On the Way to the Deep Layers of Consciousness

Assessment of severe disorders of consciousness (DoC) remains very difficult. The rate of misdiagnosis is exceptionally high and does not decrease across time. These facts have led to the idea of using paraclinical methods (EEG, PET, fMRI) in addition to the clinical methods of the diagnosis of DoC including vegetative state (VS).

In 2006, Owen et al. demonstrated, using an fMRI mental imagery paradigm, the ability to follow a complex verbal instruction (and thus the presence of lucid awareness) in a patient clinically diagnosed as VS. However, an analysis of Owen’s method indicates its high false negative rate, that is, even fully conscious patients can fail in Owen's test. This is because the test is well-designed to check for clear awareness but not for deeper layers of subjective experience such as pleasant-unpleasant, pain, or elementary sensation.

In the present article a hierarchical procedure for assessment of several levels of consciousness is proposed based on several fMRI stimulation paradigms. Preliminary data indicate that pre-linguistic, sensory and emotional experience can be preserved in many VS patients lacking all cognitive aspects of consciousness.

What is consciousness?
Is it a unity that can be either present or absent? Or are there several distinct kinds or levels of consciousness? The issue worried philosophers for centuries. For example, Descartes, and more recently logical positivists, regarded consciousness as a unitary domain. In contrast, Husserl and his pupils (among them, Heidegger and Merleau-Ponty) stressed the existence of distinct levels of consciousness. In the recent time, the unitary concept is best presented in Baars’ common working space theory, which states that cognitive processes are conscious when they are accessible for all other processing modules. On the other hand, numerous neuroscientists (e.g., [2]) and philosophers (e.g., [3]) emphasise qualitative difference between various subtypes of consciousness, even though they may largely disagree about what is the demarcation between these subtypes. In more general terms, lower-level consciousness (LOC) describes simple experiences like ‘seeing red’, ‘feeling pain’, or ‘enjoying the taste of wine’. It is assumed to be non-transitive (e.g., it is just to be in pain, not to be in some relation to pain), language-independent and phenomenal (that is, there is something ‘what it is like to be in pain’), and common for humans and many nonhuman animals (e.g., [2-5]). In contrast, high-level consciousness (HOC) is transitive (i.e., it is always ‘of’, or ‘about’ something, includes a relation to something), requires language, presumes an access of the individual to the content of his/her conscious states, and is specific for humans (although its components might, as exception, be observed in very complex animals such as apes) (e.g., [3, 6-8]). Some authors emphasise sensory and affective character of LOC, thus opposing it to the largely cognitive HOC. Panksepp et al. further suggest that ‘raw emotional feelings’ can survive even a very severe brain injury, which leads to the complete loss of cognitive awareness. Therefore, investigations of patients with disorders of consciousness (DoC) may shed light on this old controversy.

There are three major kinds of severe DoC: coma, VS, and minimally conscious state (MCS). Coma is characterised by a complete loss of wakefulness and reactivity VS patients, in contrast, are awake, and their reflexes to simple stimuli such as pain, sounds or flashes are preserved. However, there is no sign of conscious awareness, language understanding, or intentional behavior. If a patient shows weak and unstable signs of consciousness, but the communication is still impossible, the diagnosis is MCS.

The diagnosis of coma usually presents no problem and the main difficulties concern aetiology and, particularly,
prognosis of the outcome. In contrast, in VS and MCS the diagnosis is very difficult, as it requires the subtle differentiation between simple reflex movements and voluntary actions. The former are compatible with both VS and MCS, the latter contradict the diagnosis of VS in any case, and to the diagnosis MCS if they occur systematically.

Both subjective experience and conscious intention are first-person phenomena that cannot be checked for in a completely objective way. Not surprising, therefore, the rate of diagnostic errors is about 40%, and, even worse, this rate has not decreased for at least fifteen years despite considerable progress in the development of assessment techniques.13 15 The majority of these errors are the confusion of VS in any case, and to the diagnosis MCS if they occur systematically.

The obtained brain activities exist that indicate complex cognitive processing of various stimulus qualities. Yet the results of the two approaches were similar: in many VS patients neural activities exist that indicate complex cognitive processing of various stimulus qualities including word meaning. Since, however, the DoC are defined in terms of the lack (VS) or limitation (MCS) of consciousness, the question arises whether the observed cognitive processes can be regarded as indicators of consciousness. The answer is rather negative, because there is vast evidence that each function, including semantic processing, can also be performed without conscious awareness. The obtained brain information processing operations can be necessary for conscious perception or action, but they may not be sufficient.

At this point the research stagnated for a while, but then Owen et al.10 made a breakthrough. The researches asked a young patient who exactly fulfilled the clinical criteria for VS after a head injury to imagine either playing tennis or navigation in their own apartment. In accord with the instructions, the two tasks elicited two distinct patterns of brain activity (as measured using functional magnetic resonance imaging, fMRI), quite similar to the patterns obtained in healthy individuals with the same instructions.

However, an analysis of Owen's method indicates its high false negative rate. The authors demonstrated in several control experiments that a positive finding in such a test would prove the patient's awareness (i.e., the ability to think clearly or problem solving) independently of behavior. However, a negative finding would not prove anything. There is both theoretical and empirical evidence that even fully conscious patients with neurological diseases can fail in Owen's test. This is because the test aims at the higher-order language-related related awareness. If there are (see the first paragraph) other, language-unrelated layers of subjective experience such as pleasant-unpleasant, pain, or elementary sensations, these layers are not addressed.

However, just these elementary aspects of consciousness are of vital importance from the practical point of view. Not the ability to think clearly or problem solving decides whether the patient is a human person or just a mindless body, but the ability to experience

<table>
<thead>
<tr>
<th>Sex/age</th>
<th>Aetiology</th>
<th>Months since accident</th>
<th>Imagery paradigm results</th>
<th>Language paradigm results</th>
<th>Trace conditioning paradigm results</th>
<th>&quot;Empathy&quot; paradigm results</th>
<th>Pain paradigm results</th>
</tr>
</thead>
<tbody>
<tr>
<td>M56</td>
<td>anoxia</td>
<td>38</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2(s)</td>
</tr>
<tr>
<td>M47</td>
<td>vascular</td>
<td>64</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>F56</td>
<td>vascular</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2(s)</td>
<td>3</td>
</tr>
<tr>
<td>M29</td>
<td>anoxia</td>
<td>34</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>M54</td>
<td>vascular</td>
<td>60</td>
<td>0</td>
<td>no data</td>
<td>0</td>
<td>2(a)</td>
<td>0</td>
</tr>
<tr>
<td>F54</td>
<td>anoxia</td>
<td>93</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2(s)</td>
</tr>
<tr>
<td>F62</td>
<td>vascular</td>
<td>66</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F45</td>
<td>anoxia</td>
<td>287</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M59</td>
<td>anoxia</td>
<td>88</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2(s)</td>
<td>1</td>
</tr>
<tr>
<td>F16</td>
<td>anoxia</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2(s)</td>
<td>3</td>
</tr>
<tr>
<td>F38</td>
<td>anoxia</td>
<td>2</td>
<td>0</td>
<td>no data</td>
<td>no data</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M35</td>
<td>vascular</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>F64</td>
<td>anoxia</td>
<td>104</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2(a)</td>
<td>3</td>
</tr>
<tr>
<td>F69</td>
<td>vascular</td>
<td>39</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>F71</td>
<td>vascular</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2(s)</td>
<td>3</td>
</tr>
<tr>
<td>M75</td>
<td>vascular</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>M19</td>
<td>anoxia</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>no data</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F62</td>
<td>anoxia</td>
<td>4</td>
<td>2</td>
<td>no data</td>
<td>no data</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>F30</td>
<td>anoxia</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2(s)</td>
<td>3</td>
</tr>
<tr>
<td>M44</td>
<td>herpes</td>
<td>50</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>M47</td>
<td>anoxia</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2(s)</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: M, male; F, female. The results patterns are coded as follows: 0 = no significant activation; 1 = random activations in unexpected brain areas; 2 = activation of a part of the network expected on the basis of the literature or the own experiments with healthy individuals; 3 = activation in the entire network, comparable with typical activation patterns of healthy individuals; (s) = activations primarily in the sensory portion of the pain matrix (e.g., thalamus, primary sensory-motor cortex); (a) = activations primarily in the affective portion of the pain matrix (e.g., insula, anterior cingulate cortex)
pain and suffer. Furthermore, only a small portion of the diagnostic errors concerned the patients who were in full possession of HOC. Therefore, a method capable of assessing the full-blown, ‘normal’ awareness would only moderately decrease the error rate.

Thus, the aim of the present project was the development of a set of stimulation paradigms designed to investigate different levels of conscious experience without the patient’s ability to demonstrate overt behavior Lake Owen et al., we use fMRI as the recording technique whose relative slowness (as compared to the EEG) is more than compensated for by its ability to reveal the activity of various brain structures including those related to “primary” emotional processes.

The battery needed to fulfil several criteria. Firstly, it should address the different levels of cognitive functions that could possibly remain. Secondly, these functions should be related to consciousness, which is not trivial given that even very complex cognitive processes (e.g., learning) can run unconsciously. Thirdly, the patients’ ability to appropriately respond to the stimuli should be manifested in their fMRI responses. Last but not least, the overall examination time should be limited because DoC patients quickly become tired, and the probability of severe movement artefacts increases with time of testing.

For this reason, our project included the following hierarchical procedure.

1. The mental imagery paradigm was an exact replication of 20 and addressed HOC including its important components, selective attention and working memory.22
2. Patients who cannot follow verbal instructions can nevertheless understand language. In the language paradigm short correct (e.g., May is the month that follows April) and incorrect sentences (e.g., March is the month that follows April) were presented. The paradigm was based on the idea that whereas semantic associations (e.g., cat-dog) can be processed adequately at an automatic level, the understanding of the factual correctness of sentence requires its conscious apprehension. On the basis of the literature, we expected a larger activation in the classical language areas to false than correct sentences as a new physiological sign of sentence understanding.
3. Patients who do not understand language can nevertheless retain the ability to consciously learn. The simplest form of conscious learning is trace conditioning.23 We used a trace conditioning procedure in which two tones were randomly presented 30 times each. One of them (a conditional stimulus, CS) was followed 15 times by a weak electric shock (unconditional stimulus), whose intensity twice exceeded the average pain threshold in a comparable control group. The interval between the CS and the shock was 3 s. The BOLD-contrast was that between the CS not followed by the shock and the other tone, which was never accompanied by a shock.
4. Patients who lost the ability to build new explicit associations can nevertheless retain emotional responses to affective stimuli. Whereas the processes depicted above are learning-related and probably belong to HOC, at least some kinds of emotional experience might be speculated to be inborn and to belong to LOC (of course, we do not know exactly which kind of consciousness is simpler than another kind, because the criteria of simplicity/complexity are highly controversial in this respect). Brain responses to exclamations (screams) expressing pain and suffering were compared with the responses to other sounds of human voice: both positive (e.g., laughing) and negative (e.g., snoring). In healthy individuals, such pain-related sounds elicit activation of the whole pain matrix of the brain even though they are nonnociceptive.24
5. Finally, the fifth paradigm was simply the presentation of nociceptive stimuli, i.e., electrical shocks to the index finger. Here, again, the activation of the pain matrix (as compared with rest) was expected. It is also worth noticing that while several components of this matrix (e.g., the somatosensory cortex) are mainly related to sensory aspects of pain, other components (e.g., the insula and the cingulate gyrus) are closely related to its subjective, emotional aspects.

To avoid the unnecessary patient transportation, two different Siemens MRT devices (1.5 T and 3 T) were used for examinations. In the former in which fourteen patients were examined, T2* weighted MR signal was measured using a gradient echo-planar imaging sequence (TR = 3.41 s, TE = 50 ms, FoV = 192 mm, flip angle = 90°, 64 x 64, 36 slices covering the whole brain, slice thickness 3mm, no gap, voxel size 3x3x3mm). In the latter (seven patients), the corresponding parameters were TR = 2.38 s, TE = 25 ms, FoV = 210mm, 40 slices, voxel size 3.3x3.3x3mm. Individual T1 weighted anatomical images served as an underlay for the activation pictures. The data were processed using SPM8.

Figure 1. Top row: group average brain activation patterns in healthy participants. Bottom row: examples of brain activations in selected VS patients. For a better comparison, the same slice is shown for patients and controls. Leftmost column: the contrast between pain stimulation and rest. Note the activation in the structures (i.e., ACC and insula) related to the emotional rather than sensory aspects of pain. Middle left column: empathy paradigm, the contrast between pain-related and pain-unrelated sounds of human voice. Middle right column: trace conditioning paradigm, the contrast between CS+ and CS−. Rightmost column: language paradigm, the contrast between correct and wrong sentences. According to [26], the activation threshold for individual patients (p<0.05, at least ten contiguous voxels) was selected so that to balance the probabilities of Type I and Type II errors. ACC, anterior cingulate cortex; SI, secondary somatosensory cortex; IFG, inferior frontal gyrus; CS+, a tone that had previously been followed by a pain stimulus; CS−, a tone that had never been followed by pain. All the patients whose data are presented in the figure had VS following a hypoxic brain damage for at least five months.
A total of twenty-one patients (aged 16-75, 11 females) carefully diagnosed as VS took part in the study after the approval of the Ethics Commission of the University of Tübingen and the informed consent of each patient's legal representative. The characteristics of the patients are described in the Table above. In the imagery paradigm, three of the 21 patients showed responses similar to those of control individuals. In the language paradigm, activations in some of the expected brain structures were found in three of 17 patients (the language paradigm was not performed in four patients with a different mother tongue). In trace conditioning, similar positive findings were obtained in eight patients. However, none of the patients displayed a pattern of activity that would entirely correspond to that of healthy individuals in any of these paradigms. Different results were obtained in the other two paradigms. In response to emotional sounds, four patients demonstrated significant activations of the entire pain matrix of the brain including both sensory and affective components, nine patients showed activity in several (but not all) regions of this network, and eight patients showed no response or responses inconsistent with the expected ones. During pain stimulation, eight patients demonstrated activations in the entire pain matrix, practically identical to the responses of healthy controls, and three further patients showed a widespread activity in the components of this matrix related to sensory aspects of pain (thalamus, putamen, cerebellum, somatosensory cortex).

Clearly, these data do not strongly prove the patients’ real experience of negative emotions related to pain and emotional cries. However, the opposite thesis that an unresponsive patient has no subjective experience at all is difficult to defend when significant activity is observed in the entire brain network, or even a considerable part of it, which is known to strongly correlate with such subjective experience. Also, the exact quantitative data reported above should be treated with caution. There are numerous reasons as to why a particular fMRI test may yield a negative result even if the corresponding function in the given patient is preserved. However, the general qualitative trend in the data is unequivocal. Whereas neural correlates of cognitive (presumably conscious) processes are rare findings in VS, correlates of emotional processes are well expressed in many patients. This is in line with the hypothesis that emotional consciousness can remain even despite the nearly complete loss of cognitive awareness. It is furthermore worth noting that our previous experiment has indicated that patients in acute non-traumatic coma can consistently respond to emotional screams like those used in the paradigm of the present study.

From a theoretical viewpoint, the data indicate that the essential cognitive functions constituting our everyday awareness, such as explicit learning ability, biographical memory and language comprehension, do not make the whole of human subjectivity. There may be even more basic and probably simpler functions, which include not only feeling pain and pleasure, but also feeling pain (and perhaps pleasure) of others. However simple, these functions importantly contribute to being human. From a practical viewpoint, the data suggest that emotional contact with caregivers (e.g., using affective prosodic cues, music as affective stimulus, or touch) can be established even in patients with a complete loss of all major cognitive functions. People having pets, and parents of young children, know that the lack of HOE does not completely preclude communication. For many patients fulfilling the diagnostic criteria of VS the same may hold true as well. ♦

Emotional contact with caregivers (e.g., using affective prosodic cues, music, or touch) can probably be established even in patients with a complete loss of all major cognitive functions.

REFERENCES

26. Lieberman MD, Cunningham W Type I and Type II error concerns in fMRI research: Re-balancing the scale. SCAN 2009:4 423-428.