Differentiation between disorders of consciousness and disorders of movement using functional MRI

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Abstract

The differential diagnosis between disorders of consciousness (DoC), on the one hand, and conditions of severe immobility with aphasia, on the other hand, is extremely difficult. A patient is described whose morphology of brain lesions permitted both kinds of disorder. A battery of functional magnetic resonance imaging (fMRI) examinations was applied indicating that severe DoC was implausible. The following clinical course confirmed this conclusion, resulting in a severe tetraparesis/aphasia, however with clear awareness. The data suggest that fMRI can be very useful in differentiating between severe motor disorders, including a locked-in syndrome, and DoC such as the vegetative state and the minimally conscious state.

Keywords

Disorders of consciousness; functional brain imaging; intracerebral haemorrhage; locked-in syndrome; vegetative state.

Introduction

Severe disorders of consciousness (DoC) are characterized either by a complete lack of any behavioural signs of conscious experience or intentional movements (coma, vegetative state (VS)), or such signs are only sporadic and inconsistent (minimally conscious state (MCS))3–5. On the other hand, there exist extremely severe movement disorders such as the locked-in syndrome (LiS) or other combinations of tetraplegia and speech disorders. Such patients are, by definition, conscious but severely paralyzed making the exact neuropsychological assessment of their cognitive functions very difficult5,6. Therefore, the differential diagnosis between DoC and LiS is highly problematic3,6. Numerous data indicate that up to 40% of allegedly VS patients are

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misdiagnosed\cite{7–10}. Although most diagnostic errors are confusions between different DoC\cite{10}, a considerable portion of them are patients who are not in a DoC but, rather, in a locked-in state.

Since the differentiation between severe DoC and severe immobility is related to such a high error rate even when one of the syndromes is presented in a relatively pure form, the problem is particularly aggravated when there is a reason to suppose both DoC and a severe paralysis in the same patient. The present data suggest that methods of modern cognitive neuroscience, particularly functional magnetic resonance imaging (fMRI) can substantially contribute to the differential diagnosis.

Case description

A 61-year-old woman was admitted to a hospital overseas with a brain stem infarction including the pons cerebri due to a basilar thrombosis. This is the most typical brain damage leading to a LiS\cite{4,5}, but because the patient was in coma during the initial phase of the disease, it was impossible to define the extent of the paralysis. An intra-arterial lysis was performed, which resulted in a subarachnoidal and left parietal intracerebral haemorrhage (Fig. 1). When the patient was transferred to the rehabilitation hospital at week 8, she was clinically in VS; she closed her eyes in response to simple visual stimuli and withdrew arms or legs in response to pain, sleep-wakefulness cycle was present, but no indication of conscious perception or intentional action could be obtained. Spontaneous eye movements were observed, but no eye communication code could be established. The Glasgow Coma Scale score was 7. The electroencephalogram showed a prevailing 4-5/s rhythm. Auditory evoked potentials were normal on the left side and delayed on the right.

Therefore, the primary infarct indicated a possible LiS, while the 2 additional haemorrhages could have resulted in a DoC such as VS or MCS. To help in disentangling possible disorders, a battery of functional tests using fMRI was performed. The examination was approved by the Ethics Committee of the University of Tübingen and conducted twice. Informed consent was given by the patient’s legal representative.

At the first examination (day 133), the patient demonstrated startle responses to visual and auditory stimuli, oral reflexes, eye opening to tactile stimuli, but no communication code and no behavioural sign of awareness, which corresponded to a Coma Recovery Scale-Revised (CRS-R)\cite{11} score of 6. The clinical diagnosis was VS. A gradual improvement took place from the sixth month of the disease. During this time intensive behavioural, physical and speech therapy was provided. Medication with amantadine was started, and methylphenidate was added later.

Fig. 1. A computer tomogram of the patient, day 58 after the incident. The tomogram corresponds to slice 1 on the small picture in the lower right corner. Besides a large destruction in the left temporal lobe, one can see the primary upper brain stem lesion (red arrow). The bone defect is a result of the decompressive surgery performed during the acute period.
At the second examination (day 230), the patient showed orientation response to auditory stimuli, spontaneous object grasping, and inconsistent command following. This corresponded to the diagnosis of MCS and a CRS-R score of 9. The clinical condition continued to improve, and by the end of the observation period, 9 months after the incident, communication with eye code was fully reliable and used daily. The patient consistently followed commands. While the right side remained paralyzed, she was able to grip objects and use some of them appropriately with the left hand. Expressive language was lacking. Nevertheless, on the basis of eye communication it was clear that the patient was fully oriented in space, time, and her own person.

### Brain imaging methods and data

fMRI was performed on a 1.5-T Siemens Tim Symphony Scanner. The following procedures were used:

- **Mental imagery.** This task was described in Refs.\(^{12,13}\). The patient was instructed to imagine either playing tennis (instruction T), or walking through her house (spatial navigation, instruction SN). The instructions were given binaurally in the patient's mother tongue and accompanied by 30-s intervals during which the patient was supposed to perform the task. Each instruction was presented 3 times. The contrasts T minus SN and SN minus T were calculated.

- **Trace conditioning.** This procedure has been suggested as a model for explicit (conscious) working memory\(^{14,15}\). In an event-related design, 2 sounds were presented in a randomized order, 30 times each. One of the sounds (CS\(^+\), conditioned stimulus) was followed 15 times by a noxious stimulus (UCS, unconditioned stimulus; electrical stimulation of the left index finger whose intensity twice exceeded the average pain threshold in a comparable control group). The other sound (CS\(^-\)) was never followed by a UCS. The critical contrast was that between CS\(^+\) not followed by a UCS and CS\(^-\).

- **Pain.** In a block design, 60 electrical pain stimuli were presented at the left index finger one per second, followed by a 60-s rest interval. The blocks were repeated 3 times.

Changes in blood oxygenation level-dependent (BOLD) T2*-weighted magnetic resonance signal were measured using a gradient echo-planar imaging sequence (repetition time = 3410 ms, echo time = 50 ms, field of view = 192 mm, flip angle = 90°, 64 × 64, 36 slices covering the whole brain, slice thickness 3 mm, no gap, voxel size 3 × 3 × 3 mm). A T1-weighted anatomical image served as an underlay for the activation pictures. The data were processed using the Statistical Parametric Mapping package, version 8. The contrasts are reported if they attained the level of \(P<0.005\) (uncorrected) in at least 10 adjacent voxels\(^{16}\).

In the first examination, tennis imagery elicited a larger activation than SN in the left and right inferior parietal lobe (IPL), the secondary somatosensory cortex (Brodmann area (BA) 40), the left supramarginal gyrus, and the middle frontal gyri (BA8, BA10). In contrast, SN elicited a larger activation than tennis in the left and right premotor cortex, left supplementary motor area (SMA) and the right postcentral gyrus (Fig. 2).

Pain stimuli elicited activity in the contralateral primary motor and somatosensory cortex. During trace conditioning, significant activity to CS\(^+\) versus CS\(^-\) was found in the anterior portion of the vermis cerebri, putamen, and the inferior parietal cortex.

In the second examination, tennis imagery, compared with SN, was characterized by a larger activity in the left premotor cortex, whereas SN elicited larger activation in the left middle frontal gyrus and the right hippocampus. Pain stimuli elicited large areas of activity in the left and right somatosensory cortex, left and right superior temporal gyrus (STG), left precuneus, and the right motor cortex. The CS\(^+\) in trace conditioning yielded a significant activity in the right IPL and STG.

### Discussion

While the primary basilar thrombosis indicated a severe paralysis (possibly LiS) with a mild (if any) DoC, the subsequent intracerebral haemorrhage may have resulted, additionally, in a severe DoC such as VS or MCS. The clinical pattern of VS was observed during the first 4 months, but it is known that the two conditions can easily be confused.

The significance criterion chosen for fMRI data analysis (i.e., \(P<0.005\) in 10 voxels) is rather liberal. More conservative criteria imply a very high probability of type II errors, i.e., that clinically significant brain activations would remain undetected. In basic studies, the strong preference for
the null hypothesis is justified with the argument that it is better to exclude spurious discoveries due to false alarms. In a clinical examination, however, this strong preference of type II errors in order to avoid type I errors is ethically problematic. It implies that the default diagnosis is always the worst until the patient has proven that she is in a better condition. Although from this point of view even the presently applied criterion appears conservative, it was recently shown to allow researchers a reasonable balance between the 2 types of error\textsuperscript{16}.

Under these criteria, significant activations were found in all 5 contrasts tested. None of the 12 VS patients we have examined to date demonstrated significant activations in the imagery test.
Monti et al. \[17\] examined 54 DoC patients and found a significant activation in the imagery task in 5 of them.

The activations were frequently found in unexpected brain locations. This is particularly important for the critical imagery task, in which both published \[12\] and our own unpublished data in healthy individuals converge on the activity in the SMA in the T–SN comparison, and in the premotor cortex, posterior parietal cortex and parahippocampal gyrus in the SN–T comparison. Only the activation in the premotor cortex was found in the present patient as well. The T–SN comparison largely revealed activity in the somatosensory and frontal regions. The possibility of unexpected regional activations in this task was discussed in relation to the study of Monti et al. \[18, 19\].

To our best knowledge, there is only one study examining functional brain responses in a patient with classical LiS, using a picture-naming task \[20\]. Theoretically, the syndrome implies intact consciousness within a paralyzed body, and, therefore, the results might be identical to healthy individuals. Subjective reports of former LiS patients indicate, however, that many of them have experienced some degree of DoC \[21, 22\]. The difference between the present and previous findings can be attributed to the complexity of the lesion in our patient. Other important factors may be age and etiology. The control subjects used in the basic studies \[12\] were usually university students, and Owen’s \[13\] patient was only 23 years of age compared with 61 years in our case. All reported DoC patients having normal or close-to-normal responses in this task had traumatic head injury \[17\], in contrast to the haemorrhage in our case. Thus, the present patient is the first patient with non-traumatic brain damage who was clinically in VS but showed significant effects in the mental imagery task.

fMRI has been increasingly used in DoC, and recent articles discuss potentials \[17, 20, 23–25\] and possible limitations \[16–18\] of the proposed methods. These potentials can be enhanced, and the limitations removed, with the invention of new stimulation paradigms \[23, 24\]. Thus, a battery of 3 auditory semantic tests provided for a very high correlation (0.81) between fMRI data and the subsequent behavioural recovery \[29\], indicating a possible predictive value of functional brain imaging.

Keeping all these factors in mind, we concluded after the first examination that the patient’s condition would gradually evolve towards LiS or another state of severe immobility rather than VS or MCS. This conclusion resulted in a decision for more aggressive behavioural therapy, later in combination with pharmacological treatment. On the basis of our data, we were able to obtain funding to prolong the patient’s stay in the rehabilitation unit.

We do not claim that already during the first examination the patient was in full consciousness despite the VS-like clinical pattern; such a claim would probably overestimate the clinical significance of the present-state functional brain imaging \[28\]. Rather, we conceived of the fMRI data as indicating the positive potential of the patient’s brain. Likewise, we do not assert that the observed progress can be attributed to the active therapy; obviously, in a single patient the effects of therapy cannot be distinguished from spontaneous recovery.

Teaching point

The lesson from the case is that, in a patient with a complex brain lesion indicative for both LiS and a DoC, fMRI with appropriate stimulation presents a unique means to learn more about the patient’s condition and to assess the remaining cognitive functions.

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