A brain–computer interface tool to assess cognitive functions in completely paralyzed patients with amyotrophic lateral sclerosis


Objective: Brain–computer interface methodology based on self-regulation of slow-cortical potentials (SCPs) of the EEG was used to assess cognitive abilities of two late-stage ALS patients.

Methods: A monitor presented visual information in two targets. Patients used their SCPs to steer a cursor to one of the targets. Within-subject methodology tested the ability to discriminate odd/even numbers, consonants/vowels, nouns/verbs, small/large numbers, and the ability to perform simple computations.

Results: Both patients reached accuracy near 90% correct on simple tasks showing that they understood the instructions, discriminated the visual stimuli, and could use the SCP to control the cursor. Both patients showed some deficit on the task that involved computations. The patient with the short-term memory task showed a large reduction in accuracy on delay trials but retained high accuracy on non-delay trials.

Conclusion: The fully computerized method is a useful tool for presenting a variety of two-choice tasks to assess certain cognitive functions in the severely paralyzed patient.

Significance: The task can potentially be used to examine maintenance or decline of cognitive abilities in individual ALS patients.

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1. Introduction

Some neurological disorders, such as amyotrophic lateral sclerosis (ALS), can lead to motor disability so severe that the condition has been described as the "locked-in" syndrome. The patient is unable to move or speak and has lost customary means of communication and expression (Smith, 1992). Adequately assessing the cognitive abilities of a patient at the advanced stage of paralysis is a challenge because the patient has no reliable control over a motor response that can serve as a reaction to questions that relate to his or her cognitive abilities. All standard assessment tools for both verbal and non-verbal cognitive abilities involve a motor response (Carroll, 1993; Anastasia and Urbina, 1997). Even existing tests for motor impaired patients rely on some form of rudimentary motor function such as blinking, nodding, or pointing (Anastasia and Urbina, 1997; Lakerveld et al., 2008). Therefore, it is a considerable challenge to design assessment tools for the completely paralyzed patient. We describe here an automated method that enables locked-in patients to answer yes/no questions that pertain to their cognitive abilities. We use a brain–computer interface method in which the voluntary control of the electroencephalogram (EEG) serves as the patient’s response. The method is based on the previous work on teaching self-regulation of the EEG to ALS patients as a means for them to communicate using a non-motor yes/no response (Birbaumer et al., 1999; Kübler et al., 1999, 2001; Birbaumer, 2006). With long-term practice, self-regulation of EEG becomes a skill that results in a high accuracy of yes/no answers to simple questions (Neumann et al., 2004). Using a modification of this paradigm, we designed some relatively simple two-choice tests to assess word comprehension, computational skills, and short-term memory.

A review of the literature on cognitive abilities in ALS patients, for whom speech was still sufficiently intact to allow for neuropsychological assessment, found that ALS patients often do have cognitive deficits, even at early stages of the disease (Strong et al., 1996). Several comprehensive studies using a range of standard...
neuropsychological tests with a high number of ALS patients (ranging from 44 to 279) compared to age-matched control groups have found deficits in cognitive function for 20–60% of ALS patients depending on tests and disease progress; in particular, verbal fluency, word recognition, executive functions such as Wisconsin card sorting abilities were impaired (Abrahams et al., 1997; Frank et al., 1997; Lomen-Hoerth et al., 2003; Ringholz et al., 2005; Flaherty-Craig et al., 2006). Other studies show, however, that cognitive deficits in ALS patients may only be found in a few patients and in some cognitive tasks (Rötting et al., 2006; Lakervdeld et al., 2008).

The literature, therefore, is not entirely clear regarding the certainty of cognitive deficits in ALS patients. Patients at different stages of disease progress may show different degrees of symptoms if any. For example, cognitive deficits worsened with disease progression in a study with 74 ALS patients (Frank et al., 1997). Advancing motor handicaps may also slow the motor responses used in testing and thereby result in lower scores on cognitive tests. The literature also indicates that some ALS patients show evidence of cortical atrophy in the frontal and temporal lobes (Iversen et al., 1981; Abrahams et al., 1997). In particular, frontal dysfunction, as seen in a letter fluency fMRI task, is associated with cognitive deficits (Abrahams et al., 2004). Deficits in both visual and verbal memory have also been reported for some ALS patients, with worsening of symptoms over time (Mantovan et al., 2003; Robinson et al., 2006).

Regarding the relation between cortical abnormalities and cognitive deficits in ALS patients, a comprehensive review concluded that increasing levels of cortical abnormalities are found with increasing levels of cognitive impairments (Irwin et al., 2007). In support for this connection, cognitive deficits (as determined by standard neuropsychological tests) and frontal lobe atrophy (as determined by magnetic resonance imaging, MRI) were found in the same patients from a group of 26 ALS patients (Abe et al., 1997). Similarly, outcomes of neuropsychological tests with MRI found reduced volumes of the frontal lobe only in the ALS patients who also showed cognitive abnormalities (Murphy et al., 2007). Thus, the literature indicates that, when tested while motor skills and speech are still intact, at least some ALS patients may show evidence of cognitive deficits and also of frontal lobe atrophy. However, the pronounced speech and motor impairments in advanced cases of ALS with the locked-in syndrome prevent adequate assessment of cognitive skills for this group of patients. Some attempts directed at assessing cognitive function for patients with severe or complete paralysis using non-motor tasks have been based on EEG recording of evoked potentials in odd-ball tasks (where the patient is instructed to count rare events) (Kotchoubey et al., 2003; Neumann and Kotchoubey, 2004; Hinterberger et al., 2005a,b). Results from such research showed that some of the late-stage, severely paralyzed patients had intact cognitive mechanisms needed for the task tested. However, the method of using EEG recording of evoked potentials often results in low accuracy of stimulus detection for this group of patients (Hinterberger et al., 2005a).

Some late-stage ALS patients can learn to communicate reliably, at high accuracy, using only their EEG (McFarland et al., 1993; Pfurtscheller et al., 1987; Birbaumer, 1997; Kotchoubey et al., 1997; Kümmer et al., 2001). These studies are based on the finding that patients can learn to control certain components of their EEG after biofeedback training. The EEG signal is filtered and relevant features are extracted by brain–computer software which then converts the signal to on-line visual feedback for the patient such as vertical movement of a visual symbol on a monitor. With training, patients can learn to direct the movement of the visual symbol by regulating their EEG. Thus, a method exists that enables a patient to use the EEG to make a voluntary response that requires no neuromuscular control but which can nonetheless be observed by other people in the form of the visual feedback of the EEG change. Because some locked-in patients can learn to make such a response with their EEG, they can thereby learn to communicate (Birbaumer, 1999). In addition, development of such a self-controlled EEG response opens up the possibility for objective assessment of the patient’s cognitive abilities, as described in this paper.

The basic EEG-control task was used previously to teach ALS patients to compose words, letter by letter, using cursor movement to select characters of the alphabet (Birbaumer et al., 1999, 2000; Kümmer et al., 2001). The task has been described in detail elsewhere (Kümmer et al., 2001). In brief, changes in the slow-cortical potential (SCP) of the EEG are converted to visual or auditory feedback, which consists of movement of a cursor (a small disk) on a monitor in front of the patient. The cursor can be moved toward one of two visual target stimuli placed at the top and bottom of the screen. By making voluntary changes in the EEG, the patient can steer the vertical movement of the cursor toward one of the targets. Thus, with training the patient can learn to make one of two computer-generated responses on each trial, move the cursor up or down. This task enables the paralyzed ALS patient to convert a non-motor electrophysiological change in the brain to the equivalent of an overt motor response that is measured in terms of its effect on the environment. That is, the up or down movement of the cursor is equivalent to pressing one of two keys on a keyboard for “yes” or “no” and can be scored and stored objectively.

The present experiment is based on the assumption that if patients can learn to respond with high accuracy in a two-choice task, they should in essence be able to answer questions that relate to their cognitive skills. For example, by presenting a noun and a verb, one in each target, and by giving the patient the verbal instruction to steer the cursor to the noun on each trial, one can assess at least an element of the patient’s verbal abilities. Thus, we presented several two-choice tasks that assessed different basic abilities such as: noun/verb discrimination, odd/even number discrimination, and discrimination of larger/smaller numbers. Performance was also assessed when instructions differed from trial to trial using a matching-to-sample paradigm (Mackay, 1991). On each trial, the instruction appears on the monitor in the form of a visual symbol. In this manner we examined the ability to discriminate numbers, letters, colors, and to perform simple calculations. For example, the sample may be “2 + 5” with choices “7” and “8”. From trial to trial the sample varies and may show a sum or a difference. If the patient’s ability to add and subtract is intact, then the patient should be able to respond correctly on this task (Fig. 1). We also used the matching-to-sample paradigm to test short-term memory by presenting the choice stimuli some time after the sample stimulus. This study examined the performance of two ALS patients. Because of the small number of patients, we used a within-subject experimental design (Kazdin, 1989; Iversen, 1991; Perone, 1991). Each patient, therefore, served as his own control such that performance under different experimental conditions was compared for the same patient.

The specific hypothesis of the study was if a given ALS patient is able to perform some cognitive tasks with high accuracy using the brain–computer interface method, then reduced accuracy on other cognitive tasks that use the same brain–computer interface method should be indicative of potential cognitive deficits for that patient for skills needed to execute those particular tasks.

2. Method

2.1. Patients

Two male patients with advanced ALS participated in the study. Patient JB had genetic, bulbar onset ALS with disease onset at age 45 and was 52 at the time of the study. He was nearly completely paralyzed except for some control of eye movements and some minimal control of the triceps muscle in one arm. He was...
artificially ventilated and fed since one year after disease onset. Patient JB was German and fluent in spoken and written German. He served as the director of a bank prior to disease. Patient ER had sporadic ALS with disease onset at age 38 and was 44 at the time of the study. He had tetraplegia, respiratory weakness, and his speech was not comprehensible. He had some control over eye movements and one foot. He was not artificially ventilated or fed. Patient ER was fluent in Turkish and could understand but not read German. Both patients lived at home being cared for by family members and professional caregivers. Prior to this study both patients had participated in EEG training for several months and had learned to control cursor movement very efficiently. Patient JB had learned to spell words and write personal wishes using the EEG method (Birbaumer et al., 1999; Kübler et al., 2001), whereas patient ER used a specially designed program to communicate messages to his caregivers (Kaiser et al., 2001, 2002).

In this study, the patients were trained intermittently once or twice each week. Each training day usually lasted 2–3 h and consisted of several 5–10 min training sessions separated by 5–10 min breaks. Because the patients were assessed one year apart by different trainers, and because training protocols could not always be followed in the home environment of each patient, the procedure differs somewhat for the two patients. For patient ER, 6 months without training intervened between training days 6 and 7. During training for Part 3 (see procedure), patient ER received one training period per test day because he was also trained apart by different trainers, and because training protocols could not always be followed in the home environment of each patient. SCPs were extracted from the on-line EEG signal and corrected for eye movement artifacts (Birbaumer et al., 1999). The SCP amplitude changes that constituted a detected response were usually in the 5–8 μV range for patient JB and in the 30–50 μV range for patient ER, and were converted to visual feedback in the form of vertical movement of a small cursor on the monitor of a notebook computer (Toshiba Satellite 210CT), which was placed about 1 m from the patient’s face (Kübler et al., 1999). The SCP change for JB was relatively small, but this difference was sufficient to be detected by our software; JB was also able to select letters in a language support program for communication with the same parameter setting (Birbaumer et al., 1999; Kübler et al., 1999), and he was obviously also able to perform at high accuracy in some of the present tasks, as shown below.

2.3. Trial structure

Each training session consisted of a series of trials that each lasted 5 s. The patient faced a screen that showed a cursor and two targets (Fig. 2, top left). The onset of a trial was indicated by the presentation of stimulus material on the monitor and a 50 ms high-pitched tone. The cursor remained stationary on the monitor for 2 s (the preparatory phase) to the left of and between the two target stimuli. A baseline of SCP was recorded for the last 0.5 s of the 2-s preparatory phase (Fig. 2, bottom). This baseline served as an on-line immediate reference for SCP changes in the subsequent feedback phase, which lasted 3 s and was initiated by a 50 ms low-pitched tone (Kübler et al., 1999). The cursor began to move at a constant speed from left to right, 0.5 s into the 3-s feedback phase and moved for 2.5 s. The cursor’s vertical movement was determined by the average SCP change relative to the 0.5-s baseline SCP value. During the feedback phase, SCP was updated every 62.5 ms and smoothed by a 500 ms moving average. If the patient produced a negative SCP change relative to the immediately preceding baseline the cursor moved up, and if the patient produced a positive SCP change relative to baseline the cursor moved down. If the SCP remained the same as during the baseline, then the cursor did not move vertically. When the patient steered the cursor to hit the correct target, a “smiley” face appeared on the monitor as a reward during the last 0.3 s of a trial (Fig. 2, top right frame). If the patient made the cursor hit the incorrect target, no smiley appeared at the end of a trial. A new trial started as soon as the previous trial ended. Each session had 70 trials.

A trial rejection occurred when an eye movement artifact or other artifacts such as from swallowing occurred (Kübler et al., 1999). A trial was repeated when the trial was rejected or when the cursor did not hit either target. Each training day was initiated with one or more sessions with a simpler two-choice task where the patient had to move the cursor to a target that was simply highlighted. This training served as a “warm-up” period, and data are not included here.

2.4. Procedure

Because no control subjects were used, the study used a within-subject control design so that each subject was compared to himself (e.g., Kazdin, 1989). Thus, performance on simple tasks served as control for performance on more difficult tasks. Therefore, a deficit in performance on difficult tasks was assessed against the same...
patient's performance on simple tasks, which served as the control condition.

Part 1. Both ALS patients had prior experience in the overall tasks design and could control the cursor on the computer screen by means of SCP changes in their EEG when the study began. On each training day, each patient had several sessions. On each trial, they had to move the cursor to one of two targets. In Part 1, the instruction about the correct target was the same for all trials throughout a session, and the instruction was given verbally immediately prior to the start of a session. To facilitate acquisition of the more complex tasks, we presented the tasks to the patients in a progression of increasing complexity. Thus, the first task, labeled T1, served as a simple training exercise, which involved merely moving the cursor to the correct target, which was highlighted or contained an alphanumerical stimulus, such as an A, while the other target was empty. This first task also was used later to ensure that the patient's control of the EEG was intact in sessions that tested the patient's cognitive abilities required for the more advanced tasks. In task T2, the patient had to discriminate two different alphanumerical stimuli such as a letter and a number or to discriminate two different items of the same kind. In task T3, the discrimination was between an even and an odd number. In task T4, the patient had to select the consonant when the choice was a consonant and a vowel. In task T5, the stimulus material was more complex because it involved nouns and verbs (in German), and the patient was instructed to move the cursor to the noun. It should be noted that for patient ER, who could understand but not read German, this task (T5) served as an important validation of the diagnostic tool developed here. Because the patient was known to be unable to tell nouns from verbs, the prediction was made that his score on this task would be near 50%, as he could only guess the correct answer (T5 was only presented once for ER to minimize the stress of presenting him with an unsolvable task). The last task, T6, required an understanding of quantities. The instruction was to move the cursor to the larger of two, two- or three-digit numbers. For all tasks, the position of the correct target varied randomly from trial to trial.

Part 2. The design was based on the matching-to-sample procedure. The instruction about which target was correct for a given trial varied from trial to trial and was indicated as a sample (model) on the monitor. The sample and the choices differed from trial to trial, and the location of the correct target varied between the upper or lower position randomly from trial to trial as well. Thus, the patient had to look at both the sample and the choice stimuli on each trial to solve the task correctly. In task T7, the monitor showed on the left side a single sign (letter, number, or symbol) as the sample for a given trial; the correct target showed the same sign and the incorrect target showed a different sign. Ability for simple computations was tested in task T8 by having the sample show two single digits with a sign for calculation, + or −, for example 4 + 2; the choices were single digits one of which showed the correct answer. Task T9 tested for letter identification; the sample showed a single letter, and the choices were two sequences of three letters, one of which contained the sample letter (e.g., sample = X with choices PYX and ATZ). In task T10, number identification was tested as letters were in task T9.

Part 3. The matching-to-sample paradigm from tasks T7–10 was modified to test short-term memory by inserting delays between seeing the sample and seeing the choice stimuli. Stimuli were geometrical forms (disks, triangles, squares, and diamonds) in different basic colors. The method was identity matching such that the correct choice was identical to the sample shown on the screen. In each session, 62 trials presented the sample and the choice.
3. Results

Both patients acquired control over cursor movement such that the accuracy of target selection in the two-choice tasks for discrimination of objects, letters, and numbers (tasks T1 and T2) was considerably higher than the 50% level of random performance. For tasks T1 and T2 combined, the mean % correct, SD, and N were 85.6, 7.8, and 45 for JB and 82.8, 9.2, and 18 for ER. As additional indication of control, accuracy was at 90% or higher for 40% and 44.4% of the sessions for JB and ER, respectively. Patient ER improved over the course of the project and had even higher accuracies for other tasks that were more complex (see below). Thus, the patients performed the basic task correctly and therefore understood the instruction for the task. The results also show that both patients could perform the necessary visual discriminations of the symbols and were able to control the cursor by the SCP. Given this demonstration that these basic abilities were intact in both patients, possible performance decrements on other tasks could be interpreted as indicative of deficits of the specific cognitive abilities related to those tasks.

Using a within-subject design, each patient’s performance on a given task was compared to the same patient’s performance on a different task. Thus, each patient was used as his own control. Performance on all sessions for patient ER on training day 2 (cf. Table 2) is presented in Fig. 4. Accuracy is high on the simple task T1 (correct target contains a symbol, incorrect target is empty) and task T2 (correct target has a number, incorrect target has a letter). Task T3 presented a choice between even and uneven numbers.
which target to steer the cursor toward. The chance-level perfor-
ence the information conveyed by the targets, then the ability to
identify the correct target due to lack of a cognitive ability to pro-
that the accuracy was high on the two sessions with task T4 that
dropped to near 50%. It is illustrative of the within-subject design
between nouns and verbs. Correspondingly, the accuracy
not expected to perform well on task T5, which tested the differ-
tient ER could not read the German language and therefore was
discrimination of consonants and vowels, had high accuracy. Pa-
and the accuracy was somewhat reduced. Task T4, which tested
discrimination of consonants and vowels, had high accuracy. ... the same task was repeated on a given day.

<table>
<thead>
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<th>Task model/instruction</th>
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<th>Sessions</th>
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<td><strong>Part 1: Instruction is given before the session and is the same for each trial</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T1 Select sign</td>
<td>Letter, number, form</td>
<td>Empty</td>
<td>JB 35</td>
</tr>
<tr>
<td>T2 Select specific sign</td>
<td>Letter, number, form</td>
<td>Other letter, number, form</td>
<td>JB 10</td>
</tr>
<tr>
<td>T3 Select even</td>
<td>Even number</td>
<td>Uneven number</td>
<td>JB 4</td>
</tr>
<tr>
<td>T4 Select consonant</td>
<td>Consonant</td>
<td>Vowel</td>
<td>JB 9</td>
</tr>
<tr>
<td>T5 Select noun</td>
<td>Noun</td>
<td>Verb</td>
<td>JB 6</td>
</tr>
<tr>
<td>T6 Select larger number</td>
<td>Large number</td>
<td>Small number</td>
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<td><strong>Part 2: Instruction is on the screen and differs for each trial</strong></td>
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<tr>
<td>T7 Color, letter, number</td>
<td>Color, letter, number</td>
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<td>JB 20</td>
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<tr>
<td>T8 Addition, subtraction</td>
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<tr>
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<td><strong>Part 3: As Part 2, but with a delay between sample and choice screens</strong></td>
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<td>T11 Form (delay 0 and 5 s)</td>
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<td>T12 Form (delay 0, 5, 10, 15 s)</td>
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On each task, the patient uses a verbal instruction given before the session (Part 1) or a visual instruction on the monitor during the session (Parts 2 and 3) to select one of two targets.

and the accuracy was somewhat reduced. Task T4, which tested
discrimination of consonants and vowels, had high accuracy. Pati-
ent ER could not read the German language and therefore was
not expected to perform well on task T5, which tested the differ-
ence between nouns and verbs. Correspondingly, the accuracy
dropped to near 50%. It is illustrative of the within-subject design
that the accuracy was high on the two sessions with task T4 that
surrounded (immediately before and after) the single session with
task T5. Thus, the within-subject design separates the two different
abilities; the ability to identify the correct target and the ability to
steer the cursor toward the correct target. If the patient is unable to
identify the correct target due to lack of a cognitive ability to pro-
cess the information conveyed by the targets, then the ability to
steer the cursor is of no use because the patient does not know which
target to steer the cursor toward. The chance-level performance
obtained on the single session with nouns and verbs, which

The patient was known not to have the ability to differentiate, thus
serves as an important validation of the present method because it shows
that the method can correctly identify the lack of a specific
cognitive ability. One session was sufficient for this illustration gi-
ven the otherwise high accuracy level for patient ER.

As a further illustration of the value of the within-subject de-
design, Fig. 5 shows the results for patient JB from training day 7
(cf. Table 2). Letters at the top (A through E) identify the different
phases of the within-subject design. Several sessions were required
with task T1 before accuracy approached 90%. The noun/verb dis-
crimination in task T5 reached 90% correct. However, accuracy
never exceeded 75% even after several consecutive sessions with
task T7 (selection of the target identical to the sample). After a re-
turn to the simple task T1, the accuracy immediately rose to 90%. It
again fell to below 75% when task T7 was repeated in one session.
Accuracy fell to just 57% with presentation of task T8 (selection of
correct result from simple addition or subtraction shown as a sam-
ple). Reintroduction of task T1 made the accuracy rise again to 80%.
Thus, the high accuracy on some sessions, marked as A, D, and E, illustrates that the patient had the ability to control the cursor when the correct target could be identified. Low accuracy on other sessions, marked as C, F, and G suggest that the patient may have had a reduced ability to identify the correct target on those tasks. Patient JB was a successful banker prior to disease onset, so one
reasonably surmise that he should have had perfect and prompt command of the extremely simple computations required
in task T8. Thus, for patient JB, the disease could possibly have led to a deficit in cognitive processing of some types of numerical information required for the computation task.

FIG. 6 shows the overall accuracy for each task for each patient.
The number of sessions varied for each task (cf. Table 1). Already
identified is the expected deficit in task T5 (verb/noun discrimina-
tion) for patient ER. In general, Patient ER had lower accuracy on
tasks T8 and T9 but did very well on task T10. By combining ses-
sions, the numbers of sessions for groups of tasks are sufficient
for simple statistical comparisons using the t-test for independent
samples. For patient JB, the combined accuracy for tasks T3, T4, and
T5 was slightly lower than the accuracy on T2, but the difference
fell short of a statistical significance, t(27) = 1.5, p < .15. However,
the combined accuracy for tasks T8, T9, and T10 was lower for pa-

tient JB than the accuracy for T7 with a statistically significant dif-
fERENCE, t(23) = 2.57, p < .017. For patient ER, the accuracy on task
T9 was lower than the accuracy on task T10, with a significant dif-
fERENCE t(16) = 7.08, p < .001. Similarly, the accuracy on task T8 was

Table 1
Descriptions of specific cognitive assessment tasks and the number of training/test sessions for each task

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lower than the accuracy on task T10, with a significant difference \( t(19) = 8.17, p < .001 \).

When delays were inserted between sample and choice screens in Part 3, patient ER showed a deficit on trials with delays. Fig. 7 shows the accuracy on baseline trials and delay trials for all sessions. Patient ER performed at high accuracy, above 90% correct, on all baseline trials except for session 3 when the longer delays were introduced. Accuracy on delay trials for all sessions was considerably lower than baseline trials and performance was not different from random (50% correct). A \( t \)-test for independent samples comparing performance on baseline and delay trials for all eight sessions showed a significantly reduced accuracy on delay trials (\( t(14) = 8.58, p < 0.001 \)). Notice that procedurally the 0-s delay trials are different from baseline trials because the sample and choice stimuli are presented successively on the 0-s delay trials but are presented simultaneously on the baseline trials (see Section 2). Fig. 8 shows the accuracy as a function of delay for the six sessions with equal distributions of all delay values. The performance was essentially at chance-level (50% correct) for all delay values with no tendency in the data for shorter delays to generate higher accuracy than longer delays.

4. Discussion

The diagnostic instruments developed here are for use with severely paralyzed persons, who cannot be adequately examined for possible cognitive deficits with traditional neuropsychological instruments that require a reliable motor skill of some form. The tasks presented here required pretraining to learn to use the SCP of the EEG to control a brain–computer interface. Both patients were able to use their SCP to steer the cursor on the monitor to a correct target under control by verbal instructions and the visual stimuli on the monitor. High accuracy on many training sessions indicates that both patients understood the verbal instructions and were able to voluntarily modify their SCP within the short time frame of a few seconds for each trial. Thus, the results indicate that
both patients had intact auditory and visual discrimination because they showed in their choices of target stimuli on most tasks that they followed the verbal instructions and selected the correct visual target.

A within-subject design was used to compare each patient to himself as a control (Perone, 1991). Thus, when a patient was excellent on one task but performed poorly on the second similar task, the inference can be drawn that the patient lacked some ability to process information for the second task. The validity of this method was demonstrated in one test session for patient ER. He was given a task that he was known to be unable to solve. The task (T5) presented nouns and verbs in a language he could not read, and his accuracy accordingly dropped to chance-level in comparison to accuracy near 100% for other tasks on the same test day.

Given this demonstrated task validity, deviations from high accuracy are revealing of potential cognitive deficits. Overall, the data demonstrate some reduced performance on task T8, which involved simple computations. Both patients had lower accuracy on this task compared to other tasks. For patient JB, only a few sessions with this task were scheduled, and they all had lower accuracy than control tasks. For patient ER, several sessions with task T8 were scheduled, and the reduction in accuracy was in fact statistically significant compared to the accuracy on other tasks. The extremely simple computations presented in task T8 should presumably not require a higher cognitive load or processing time than the other tasks used in the present research. For the task (T3) that required a distinction between odd and even numbers, patient ER also had a reduction in performance compared to other tasks presented in the same training session. Unfortunately, only one test session was scheduled with this task for patient ER. The task (T9) that required identification of a single letter in a string of three-letter nonsense words also had a significant reduction in accuracy for patient ER. Yet, patient ER was excellent in identifying a single digit in a string of two or three digits (task T10). Overall,
patient ER performed considerably better than patient JB on the matching-to-sample tasks (77–10).

Because patient ER performed so well on the matching-to-sample task, he was tested on a version that inserted delays between the sample screen and the choice screen to determine if the task could be used to assess short-term memory. The insertion of a delay produced a large and statistically significant reduction in accuracy to near chance-level on delay trials while the accuracy on baseline trials without delay remained close to 100%. Thus, a clear deficit in short-term memory is revealed by this test. However, with just a single patient there is no opportunity for comparison to other ALS patients at a similar disease stage or to healthy individuals. The task used very simple visual symbols that varied both in color and form and delays that lased up to 15 s. Therefore, a reasonable assumption is that healthy volunteers would have performed at a much higher accuracy during delay trials than did patient ER. Ordinarily, in research on short-term memory, the accuracy is high for short delays (0–5 s) and decreases gradually across delay intervals (Neisser, 1967). Such a finding was not obtained in the present test, further indicating that patient ER may have had a deficit in short-term memory. Deficits in memory have previously been reported for some ALS patients (Frank et al., 1997; Mantovani et al., 2003; Robinson et al., 2006).

One limitation of this study is that the ability to control the SCP of the EEG is a prerequisite skill for responding correctly in the two-choice task used here. Such training to control the SCP may take weeks, and some ALS patients do not learn the skill (Kübler et al., 1999; Kübler et al., 2001). A second limitation of the present experiment is that some tests were presented in only one or a few test sessions. This was partly by design (in the case of the noun/verb validity test for patient ER) or a result of logistical issues related to testing the patients in their home, which sometimes prevented the trainer from following a planned protocol. A single test session, however, is not necessarily a serious limitation as it should be recognized that customary neuropsychological tests often consist of just a single session of assessment, where a possible cognitive deficit is assessed in comparison to performance of a group of healthy subjects. With the within-subject methodology, a deficit in performance on one task is compared to the same patient’s performance on other tasks. Yet, in the present experiment, several tests were, in fact, repeated for a sufficient number of sessions so that the tentative or suggestive conclusion could be reached that the late-stage ALS patients we tested may have had some selected cognitive deficits, specifically in terms of ability to perform simple calculations (both patients) and maybe also in visual short-term memory (one patient was tested only).

The present method is useful for binary answers to yes/no questions. In the various tasks we presented, the stimulus material varied considerably from simple to complex, and further variations are entirely possible. However, the method is of no use for tasks based on recall or where a choice must be made among more than two stimuli; with the present method, the maximal choice is obviously between two stimuli. Also, there are only a few seconds available for the patient to process the information on the screen, 2 s of stimulus presentation and baseline recording and 3 s of steering the cursor to one of the targets. While this is a temporal limitation for processing of the presented stimuli, the tasks were designed to be so simple that the 5-s trial period should presumably be sufficient for information processing. The present task should also be useful for longitudinal studies of possible decline of cognitive abilities in individual patients. As long as a patient can control the cursor on the monitor by regulating the SCP he/she can participate in the assessment of various cognitive abilities based on the paradigm presented here.

The main impetus of the present research was to develop a method that could assess cognitive function in late-stage paralyzed ALS patients with no remaining reliable motor control. With only two patients, the present results should be considered preliminary. Further refinements of the task and a larger sample of patients are needed to determine more conclusively what sorts of cognitive deficits, if any, ALS patients may have at the late-stage of their disease. Thus, while there may be some potential cognitive deficits associated with ALS, it should be emphasized that even late-stage, locked-in patients, who may appear completely separated from their world in terms of communication, actually still may have considerable cognitive abilities and can be enabled to express their thoughts and wishes by means of brain–computer interfaces via SCP training as described here and elsewhere (Neumann et al., 2004; Birbaumer, 2006).

References


