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# High cognitive function of an ALS patient in the totally locked-in state

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**Abstract**

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease characterized by progressive degeneration of upper and lower motor neurons. Patients with ALS progressively lose their ability to control voluntary movements and occasionally enter the totally locked-in state (TLS), in which they cannot move any part of their bodies including the eyes. In this study, we clarified the preserved abilities and reorganization of the motor system of a 73-year-old patient with ALS in the TLS using optical topography, a recently developed extension of near-infrared spectroscopy. The patient performed four cognitive tasks: dichotic listening, covert singing, word fluency, and motor imagery. The bilateral prefrontal and bilateral sensorimotor areas were activated during the two language-related tasks (dichotic listening task and the word fluency), the right prefrontal and sensorimotor areas during the covert singing task, and the right prefrontal and dorsal sensorimotor areas during the motor imagery task. Contralateral sensorimotor activation was not observed in the motor imagery task. These results suggest that cognitive functions can be preserved in ALS in the TLS, with sensorimotor areas playing an important role.


*Keywords:* Amyotrophic lateral sclerosis; Totally locked-in state; Cognitive function; Reorganization; Optical topography

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease characterized by progressive degeneration of upper and lower motor neurons. Patients with ALS progressively lose their ability to control voluntary movements and occasionally enter the totally locked-in state (TLS), in which they cannot move any part of their bodies including the eyes [9]. Consequently, patients with ALS in the TLS are impaired, and can be completely impaired in expressing their intentions.

It is well known that even non-demented patients with ALS show cognitive dysfunction resulting from frontal and temporal lobe abnormalities [1,2]. Without any visible reactions, it is not clear whether cognitive function is preserved in patients with ALS in the TLS. Although a previous report showed that cognitive function was preserved in such patients, as measured by event-related brain potentials [13], suspicion remains that acoustic stimuli could automatically trigger the pattern of activation observed in each task. Therefore, it is important to clarify the long-persisting temporal changes of activation.

It is also important to clarify the patterns of activation in patients with ALS in the TLS during cognitive tasks. Previous reports have documented reorganization of motor areas in patients with ALS [11,18,21]. In this study, we used optical topography (OT) to clarify both the preserved cognitive abilities of a patient with ALS in the TLS and the reorganization of cortical areas. This method, a recently developed extension of near-infrared spectroscopy (NIRS) that measures hemodynamic changes in multiple regions simultaneously [14], is a non-invasive optical imaging technique for measuring higher temporal changes in hemoglobin concentration and oxygen saturation in brain tissues in response to functional neural activity. OT is conveniently performed, as the equipment is compact and portable enough to be used in a bedside setting [14], without imposing undue load on a patient who needs to be transported anywhere. We also presently utilized independent component analysis (ICA), which separates measurement signals into independent source signals based on statistical independency of

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the source signals under the assumption that the measurement signals are liner combinations of independent source signals [6,5,15,23,3,10].

A 73-year-old male with no history of any neurological or psychiatric disease other than ALS participated in this study. The study was approved by the ethics committee of Tokyo Metropolitan Neurological Hospital and informed consent was obtained from the patient's legal representatives.

The onset of his disease at the age of 66 was marked by difficulty in moving his right leg, followed by difficulty in moving his right arm. At the age of 67, he was diagnosed as having sporadic ALS according to the El Escorial criteria [4]. Over the following year, gait disturbance developed, and he was intubated and then tracheostomized because of respiratory distress. At the age of 69, although his eye and tongue movements were preserved, he underwent percutaneous endoscopic gastrostomy because of difficulty in swallowing. During the next 2 years he was able to communicate using eye movements to signal "yes" or "no" in response to questions. He was diagnosed as being in the TLS 18 months prior to our examination.

The patient performed four cognitive block-design tasks: dichotic listening, covert singing, word fluency, and motor imagery. The respective task paradigms consisted of 11, 17, 11, and 17 periods alternating between task periods and control periods. All stimuli were presented acoustically with the intensity being about 70 dB sound pressure level (SPL) near the patient's head. During the examination, the patient was lying in bed with his eyes closed.

In the dichotic listening task, we presented speech and non-speech auditory target stimuli [17]. The target stimuli were alternatively presented to the left and right ear. The frequency of target presentation was balanced between the ears. The task paradigm consisted of 11 periods alternating between a 40-s task period and a 30-s control period. During the task periods, the patient was instructed to track target stimuli, which were successively different sentences of a continuous story. The sentences were divided into phrases at natural break points. During the control periods, he was instructed to track the target tone (sine wave: 1000 Hz).

In the covert singing task, the task paradigm consisted of 17 periods alternating between 15-s task periods and control periods of 30–35 s. During the task periods, he was instructed to sing a song ("red dragonflies" in Japanese) covertly. During the control periods he was instructed to relax.

In the word fluency task [20], the task paradigm consisted of 11 periods alternating between 20-s task periods and 30-s control periods. During the task periods, he was instructed to generate as many words using an assigned first syllable /ka/, /sa/, or /na/ as possible. The assigned first syllable was changed every 10 s during the 20-s task period. During the control periods, he was instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ so that he could not generate words not related to the task periods.

In the motor imagery task, the task paradigm consisted of 17 periods alternating between 15-s task periods and control periods of 30–35 s. During the task periods, he was instructed to imagine himself flexing and extending each finger of the right hand in an orderly manner. During the control period, he was instructed to relax.

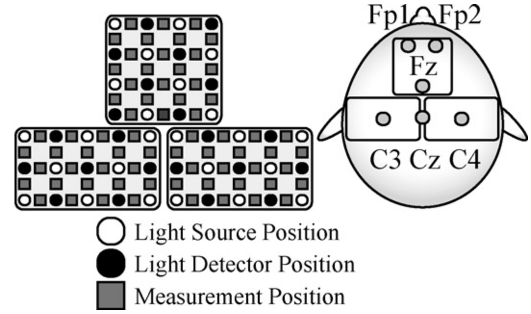


Fig. 1. Arrangement of the measurement positions. Probe patterns over the frontal area, left and right sensorimotor areas positioned on Cz, C3, C4, Fp1, Fp2, and Fz locations were selected according to the international 10/20 system used in electroencephalography.

We used an ETG-7000 OT system with 68 measurement channels (Hitachi Medical Corporation, Tokyo, Japan). The light sources were NIR laser diodes with wavelengths of 695 and 830 nm. Reflected light was detected by avalanche photodiodes positioned 30 mm from the emitters. Changes in the wavelengths of reflected light at the 68 positions were measured by configuring 24 irradiation positions and 22 detection positions (Fig. 1). The signals of all measurement positions were saved simultaneously at a sampling interval of 100 ms. We calculated the relative changes in the concentrations of oxygenated hemoglobin (oxy-Hb) using a modified Beer–Lambert law [14].

The probe holders of the OT system were placed on a participant's frontal region and bilateral hemisphere. The centers of the left and right probe holders were adjusted to coincide with C3 and C4, respectively, according to the international 10/20 system used in electroencephalography. We inferred from previous studies examining the relationship between the international 10–20 locations and cortical areas that the centers of the bilateral measurement areas corresponded to the centers of the primary sensorimotor areas in each hemisphere [22,16]. The lowest measurement positions' line in the frontal probe was positioned along the Fp1–Fp2 line and the center of the highest measurement positions in the frontal probe was adjusted to Fz.

Analysis focused on oxy-Hb, and oxy-Hb data were analyzed using Matlab (The MathWorks, Natick, MA, USA) software. We removed data including artifacts originating from systematic unstable signals, defined as data that changed by more than 0.3 mM mm over three consecutive samples, after being bandpass filtered between 0.01 and 0.8 Hz. To remove signals originating from task design and systematic fluctuations, we filtered the data using a 0.01 Hz cutoff lower frequency, and smoothed the data points using a 15 point moving average.

We used principal component analysis (PCA) to de-noise the data and truncate the data dimension. PCA truncation neglects components contributing <0.5% of the energy. ICA decomposes data into component signals so as to be as statistically independent from each other as possible. In our study, the basic formulation of the single participant oxy-Hb data matrix $X$, measurement points (MP) × time points ($T$), was represented through a linear of truncated matrix dimension ($M$) independent

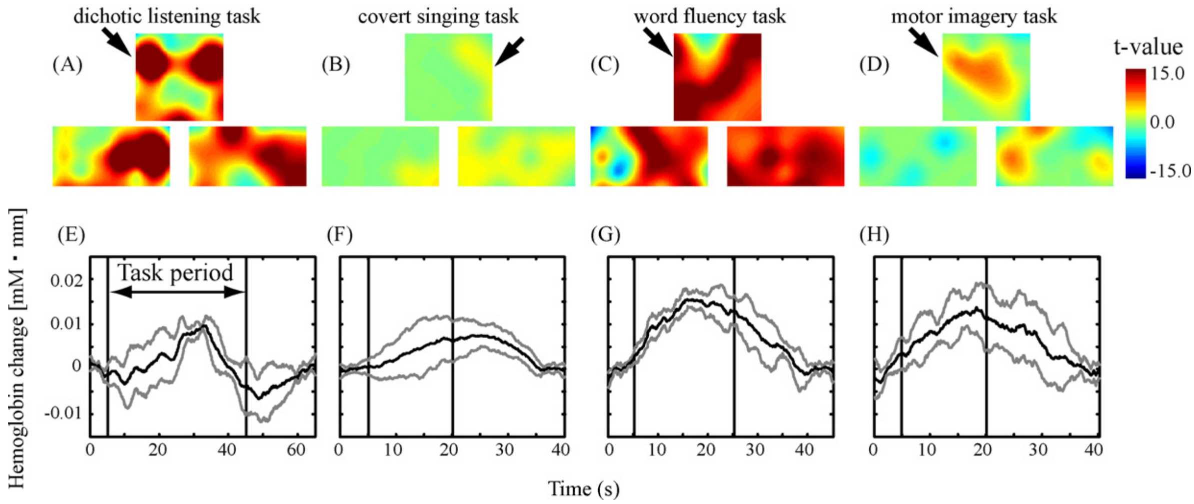


Fig. 2. The *t*-maps (A–D) and the time courses (E–H) of changes in reconstructed oxy-Hb (RECO) at a typical frontal measurement position. (A–D) Arrows indicate the maximum *t*-values of a measurement position from the frontal area. Each *t*-map fulfilled the criteria of significance ($P < 0.05$). (E–H) The mean of RECO is shown as a black solid line. Gray solid lines indicate standard deviation of RECO.

component matrix $S$, $M \times T$, in the T-dimensional domain:

$$X = AS \tag{1}$$

where $A$ is a mixing matrix ($MP \times M$), and the $i$-th row of $S$, the $i$-th independent source component (IC), consists of the time course associated with the $i$-th column of $A$. We used ICA based on time delayed decorrelation algorithm (TDD) [6,5,15,23,3,10]. We applied TDD to the preprocessed data set. The time delay was set to each task and ICs were calculated to minimize cross-correlations at any time delay. Time delays were 0–33 s with a 3.3 s step in the dichotic listening task, 0–23 s with a 2.3 s step in the word fluency task, and 0–20 s with a 2.0 s step in the motor imagery and covert singing tasks.

Global systemic ICs were excluded and task-related independent components (TRICs) were selected from all ICs. Mean inter-trial cross-correlation (MITC) was derived from the time courses of repetitive trials as a measure of inter-trial reproducibility. The actual criterion for detecting TRICs was that the MITC was >0.4. We applied smoothing for all trial data with a Gaussian kernel in the calculation of MITC (FWHM 5 s).

To evaluate the distribution of activation, we calculated the reconstructed oxy-Hb from TRICs (RECO) and depicted the brain mapping of *t*-values in each cognitive task. Thereafter, a first-degree baseline fit was estimated for each channel. The fitting was applied between the average RECO in the 5 s before the onset of the task period and the average RECO in the 5 s between 15 and 20 s after the end of the task period. We calculated the average RECO in the 5 s before the onset of the task period and the maximum average RECO in the 5 s for the task period. We calculated the *t*-value (paired *t*-test) between the average RECO before the onset of the task period and that in the task periods in each cognitive task. Then, we depicted significant *t*-values ($P < 0.05$) as the functional activation map in each cognitive task.

The dichotic listening, covert singing, word fluency, and motor imagery tasks were associated with 35, 41, 34, and 42 ICs, respectively. The respective numbers of TRICs were 4, 2, 4, and 2, and the average MITCs that expresses reproducibility were 0.61, 0.58, 0.76, and 0.56.

We clarified the cortical activations occurring during these four tasks (Fig. 2A–D). In the dichotic listening task, significant activations were observed in bilateral prefrontal areas and bilateral sensorimotor areas (Fig. 2A). In the covert singing task, significant activations were observed in the right prefrontal and sensorimotor areas (Fig. 2B). In the word fluency task, significant activations were observed in bilateral prefrontal areas and bilateral sensorimotor areas (Fig. 2C). In the motor imagery task, significant activations were observed in the right prefrontal and dorsal sensorimotor areas (Fig. 2D).

A measurement position from the frontal area was selected that indicated the maximum *t*-value as a typical measurement position in each task (Fig. 2A–D, arrow). The differences between the temporal changes of RECO in a typical measurement position were also clarified (Fig. 2E–H). The averaged temporal change of RECO in the dichotic listening task decreased approximately 5 s after the onset of the task period, peaked at approximately 15 s, immediately decreased to the level of deactivation, and then, within about 10 s it increased to the background level (Fig. 2E). The averaged temporal change of RECO in the covert singing task gradually increased during the task period, peaked approximately 5 s after the end of the task period, and then, within about 10 s it decreased to the background level (Fig. 2F). The averaged temporal change of RECO in the word fluency task peaked approximately 10 s after the onset of the task period, and then, within 30 s it decreased to the background level (Fig. 2G). Finally, the averaged temporal change of RECO in the motor imagery task increased during the task period, peaked at the end of the task period, and then, within about 20 s it decreased to the background level (Fig. 2H).

In this study, we clarified the cortical activations of a 73-year-old patient with ALS in the TLS during four cognitive tasks by taking OT measurements at his bedside. Different patterns of activation and different temporal changes of RECO were observed in each task. These results suggest that cognitive functions are preserved in this patient.

The suspicion that acoustic stimuli may have automatically triggered the pattern of activation observed in each task can be ruled out based on two standpoints. First, the reproducibility of each task was high enough. We detected at least two TRICs with MITCs exceeding 0.4. The average MITCs were 0.61, 0.58, 0.76, and 0.56 in the dichotic listening, covert singing, word fluency, and motor imagery tasks, respectively. Furthermore, other data not presented in this manuscript established that the average MITC of the non-task conditions, where stimuli were presented and the participant was instructed to relax, is 0.28. If the patient did not do anything in each task, the average MITC would have been as small as that under the non-task condition. Also, the task period was of sufficient length to detect temporal changes of RECO (Fig. 2E–H). If the patient unconsciously responded only to the acoustic stimuli, temporal changes of RECO would not persist, but would rather be characteristically transient.

The sensorimotor area is activated in a motor imagery task [7]. In this case, contralateral sensorimotor activation was not observed in the motor imagery task; however, a significant activation was observed in the ipsilateral dorsal sensorimotor area. Sensorimotor activation may be reduced to ipsilateral dorsal sensorimotor activation due to the progression of ALS.

In this patient, the bilateral sensorimotor area is activated in two language-related tasks (dichotic listening and word fluency). One possible explanation is that reorganization of the motor cortex occurred. This is known to occur in the motor region in ALS [11,18,21]. In our study, the sensorimotor area was activated in the language-related tasks. Whether reorganization occurred cannot at present be concluded or ruled out.

Another possibility is that the motor system is necessary for language processing included in generating words and comprehension of language in patients with ALS. A previous report showed that action words referring to the actions of body parts induce motor and premotor activation [8]. In general, it is conceivable that in the word fluency task, a patient with ALS in the TLS might generate action words, and, as a result, induce sensorimotor activation [12]. In our patient, the motor system is involved in language processing. The bilateral sensorimotor area was activated in the dichotic listening task. A previous report using a listening speech task showed that the sensorimotor area was not activated in an audio-alone condition, where participants listened to narrated stories, but it was activated in an audio–visual condition, where participants watched and listened to the video clips of the storyteller [19]. We used speech sounds alone, since our patient was examined with his eyes closed, obviating the speech sound-mediated activation of sensorimotor activation.

These interpretations of sensorimotor activation related to language processing remain speculative in view of task design and since only one patient has been examined. To find out the sensorimotor activation during language processing tasks, the effect of the progression of sickness on the sensorimotor activation will need to be evaluated in a larger patient population. Nonetheless, it may be noteworthy that the sensorimotor area has been presently demonstrated to assume an important role in language-related tasks in a patient with ALS in the TLS.

In this study, we clarified the cortical activations in a 73-year-old patient with ALS in the TLS during four cognitive tasks using OT at his bedside. Different activation patterns and temporal changes of RECO were observed during each task, and these results suggested that cognitive functions are preserved during ALS in the TLS. The bilateral sensorimotor area was found to be activated in two language-related tasks, the dichotic listening and word fluency tasks. However, a contralateral sensorimotor activation was not observed in the motor imagery task. The sensorimotor areas are thought to retain their functions and play an important role in language-related tasks in patients with ALS and in the TLS.

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