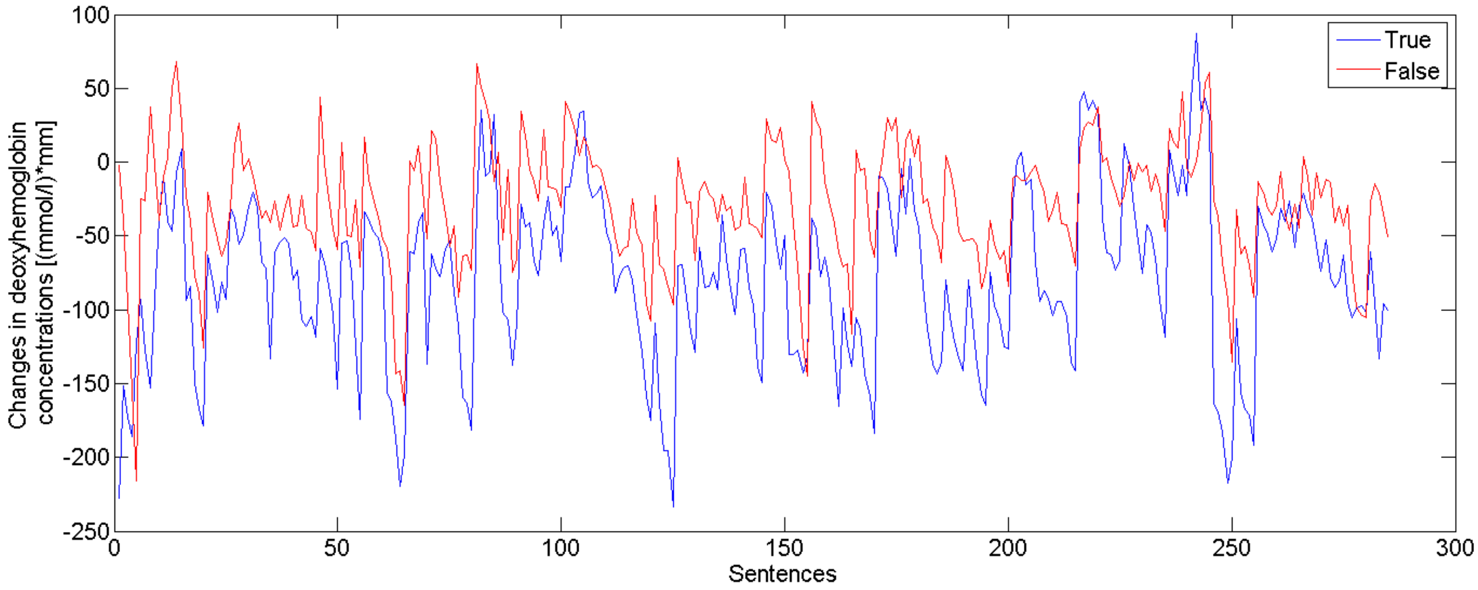

figure e-2. Changes in Deoxyhemoglobin concentrations for 570 sentences (285 true and 285 false).

This figure depicts the difference in the change of the deoxyhemoglobin concentration between the true and false sentences for all sentences used in the third period. This included 300 questions to train the classifier and 270 questions used in the test phase with feedback to the patient. Note that the NIRS signal of the patient was comparable to that of the healthy controls we have previously tested.[1] The sentences with known answers used to train the classifier and the sentences with known answers used to train the patient were identical. It is therefore not possible to depict a response of the patient to new, not previously trained sentences with known answers.

1 Sitaram R, Zhang H, Guan C, et al. Temporal classification of multichannel near-infrared spectroscopy signals of motor imagery for developing a brain-computer interface. Neuroimage 2007;34:1416-1427.

table e-2

Percentage of correctly classified answers in the yes and no condition (Period 3). Note that 135 sentences were true and 135 sentences were false.

	"Yes" (%) (N=135)	**"No" (%) (N= 135)**	**Sum**
Correctly classified	93 (80.9)	113 (72.9)	206
Falsely classified	22 (19.1)	42 (27.1)	64
Sum	115 (100)	155 (100)	270

e-replication

Classification performance of sessions 8 and 12 of period 3.

Sessions 8 and 12 took place separated by 11 days. Both contained the following sentences with known answers. The online classification procedure with feedback given to the patient resulted in 100% performance.

False sentences:	**Answer from the classifier** (on both days)
Dein Geburtsjahr ist 1975. You were born in 1975.	False
Lotti ist die Mutter von Rene Lotti is Rene´s mother.	False
Birgit ist Svenjas Tante. Birgit is Svenja´s aunt.	False
Rene ist dein Enkel. Rene is your grandson.	False
Svenja ist deine Tante Svenja is your aunt.	False
True sentences:	
Das Wort casa heißt auf Deutsch Haus. The word casa means Haus in German.	True

Dein Vater heißt Emil. Your father´s name is Emil.	True
Lotti heißt meine Mutter Lotti is my mother‘s name.	True
Du hast 6 Enkelkinder. You have 6 grandchildren.	True
Du hast 3 Kinder. You have 3 children.	True
PERFORMANCE	100%

Classification performances of sessions 28 and 29.

Sessions 28 and 29 also took place separated by 11 days, and both contained the following open questions. The online classification procedure with feedback given to the patient resulted in the following results, and was confirmed with 100% agreement from the husband.

Open sentences:	**Answer from the classifier** (on both days)
Ein Sonnenuntergang ist hässlich A sunset is ugly.	False

Würde es Dir gefallen, noch einmal in die Dominikanische Republik zu fahren? Would you like to travel again to the Dominican Republic?	False
Dir schmeckt Eiscreme nicht. You do not enjoy ice cream.	False
Möchtest du möglichst jeden Abend fernsehen? Would you like to watch TV every evening?	False
Du spürst den Herzschlag. You can feel the heart beat.	False
Kannst du bei offenen Augen alles sehen? Can you see everything when your eyes are open?	False
Du möchtest im Sommer nach Spanien zu Birgit. You would like to visit Birgit in Spain during the summer.	False
Möchtest du nachts öfters gelagert werden? Would you like to be turned more often during the night?	True
Hast du Schmerzen? Are you in pain?	True
Möchtest du öfters Eis essen? Would you like to eat ice cream more often?	True