Part II

Proof

5 Does Task-Evoked Activity Entail Consciousness in Vegetative State?

"Neuronal-Phenomenal Inference" versus "Neuronal-Phenomenal Dissociation"

Georg Northoff

Neuroempirical Background: Is Consciousness Based on Cognition?

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Various imaging studies have been conducted during passive sensory stimulation, using mostly auditory, somatosensory, and visual stimuli (see Laureys and Schiff, 2012, for an overview). Most of these studies show somehow preserved activation in auditory and visual cortex in VS, though on a lower level compared to that in minimally conscious state (MCS) and healthy subjects. More specifically, MCS patients show a more widespread activation and higher degrees of long-range functional connectivity in midline regions and lateral fronto-parietal cortex than in VS patients.

These earlier sensory-based studies have recently been complemented by more active cognitive tasks (see later) and emotions. This is especially relevant since consciousness has often been associated with higher-order cognitive functions like imagination, memory, executive functions, attentions, and so on. Therefore, loss of consciousness in VS, for instance, was tacitly assumed to be associated with loss of cognitive functions, including their "willful modulation" by the subject itself (see Hohwy, 2012a, 2012b, for a nice overview of the different functions of consciousness in vegetative state; see focus here mainly on the purely phenomenal aspects).

Based on these findings, one may want to raise the following question: Is consciousness based on cognitive functions and thus cognition-based? I will first discuss various findings from recent studies in VS. This will lead me to reject the hypothesis that consciousness, that is, phenomenal consciousness, is based on cognitive function and thus cognition-based. Instead, consciousness is based on the phenomenal functions of the brain as they are related to its resting state activity (Northoff, 2014a, 2014b).

Neuronal Findings Ia: Cognitive Tasks Induce Region-Specific Neural Activity in the Vegetative State

As we all know only too well, life is full of surprises. And why should that be different in the case of the brain? Let us turn, therefore, to Adrian Owen.

Adrian Owen is a researcher who is interested in consciousness; he especially focuses on the absence of consciousness in VS. Back in Cambridge, England, he investigated one patient with VS during different imagery tasks. This yielded some rather amazing results, as I will describe (see Owen et al., 2006).

What did Adrian Owen do? He scanned a VS patient in fMRI and let him perform specific cognitive tasks. While lying in the scanner, the VS patient was instructed to perform motor and visual imagery tasks (Owen et al., 2006): the patient was asked to imagine playing tennis. Surprisingly this yielded neural activity in the supplementary motor area in the VS patients. This region is related to movements as one imagines or executes them when playing tennis either mentally or physically. Most interestingly, the same region was activated in more or less the same way in healthy subjects. Hence, the VS patient was apparently able to perform a cognitive task as complex as imagining playing tennis. However, one cannot exclude that the observed neural activity is less based on the task itself but generated rather by pure chance.

To exclude such a possibility, Owen conducted the imaging during yet another task, a spatial navigation task, where the patient was asked to imagine visiting and walking around in the rooms of her house. As in the first task, neural activity changes were again induced—this time in other regions like the parahippocampal gyrus and the parietal cortex regions that are closely associated with spatial cognition as required by the task. The very same regions were also recruited in healthy subjects during the same task with regard to their own house or apartment.

Taken together, the results indicate that the VS patient was apparently quite able to perform a cognitive task like seeing visual and motor imagery. Most importantly, the VS patient was very able to differentiate between both tasks in the underlying neural activity patterns.

The results were recently replicated in a larger sample by Monti et al. (2010). Analogous paradigms were here conducted in a larger group of 54 patients, of whom 23 were diagnosed with VS and 31 with MCS (Monti et al., 2010). They had to perform the same tasks, imagining playing tennis and imagining walking from room to room in their own house. Five patients (four VS, one MCS) were indeed able to willfully modulate their neural activity during the tasks in a proper way: imagining playing tennis led to activation in the supplementary motor area (SMA) in all five patients, a region typically associated with either physical or imaginary movements.

In contrast, imagining walking in their own house induced neural activity changes in the parahippocampal gyrus in three VS and one MCS patients. These neural patterns were again similar to those in the healthy control subjects. Since then, other investigations of cognitive tasks requiring task-related efforts and willful modulation have been conducted in VS and MCS, with all showing some preserved neural activity in the respective regions in these patients (see Table 3 in Laureys and Schiff, 2012, for an overview).

Neuronal Findings Ib: Can the Presence of Consciousness Be Inferred from the Presence of Stimulus-Induced (or Task-Related) Activity?

What do these results tell us about VS in particular and consciousness in general? The presence of stimulus-induced activity lets many neuroscientists and philosophers propose that consciousness must be present, too. Otherwise, subjects would be unable to perform the cognitive tasks and elicit stimulus-induced activity. They thus infer the presence of consciousness from the presence of stimulus-induced and task-related activity.

Therefore, a subset of VS patients is these days described as showing "wakefulness," which is further specified as either "responsive" or "unresponsive" (Laureys and Schiff, 2012). However, other investigators have disputed and thus opposed this inference of the presence of consciousness from the observation of stimulus-induced and task-related activity in these patients (see Bernat, 2010; Hohwy, 2012a, 2012b; Monti et al., 2010; Nachev and Hacker, 2010; Panksepp et al., 2007, for discussion).

The opponents argue that the presence of a certain type of neuronal activity itself does not imply anything about the presence or absence of consciousness. Or, they put forward a more behavioral argument stating that the presence or absence of consciousness can only be decided on behavioral grounds, i.e., by the presence or absence of particular behavioral signs, rather than on purely neuronal grounds. We will not follow this discussion at this point in detail; we will come back to it, however, when discussing the relationship between cognition and consciousness in later sections.

Are the VS patients conscious? We do not know at this point, because the VS patients themselves are unable to tell us. What we do know for sure is that the VS patient investigated initially by Owen has regained consciousness since. And we know that these patients seem to show stimulus-induced or task-related activity. That is what we know at this point in time.

In contrast, we do not know whether such stimulus-induced activity that is purely neuronal by itself is accompanied by consciousness and its phenomenal features. More poignantly, we still do not know whether stimulus-induced or task-related activity necessarily or unavoidably entails its own association with consciousness and its phenomenal features.

Neuronal Findings IIa: Electrophysiological Response to Patient's Own Name in the Vegetative State

We discussed so far how the brain in VS reacts to cognitive tasks. This, however, neglected self-specific stimuli seem to relate in a special way to the brain's intrinsic activity. The application of self-specific stimuli may therefore be of high interest in VS. How are self-specific stimuli like one's own name processed in the absence of consciousness and thus in VS?

One can present one's own name in an auditory way and record the related changes in neural activity by electrophysiological measures like electroencephalography (EEG). Do the VS patients show neural activity changes in response to their own names in the same way as they do during cognitive tasks as described earlier? A single case study investigated an MCS patient in EEG during stimulation with emotional stimuli (crying infant) and self-related stimuli (own name). They observed an almost "normal" activation pattern in the patient. The P300, a specific event-related component in EEG associated with cognitive processing, was well preserved while listening to especially the subject's own name (see Laureys et al., 2004).

A study by Perrin (Perrin et al., 2005; see also Perrin et al., 2006) observed the same during auditory evoked potentials in response to the subjects' own names in VS and MCS patients. The P300 was more or less preserved in all MCS patients and present in three of five VS patients. Only the onset or latency of the P300 was significantly delayed in MCS and VS patients compared to that in the healthy subjects.

Another study, by Schnakers (Schnakers et al., 2008), included 22 VS/MCS patients. Schnakers et al. demonstrated that subject's own name induced higher activity in another, later, more cognitive electrophysiological potential, the P300, compared to that in reaction to another person's name. This was stronger in an active (counting of names) than in a passive (mere perception without counting) mode. The difference between active and passive modes was observed only in MCS patients (14), while VS patients did not show any such difference. They were thus apparently unable to properly differentiate between the active and passive condition on a neuronal level.

Fellinger (Fellinger et al., 2011) also conducted an EEG study during one's own and unknown names that were presented in active and passive modes. Overall, the patients (13 MCS, 8 VS) showed stronger lower frequencies (delta, theta) and weaker higher frequencies (alpha, beta) than healthy subjects during hearing both their own and unknown names. Finally, frontal theta (at Fz) especially when hearing their own name was higher in the patients than the healthy subjects.

The pattern was different when the researchers compared active and passive modes of presentation. Healthy subjects showed stronger frontal theta power during the active mode compared to that in the passive mode. This was different in the patients. Like the earlier-mentioned study, the patients could not well differentiate between the two modes, i.e., active and passive, and also showed a delayed onset in frontal theta power compared to that in healthy subjects.

Neuronal Findings IIb: Preattentive Processing of One's Own Name in the Vegetative State

Probing another electrophysiological component in EEG, Pengmin Qin, from China, who is now in our group, investigated the same patients with EEG and focused on a specific electrophysiological potential, the MisMatch Negativity (MMN) (Qin et al., 2008).

The MMN taps into preattentive auditory sensory processing (at around 125–250 ms) by comparing the electrophysiological responses to the same repeating stimuli with the one during one deviant stimulus. To test for self-specificity in the MMN, Pengmin Qin determined the deviant stimulus as one's own name, while a non-self-specific name served as repeating stimulus.

The data show that Pengmin Qin's experimental design was well suited to eliciting an MMN during hearing their own name in all healthy subjects and in the seven patients (two coma, three VS, two MCS). Surprisingly there was no major difference in amplitude and latency in MMN between healthy subjects and the patients. In addition to the MMN, an earlier potential at around 100 ms (i.e., N100) could also be elicited in the seven patients and in two more patients. Interestingly, all the patients who reverted to MCS after three months showed an MMN and an N100. In contrast, no MMN (and N100) was observed in those VS patients who did not revert to MCS (see also Boly et al., 2011, for recent, more or less similar results on the MMN in VS).

What do these and other electrophysiological findings (see Cavinato et al., 2011, as well as Laureys and Schiff, 2012, for an overview of all studies) tell us about the stimulus-induced activity in VS and its relationship to consciousness? They demonstrate that self-specific stimuli can easily elicit neural activity changes in the brain of VS patients. The brain of these patients and thus their resting-state activity seem to be still reactive to stimuli like hearing one's own name. Accordingly, the electrophysiological results concerning self-specific stimuli are very compatible with the ones during cognitive tasks that, as described earlier, also showed preserved stimulus-induced activity in VS.

Neuronal Findings IIc: Neural Activity in Midline Regions During Self-Specific Stimuli Predicts the Degree of Consciousness in the Vegetative State

To investigate the functional anatomy, we turn from EEG and its electrophysiological measures to fMRI, which has a much better spatial resolution. The cortical midline regions seem to have a special role in processing self-specific stimuli. This raises the question of whether the VS patients and their midline regions' neural activity are still reactive to self-specific stimuli. There have indeed been two studies that tested for self-specificity in VS patients as conducted by our group.

Pengmin Qin from our group (Qin et al., 2010) auditorily presented one's own name to seven VS and four MCS patients while they were lying in the scanner (fMRI). He first mapped the relevant regions in healthy subjects by comparing one's own name to familiar and unfamiliar, that is, unknown, names. This yielded activity changes in various midline structures like the supragenual anterior cingulate cortex (sACC), dorsal anterior cingulate cortex (dACC), SMA, superior temporal gyrus (STG), posterior cingulate cortex (PCC), and bilateral insula.

What happens in these midline regions in VS and MCS during auditory presentation of one's own name? All patients were able to induce activity changes though to different degrees. The MCS patients showed higher neural activity in sACC, dACC, PCC, and SMA compared to that in the VS patients. This clearly suggests that these patients' midline regions are still somewhat reactive, meaning that they can induce neural activity changes during self-specific stimuli.

How is the midline activity during one's own name related to consciousness? Pengmin Qin observed significant correlation between the consciousness scores (as measured with the Coma Recovery Scale–Revised [CRS-R]) and the degree of neural activity in the dACC. The higher the signal change in the dACC during the auditory presentation of one's own name, the higher the degree of consciousness the patients exhibited. Those patients with VS showing the highest signal changes were the ones who were most likely to revert to MCS three months later.

One may now want to argue that one cannot be completely sure whether subjects really listened to their own name. The name was presented in a merely passive way requiring no active effort by the subjects to listen so that subjects may have simply not even listened to the name. One can therefore not exclude the neural activity change to stem from sources other than their own name. Hence, one would need an active task where subjects have to actively relate the stimulus to themselves, that is, their own self.

Neuronal Findings IId: Active Self-Referential Task Leads to Decreased Self–Non-Self Differentiation of Midline Neural Activity in the Vegetative State

This is exactly what a subsequent fMRI study of ours in VS by Huang did (Huang et al., 2014). Instead of letting subjects merely passively listen to their own name, they now had to perform an active self-referential task wherein they had to refer to themselves, i.e., their own self. Two types of questions, autobiographical and common-sense, were presented in the auditory mode. The autobiographical questions asked for real facts in subjects' lives as obtained from their relatives.

This required subjects to actively refer the question to their own self, thus being a self-referential task. The control condition consisted of common-sense questions as non-self-referential, where subjects were asked for basic facts like whether one minute is 60 seconds. Instead of giving a real response via button click (as it is impossible in these patients), the subjects were asked to answer (mentally not behaviorally) with "yes" or "no."

Huang first compared autobiographical and common-sense questions in healthy subjects. As expected, this yielded significant signal changes in the midline regions, including the anterior regions like the perigenual anterior cingulate cortex (PACC) (extending to ventromedial prefrontal cortex [VMPFC]) and posterior regions like the PCC.

What did the brains in the VS patients now show in the very same regions? They showed signal changes in these regions that were reduced compared to those in healthy subjects. More specifically, while the VS patients were able to somehow differentiate between the two questions in their neural activity, the degree of neural differentiation remained much lower.

How are these signal changes now related to consciousness? As in the study by Pengmin Qin, a significant correlation in anterior midline regions was observed. The midline regions' activity, the PACC the dorsal anterior cingulate cortex (dACC), and the PCC correlated with the degree of consciousness (as measured with the CRS-R scale).

How is the exact relationship between neural activity in these regions and the level of consciousness? The better the signal changes in these regions differentiated neuronally between self- and non-self-referential conditions, the higher levels of consciousness patients exhibited. Accordingly, as in the earlier-described study, we here observed a direct relationship between the degree of neuronal self–non-self differentiation and the level of consciousness in anterior and posterior midline regions.

Neuronal Findings IIe: Resting-State Activity in Midline Regions Predicts Stimulus-Induced Activity During Self-Referential Task in the Vegetative State

How about the resting-state activity in the same patients? Vegetative patients show strong alterations in the resting-state activity. One wants to know now whether the diminished responses to self-specific stimuli are related to changes in the resting state in the very same regions.

For that, Huang (Huang et al., 2014) also investigated functional connectivity and low-frequency fluctuations in exactly those regions that showed diminished signal differentiation during the self-referential task. The VS patients showed significantly reduced functional connectivity from the PACC to the PCC in the resting state. In addition, the power of particular ranges or bands in the low-frequency fluctuations was significantly lower in the PACC and the PCC in VS compared to that in healthy subjects.

Given that we investigated exactly the same regions during both resting state and task, this strongly suggests that the resting-state abnormalities in these regions are somehow related to the earlier described changes during the self-referential task. This was further supported by correlation analysis: The higher the degree of low-frequency fluctuations in the resting state of the midline regions, the better the stimulus-induced neuronal differentiation between self- and non-self-referential conditions.

Taken together, these findings demonstrate that VS patients not only can induce neural activity changes in their brain in response to merely passively presented self-specific stimuli. VS patients are apparently also able to actively refer to themselves and thus to engage by referring stimuli or questions to their own self, as required in the self-referential task. Thereby the anterior and posterior midline regions, like the anterior cingulate and its distinct parts (i.e., PACC, dACC, PCC), are recruited and seem to be of special significance for associated consciousness to the stimulus-induced or task-related activity.

Neuronal Hypothesis Ia: "Neuronal-Phenomenal *Dissociation*"

What do these findings tell us? First and foremost, they tell us that something must be "right" in the VS patients' brains. Otherwise they would not be able to induce neural activity changes during either cognitive or self-referential tasks. Nor would they be able to differentiate between the different tasks as, for instance, between motor (e.g., tennis playing) and visual (e.g., house navigation) imagery or between self- and non-self-referential stimuli.

These data suggest that what is “right” in VS concerns the induction of stimulus-induced and task-related activity and its relationship to specific tasks or stimuli. This was the easy part. Now comes the hard part. Something must also be “wrong” in the VS patients’ brain. Even though they are quite able to induce stimulus-induced activity, they nevertheless seem to suffer from loss of consciousness, thus being vegetative.

More specifically, the stimulus-induced activity is apparently no longer associated with consciousness. There is thus what one may describe as a *dissociation* between stimulus-induced activity and consciousness. In contrast to the healthy brain, stimulus-induced activity in VS is no longer associated with consciousness. The purely neuronal stimulus-induced or task-related activity is thus dissociated from the phenomenal state of consciousness; one may therefore speak of “neuronal-phenomenal dissociation.”

What exactly do I mean by the concept of “neuronal-phenomenal dissociation”? It means that neuronal and phenomenal states can no longer be characterized by co-occurrence. Even though there is neuronal activity like (more or less) proper stimulus-induced activity as in VS, it is no longer associated with a phenomenal state and thus consciousness. The stimulus-induced activity is consequently detached or dissociated from consciousness and its phenomenal features. This implies what I describe as neuronal-phenomenal dissociation (see later for a more detailed definition).

Neuronal Hypothesis Ib: “Neuronal-Phenomenal *Inference*”

One may now want to argue that such “neuronal-phenomenal dissociation” does not apply for those patients who are actively able to perform cognitive and self-referential tasks as described earlier. Does the presence of neuronal activity during the active cognitive and self-referential tasks signify the presence of consciousness? Such an inference, from the presence of stimulus-induced or task-related activity to the presence of consciousness, seems to be suggested by the most recent introduction of the terms “responsive” and “unresponsive wakefulness” to describe VS (see Laureys and Schiff, 2012).

What does the concept of “responsive and unresponsive wakefulness” mean? The terms “responsive” and “unresponsive” indicate whether these subjects show stimulus-induced or task-related activity in response to certain stimuli or tasks. The term “wakefulness” suggests the presence of an awake and somehow conscious state that is assumed to be necessary for performing the task. The presence of a phenomenal state; that is, consciousness as wakefulness, is here inferred from the presence of the purely neuronal stimulus-induced or task-related activity. Such inference from the presence of a neuronal state to the presence of consciousness and its phenomenal features can be described as the "neuronal-phenomenal inference."

Such a neuronal-phenomenal inference is problematic, however, for several reasons, both empirical and conceptual. Let us focus here on the empirical side of things (while I leave aside the conceptual-logical reasons). As Laureys and Schiff themselves remark (2012), the absence of neuronal activity in response to task-specific instructions may occur for several reasons (as, for instance, technological dependence). Therefore, the absence of neural activity cannot be taken as a marker for the absence of consciousness.

How about the reverse, the presence of task-specific neural activity indicating the presence of consciousness? Does task-specific neuronal activity require and thus presuppose consciousness? If so, these patients must be assumed to be conscious indeed and may therefore suffer from what Laureys and Schiff describe as "functional locked-in-syndrome" (2012). But one needs to be careful here.

Subjects remaining unconscious may show more or less the same activity pattern during the same kind of tasks. We perform plenty of tasks daily in a rather unconscious mode, meaning that we do not "experience" these tasks. We are thus both responsive and wakeful, but not conscious, with regard to these tasks. This means that responsiveness and wakefulness, including their underlying stimulus-induced or task-related activities, do not imply anything by themselves about the presence or absence of consciousness and its phenomenal features.

Neuronal Hypothesis Ic: "Neuronal-*Phenomenal* Inference" versus "Neuronal-*Cognitive* Inference"

Let me be clear what exactly I mean here by the concept of "consciousness and its phenomenal features." The phenomenal features I am targeting here, are the "phenomenal features" in a strict sense, including "inner time and space consciousness," phenomenal unity, self-perspectival and intentional organization, and qualia. These phenomenal features must be distinguished from other, more cognitive features of consciousness like willful modulation, attention, awareness, and access to contents, which I do not debate here (see Hohwy, 2012a, 2012b, for an overview).

This implies a strict distinction between phenomenal and cognitive functions of the brain. The observed results with the neural activity during cognitive tasks suggest that the cognitive functions are somehow preserved in VS. One may thus reason from the presence of neural activity to the presence of the cognitive functions, making a so-called "neuronal-cognitive inference." That does not imply anything about the phenomenal functions themselves, however. To infer phenomenal features and consciousness from the observed neural activity is to confuse cognitive and phenomenal functions of the brain. Accordingly, the results allow for a "neuronal-cognitive inference" but not for a "neuronal-phenomenal inference."

Why do the proponents of the description of VS as "responsive or unresponsive wakefulness" nevertheless confuse these two inferences: the "neuronal-cognitive inference" and the "neuronal-phenomenal inference"? The tacit supposition here is that consciousness is based on cognitive functions and their associated stimulus-induced or task-related activity. This amounts to a cognition- and stimulus-based view of consciousness.

That, however, as we can see, does not really account for the data in VS. Here, the presence of stimulus-induced activity during cognitive tasks is accompanied by the absence of consciousness. This implies dissociation between the "neuronal-cognitive inference" and the "neuronal-phenomenal inference," with only the former, not the latter, being valid. Most important, the rejection of the "neuronal-phenomenal inference" forces us to develop a different account of consciousness, one that is not based on cognitive functions and stimulus-induced activity but rather on phenomenal functions and resting-state activity.

Neuronal Hypothesis IIa: From "Neuronal-Phenomenal Dissociation" to "Neuronal-Neuronal Dissociation"

How about empirical reality? Empirical reality tells us that stimulus-induced and/or task-related activity is present in VS patients, while consciousness seems to be absent. How is such a dissociation between neuronal activity and phenomenal features possible? Let us briefly recapitulate what is clear and what is not in VS.

What is clear is that there is neuronal activity in VS and MCS patients in response to passive sensory stimuli and active cognitive tasks. That is a consistent finding, as described earlier. Their neural activity, the observed task-related activity, is still associated with particular psychological functions like imagining, navigation, self-referencing, and so on (see earlier). This suggests that there is apparently no dissociation between stimulus-induced activity and cognitive functions. There is no "neuronal-cognitive dissociation" in VS, as can be observed in depression or schizophrenia.

In addition, it is also clear that the VS patients show changes in their consciousness in that they are not able to properly associate their otherwise purely neuronal stimulus-induced or task-related activity with consciousness and its phenomenal features. They can no longer experience their own cognitive (and sensory, motor, affective, cognitive, and social) functions in a subjective way, in first-person perspective, as being indicative of consciousness. They thus show a phenomenal deficit, if one wants to say so. One may consequently postulate a dissociation between the neuronal activity during cognitive tasks and the phenomenal features of consciousness. As already indicated, I therefore speak of a "neuronal-phenomenal dissociation," in VS.

How can we further substantiate the concept of the "neuronal-phenomenal dissociation"? The observation of dissociation between two different states or functions usually implies that there must be two different underlying neuronal mechanisms. These two neuronal mechanisms may now dissociate from each other in VS, with one being intact and the other deficient.

What are the two neuronal mechanisms in question? There is the neuronal mechanism that enables the generation of stimulus-induced or task-related activity. And there is the neuronal mechanism that allows to associate the otherwise purely neuronal stimulus-induced or task-related activity with consciousness and its phenomenal features. What does this imply for the neuronal-phenomenal dissociation in VS? The neuronal-phenomenal dissociation suggests that the neuronal mechanisms for generating the neural activity during cognitive tasks are still more or less intact in VS. In contrast, the neuronal mechanisms related to the phenomenal features of consciousness seem to be deficient in VS.

The postulated neuronal-phenomenal dissociation in VS can be traced back to the dissociation between two different neuronal mechanisms: one for generating neural activity (during for instance cognitive functions), and the other for the association of that neural activity with the phenomenal features of consciousness. One can therefore specify the alleged "neuronal-phenomenal dissociation" by what I refer to as "neuronal-neuronal dissociation." What do I mean by "neuronal-neuronal dissociation"? This will be the focus in the next section.

Neuronal Hypothesis IIb: From "Neuronal-Neuronal Dissociation" to "Rest–Stimulus Dissociation"

Exactly what kind of neuronal mechanism are we looking for? The neuronal mechanism in question must allow for the association of a phenomenal state with the purely neuronal stimulus-induced or task-related activity.

At the same time, however, the neuronal mechanism in question must be different from the ones underlying the generation of stimulus-induced or task-related activity by itself. Why? The neuronal mechanisms underlying the generation of the stimulus-induced or task-related activity by itself must be more or less preserved in VS, allowing them to show "normal" stimulus-induced activity. We must therefore search for a neuronal mechanism that lies beneath or beyond the stimulus-induced activity or task-related itself.

How can we better illustrate the situation? Metaphorically speaking, there must be an additional factor coming in besides the stimulus or task itself. And this additional factor must be crucial for associating the purely neuronal stimulus/task and its stimulus-induced or task-related activity with the phenomenal state of consciousness.

What is this additional factor? Let's look at what happens prior to the stimulus-induced activity. The stimulus must interact with the resting-state activity in order to elicit stimulus-induced activity. Such rest–stimulus interaction shows special features like nonlinear interaction via GABA-ergic-mediated neural inhibition, as we will see in further detail in the next section. I now propose that proper rest–stimulus interaction is central for associating the otherwise purely neuronal stimulus-induced or task-related activity with a phenomenal state and thus consciousness.

If, in contrast, rest–stimulus interaction is abnormal, that is, decreased, the resulting stimulus-induced or task-related activity will no longer be associated with consciousness anymore. There may thus be "neuronal-neuronal dissociation" between resting-state activity and stimulus-induced activity in VS.

Such neuronal dissociation may, in turn, be central for the loss of consciousness in VS. Since it concerns the coupling between resting-state and stimulus-induced activity, I describe such neuronal-neuronal dissociation also as "rest–stimulus dissociation."

Conclusion

Taken all together, I propose three different concepts of dissociation in VS. First, stimulus-induced or task-related activity dissociates from the phenomenal features of consciousness, implying what I describe as "neuronal-phenomenal dissociation." I trace such neuronal-phenomenal dissociation back to the decoupling of the neuronal mechanisms underlying stimulus-induced or task-related activity from those related to associating that neural activity with consciousness. I therefore spoke of "neuronal-neuronal dissociation."

I now postulate that the neuronal-neuronal dissociation can be traced back to the decoupling between resting-state activity and stimulus-induced activity. For that reason, I speak of "rest–stimulus dissociation"; this concept can be regarded as the empirical specification of the more general concepts of "neuronal-phenomenal dissociation" and "neuronal-neuronal dissociation." Rest-stimulus dissociation means that the intrinsic resting state activity and the extrinsic stimulus no longer properly interact with each other anymore leading to altered or deficient rest-stimulus interaction (Northoff, 2014a, 2014b; Northoff et al., 2010).

The notion of rest-stimulus dissociation entails that the question for the presence versus absence of consciousness can no longer be decided upon the presence or absence of stimulus-induced activity with the consecutive neuronal-cognitive inference. Instead, the question for the presence versus absence of consciousness in UWS/VS is delegated to the investigation of how the stimulus interacts with the resting state activity. Such empirical investigation of rest-stimulus interaction allows then for what can be described as neuronal-phenomenal inference on the conceptual level.

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