

## Why Is the Distinction Between Neural Predispositions, Prerequisites, and Correlates of the Level of Consciousness Clinically Relevant? Functional Brain Imaging in Coma and Vegetative State

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**A**dvances in cardiopulmonary resuscitation and critical care management of acute severe traumatic, anoxic, or toxic brain injury, have resulted in the survival of many patients who would previously have died. Often patients who had severe brain damage fall into a coma characterized by complete absence of wakefulness and awareness. If not resulting in death, this coma might develop into an acute vegetative state/unresponsive wakefulness syndrome (VS/UWS), when the patient seems awake but unaware, uncommunicative, and unresponsive to the environment.<sup>1</sup> If recovery continues, patients regain minimal responsiveness to external stimuli but remain unable to communicate (the so-called minimally conscious state [MCS]).<sup>2</sup> Otherwise, patients may remain for a long time in a persistent vegetative state (PVS).

Accurate differential diagnosis is essential for the clinical management of patients with disorders of consciousness, but difficult and often leading to diagnostic errors. As a consequence, consensus diagnosis of VS was incorrect in >40% of patients.<sup>3</sup> The reliable assessment of the individual patient's prognosis on the sole basis of clinical findings is even more difficult and in the early stages of the disorder often impossible. However, clinical signs, laboratory, or functional tests (eg, electroencephalography and evoked potentials), as well as conventional neuroimaging methods (eg, computed tomography and MRI) only permit an estimation of the extent of structural brain damage but render only an indirect and incomplete estimation of the functional level that may be relevant for the loss of consciousness.<sup>4–7</sup> One may consequently search for more functional measures, such as positron emission tomography (PET) and functional MRI (fMRI) that may specifically target the neural correlates of the (decreased) level of consciousness rather than the underlying structural damage. Our article aims to review the more recent results from functional brain imaging, such as PET and fMRI in VS/UWS; it is special in that we aim demonstrating differential roles of

metabolic-energetic and molecular (as predispositions) and neuronal-functional (as correlates) markers in disorders of consciousness and the level of consciousness.

### Metabolic and Energetic Deficits as Indexed by Glucose Metabolism

The first functional nuclear medicine studies with <sup>133</sup>Xenon and the scintillation camera demonstrated already a significant diffuse decrease of cerebral blood flow in VS patients, which was correlated to the neurological outcome, that is, the level of consciousness<sup>8</sup>; those patients who recovered had higher mean cerebral blood flow values than those with residual deficits or those who died. These results were confirmed by single-photon emission tomography with <sup>99m</sup>Tc-HMPAO<sup>9</sup> suggesting a global reduction of cortical blood flow to be a reliable predictor of poor long-term outcome: therefore, further investigations have been concentrated on studies of brain metabolism and of early indications of neuronal integrity or on demonstration of responsiveness to external stimuli.<sup>6,7</sup>

The energy metabolism of the brain relies on the supply of glucose, and glucose consumption can be quantified by PET of <sup>18</sup>F-fluorodeoxyglucose. Fluorodeoxyglucose-PET has been used extensively in various normal conditions and in many diseases resulting in an extensive body of data. In brain death, which results from irreversible and complete loss of brain function, functional imaging with fluorodeoxyglucose-PET typically shows a hollow skull phenomenon confirming the absence of neuronal function in the whole brain. In coma, resulting from diffuse bihemispheric cortical or white matter damage after neuronal or axonal injury, or from focal brain stem lesions, gray matter metabolism is on average 50% to 70% of the normal range. However, in patients with traumatic diffuse axonal injury both hyperglycolysis and metabolic depression have been reported.<sup>10</sup>

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Cerebral metabolic rates for glucose (CMRGlc) at 75% of the normal range (measured  $\geq 1$  month after brain anoxia) might predict recovery from postanoxic coma, but a clear relation between CMRGlc and outcome has not been established. In some studies, CMRGlc was related to the level of consciousness and clinical recovery is accompanied by a general increase in glucose metabolism.<sup>11,12</sup>

In the VS, overall cortical metabolism usually is 40% to 50% of the normal range, but in rare cases with residual cerebral activity CMRGlc can be in the normal range.<sup>1,11–13</sup> With prolonged duration of the VS, that is, with the transition from acute vegetative state to PVS, a further reduction of glucose metabolism to 30% to 40% is observed. Differences in the metabolic pattern can be seen according to the underlying cause: in the hypoxic brain, supratentorial glucose hypometabolism was generally homogeneous, but might be accentuated in territorial borderzones. Patients with traumatic VS often show inhomogeneous metabolic patterns with deficits or severely reduced metabolism at sites of primary tissue injury and reduced glucose metabolism of different degrees in the remaining cortical and subcortical structures. Several studies in post-traumatic, as well as in postanoxic VS/UWS reported the glucose metabolism of the cerebellum to be less impaired (18% to 30% below normal controls).<sup>11</sup> A relative sparing of metabolism in the brain stem is usually seen in VS/UWS patients, and is related to maintenance of arousal and autonomic functions in these patients.<sup>14</sup> When patients in a VS recover awareness of self and environment PET shows improvement of regional metabolism in polymodal association cortices and thalamic nuclei.<sup>14</sup>

As demonstrated in a recent comparative study,<sup>13</sup> the VS/UWS can be differentiated from the MCS by quantitative rates of brain glucose metabolism: global cortical CMRGlc averaged 42% in VS/UWS ( $n=14$ ) and 55% in MCS ( $n=21$ ) of normal ( $n=29$ ; mean values and errors: VS/UWS,  $0.127 \pm 0.025$   $\mu\text{mol/g per min}$ ; MCS,  $0.167 \pm 0.005$   $\mu\text{mol/g per min}$ ; controls,  $0.300 \pm 0.306$   $\mu\text{mol/g per min}$ ). Differences between VS/UWS and MCS were most pronounced in the frontoparietal cortex (42% versus 60% of normal). The differentiation between patients with MCS and VS/UWS based on cortical metabolism was accurate in 82%, metabolism in brain stem and thalamus was equally reduced in both the conditions. These findings reveal a relationship between the degree of between cortical metabolism and the level of consciousness (VS/UWS or MCS) and indicate islands of preserved activity across the cortex pathognomonic for MCS.

Patients with locked-in syndrome because of a lesion at the upper pontine level are quadriplegic and seemingly irresponsive to their surroundings, but actually are conscious and can communicate via eye contact with eye blinking or vertical eye movements. PET scanning has shown high metabolic levels in these patients compared with those in VS<sup>11</sup> and can help in early diagnosis of this terrifying condition. EEG in locked-in syndrome exhibits all frequencies, arousal reaction, and sleep spindles. In contrast, EEG shows reduced activity, slowness, no arousal reaction, and no sleep

spindles, whereas MCS exhibits arousal reaction and some sleep spindles.

### Structural Damage as Indexed by GABA-A Receptors

Although fluorodeoxyglucose-PET shows the severe reduction of cerebral glucose metabolism in patients in coma and in VS, it does not indicate whether these changes represent functional inactivation or irreversible brain damage. Structural brain damage is reflected in cortical density of the benzodiazepine receptor, which is a part of the  $\gamma$ -aminobutyric-acid (GABA)-receptor complex. This receptor complex is abundant in the cortex and a highly sensitive indicator of even subtle structural damage. The distribution of the benzodiazepine receptor can be assessed by the ligand 11C-flumazenil and is an early marker of irreversible ischemic structural damage in stroke.<sup>11</sup> In patients with posthypoxic (not traumatic) acute vegetative state ( $<1$  month duration) flumazenil-PET showed a significant reduction of benzodiazepine receptor binding sites in all cortical regions that grossly corresponded to the extent of reduction of cerebral glucose metabolism, whereas the cerebellum was spared from neuronal loss (P. Qin et al, unpublished data, 2015). During follow-up, only 1 of 9 patients gained a state of minimal responsiveness, 4 patients died and 4 progressed to PVS. These results demonstrate that irreversible neuronal damage can be assessed early in posthypoxic or post-traumatic states, a result which is important for prognosis of these critical conditions.

This earlier study has recently been complemented by another on GABA-A receptor by (P. Qin et al, unpublished data, 2015), using <sup>11</sup>F-flumazenil-PET and fMRI. They demonstrated reduced GABA-A receptor binding throughout the whole brain, which is replicating the earlier finding of a global GABA-A receptor deficit. In addition, he observed particularly strong reduction of GABA-A receptors in specifically the salience network that includes the supragenual anterior cingulate cortex (SACC) and the insula as main regions (after normalization for global values).

Most interestingly, the degree of reduced GABA-A receptor binding in whole brain and SACC predicted the degree of the level of consciousness 3 months later. Patients with rather low global and SACC GABA-A receptor binding did show lower consciousness scores 3 months later than those that initially showed less reduced values. The specific involvement of salience network and SACC was further confirmed by resting state fMRI where the same patients showed reduced functional connectivity scores. Taken together, these findings further support the observation of structural damage as indexed by GABA-A receptors throughout the whole brain, as well as specifically in SACC. Clinically important, these data suggest that, if confirmed in a larger sample, the degree of GABA-A receptor binding may serve as predictive marker of therapeutic recovery.

### Resting State Activity Deficits as Indexed by Functional Connectivity and Variability

We to date demonstrated reduced energy metabolism and structural damage in VS/UWS to be central for their loss of

consciousness. How do deficits in both affect the actual function of the brain's neural activity? The functional level of the brain's neural activity can be investigated in both its resting state activity and its stimulus-induced or task-evoked activity. One would expect the metabolic and structural deficits to affect and impede the functional level of resting state and task-evoked activity. Although deficits in both the resting state and the task-evoked activity can indeed be observed (see below), their relationship with metabolic and structural deficits remain unclear at this point in time.

A landmark study by the group around Audrey Vanhaudenhuyse<sup>15</sup> investigated functional connectivity in the resting state using fMRI. They included healthy subjects, as well as 4 VS patients, 5 coma patients, 4 MCS patients, and 1 locked-in syndrome patient. The focus was here, especially, on the functional connectivity within the default-mode network (DMN) that shows particularly high resting state activity. Functional connectivity was the highest in the anterior (like anterior cingulate cortex) and posterior (like posterior cingulate cortex [PCC]) regions of the DMN (and the thalamus and the brain stem) in healthy subjects. The one locked-in syndrome patient exhibited almost similar degrees of functional connectivity as the healthy subjects. In contrast, the MCS patients showed lower degrees of functional connectivity in perigenual anterior cingulate cortex (PACC) and PCC, which were still considerably higher than the ones in VS/UWS in the same regions. VS/UWS patients' degree of functional connectivity in PACC and PCC was, in turn, higher than the 1 in the coma patients. These results suggest the degree of consciousness to be directly dependent on the degree of functional connectivity in PACC and PCC as central DMN nodes. This was further confirmed in subsequent correlation analyses where the degree of PACC and PCC functional connectivity was correlated with the degree of consciousness as measured by the Coma Recovery Scale-Revised. The higher the degree of functional connectivity between PACC and PCC within the DMN, the higher the degree of consciousness obtained on the Coma Recovery Scale-Revised in the clinical patients. These findings have been confirmed in other studies thus pointing to a special yet unclear role of the DMN in VS/UWS.<sup>1,7,11–13</sup>

Because fMRI measures functional connectivity in the infraslow frequency range (0.001–0.1 Hz), 1 would assume these low frequencies to be central for the level of consciousness.<sup>7</sup> This is supported by a recent study by Huang et al,<sup>16</sup> who investigated not only functional connectivity but also variability, that is, temporal variance (SD) of resting state activity. He observed significantly reduced temporal variance in resting state activity in midline regions, such as perigenual anterior and PCC (as part of the DMN) in, especially, the infraslow frequency ranges (0.001–0.023 Hz; slow 5) in VS/UWS. Hence, the degree of spontaneous change as index by temporal variance seems to be significantly reduced in VS/UWS.

One may now assume that reduced resting state variability may be a consequence or results of reduced energetic and metabolic supply, which in turn may be traced to structural damage. For the resting state to be variable costs energy and if the latter is lacking the former may be reduced. However, the exact relationship between energetic metabolism and resting

state activity, that is, variability remains unclear. Therefore, future investigations may want to combine resting state fMRI with fluorodeoxyglucose-PET and <sup>11</sup>F-flumazenil-PET.

### Stimulus-Induced Activity as Measured by H<sub>2</sub><sup>15</sup>O PET

PET studies with fluorodeoxyglucose or flumazenil, as well as HMPAO—single-photon emission tomography are done to estimate the extent of brain damage. Recently, considerable interest has focussed on the ability of the patient in VS to respond to external stimuli because some patients show reactions to noxious stimuli, such as noise and pain. Although distinctive and directed responsiveness to outer stimuli excludes the diagnosis of acute vegetative state or PVS, some reactions could indicate the transition from VS to MCS and might be interpreted as amelioration in the patient's condition predictive of further recovery. However, the observations are scarce and limited to single cases and up to now cannot be considered a reliable tool for clinical assessment and for management decisions.

In 1 post-traumatic VS patient, regional flow changes were observed by H<sub>2</sub><sup>15</sup>O PET in anterior cingulate and temporal cortices during a story was told by his mother. This reaction was interpreted as processing of the emotional attributes of speech or sound. In another patient, presentation of photographs of familiar faces activated visual association areas. In cohort studies, simple noxious somatosensory and auditory stimuli activated primary sensory cortices, but did not affect higher order associative cortices, from which the primary centers were functionally disconnected.<sup>11,12</sup>

These functional disconnections suggest that the observed residual cortical processing in the VS does not lead to integrative processes, which are necessary for awareness.<sup>14</sup> Pain stimulation increased regional cerebral blood flow not only in visual, somatosensory and posterior insular regions, but also in cingulate cortex; this finding was interpreted as residual activation of a pain-related cerebral network in this PVS patients. In patients with MCS who show slightly higher metabolism in medial parietal and adjacent posterior cingulated cortex than VS patients, simple auditory stimulation induced more widespread activation suggesting more complex processing.<sup>17</sup> Cortico-cortical functional connectivity was, therefore, more efficient in the MCS between auditory cortex and a large network of temporal and prefrontal cortices.

### Stimulus-Induced Activity as Measured by fMRI

Recent studies with fMRI have confirmed the previous H<sub>2</sub><sup>15</sup>O PET results showing preserved activation of lower level primary sensory cortices, which are disconnected from higher order associative cortical networks using auditory, visual, or somatosensory stimulations.<sup>12</sup> These investigations again reported that minimally conscious patients showed more widespread activations with cortico-cortical functional connectivity compared with vegetative patients.

Stimuli with emotional content induced a more widespread cortical response than did meaningless noise in MCS. A higher atypical level of cortical activation may even serve as a



surrogate marker of good prognosis. In addition, mental imagery paradigms may permit to identify signs of consciousness in noncommunicative brain-damaged patients.<sup>12,18</sup> However, the widespread clinical application of activation tests in functional neuroimaging requires validation of the relevance and reliability of these techniques in larger cohort studies of patients with chronic impairment of consciousness.<sup>12</sup>

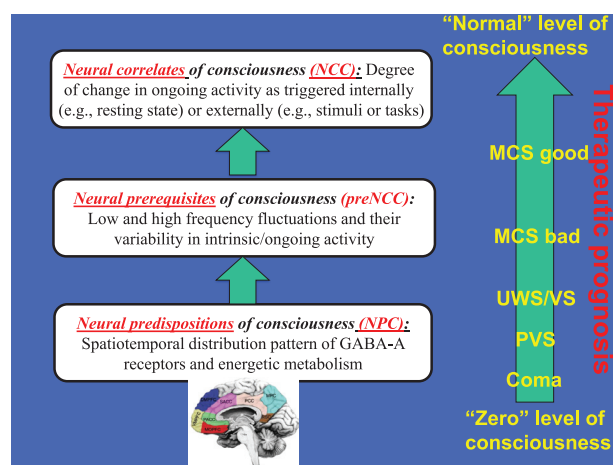
Although the different kinds of activation studies using mostly cognitive paradigms demonstrate the presence of stimulus-induced activity in VS/UWS, the latter's exact relationship to the level of consciousness remains unclear. Correlations between the degree of stimulus-induced activity and the level of consciousness could not be observed, to date, in these studies. The sole exception are studies in which self-related stimuli, such as own name<sup>19</sup> or autobiographical events<sup>16</sup> are used to elicit stimulus-induced activity.

Stimulus-induced activity can be observed in response to own name<sup>19</sup> and autobiographical events<sup>16</sup> in VS/UWS and MCS in, especially, midline regions, such as anterior and posterior portions of the cingulate cortex. The degree of neuronal self–nonself differentiation in these midline regions (and especially, the SACC but not auditory cortex) predicted the level of consciousness at the time of scanning: the better self-related stimuli and nonself-related stimuli can be neurally differentiated from each other in specifically midline regions, the higher the level of consciousness. These data further suggest the central role of midline regions (and DMN) in VS/UWS in mediating the level of consciousness for which, especially, self-related (rather than merely cognitive) processing seems to be essential.

Further support comes from correlation: the higher the degree of neuronal self–nonself difference in midline regions, the higher the patients' level of consciousness.<sup>16,19</sup> Pending confirmation in healthy subjects, the neuronal self–nonself difference may be a marker or neural correlate, that is, sufficient neural condition, of the level of consciousness (NCC). The NCC signify that a certain level of activity change as triggered either externally (by self-related stimuli) or internally (by spontaneous activity changes as during mind wandering and dreams) may be sufficient for the actual level of consciousness.

How are these findings related to the resting state abnormalities? Huang et al<sup>16</sup> investigated both resting state and self-related activity in VS/UWS. He observed that specifically the reduced degree of posterior midline (PCC) resting state variability (see above; but not functional connectivity) predicted the degree of self–nonself stimulus-induced activity. However, unlike the self–nonself-related activity, resting state variability itself was not correlated with the level of consciousness. Therefore, resting state activity and its temporal features, such as variability may play a different role in consciousness: they may be necessary although nonsufficient condition of the actual level of consciousness and signify, therefore, the neural prerequisites of (the level of) consciousness (preNCC; Figure).

The degree of the resting state's spontaneous fluctuations and its variability may, in turn, be predisposed by the spatiotemporal distribution of GABA-A receptors and energetic metabolism. GABA-A receptor density and distribution of energetic metabolism may henceforth be regarded necessary



**Figure.** Different levels of neural activity and mechanisms that generate the level of consciousness and altered in minimally conscious state (MCS), unresponsive wakefulness syndrome/vegetative state (UWS/VS), and coma. The spatiotemporal distribution of  $\gamma$ -aminobutyric acid (GABA)-A receptors and energetic metabolism in, especially, cortical midline regions are neural predisposition of the level of consciousness (NPC).<sup>7</sup> Deficits in NPC in persistent vegetative state (PVS) and coma show the worst clinical prognosis. They lead to abnormal changes in spatiotemporal features of resting state activity as neural prerequisites of consciousness (preNCC). Deficits in preNCC, such as UWS/VS show a better prognosis than NPC deficits (Coma and PVS). The degree of activity change in response to self-related stimuli, that is, stimulus-induced activity is a neural correlate of the level of consciousness (NCC). MCS patients with good (high response) and bad (low response) prognosis, MCS good and MCS bad, show high or low degrees of stimulus-induced activity. The brain shows the main cortical midline regions. MPC, medial parietal cortex; MOFC, medial orbitofrontal cortex; PACC, perigenual anterior cingulate cortex; PCC, posterior cingulate cortex; RSC, retrosplenial cortex; SACC, supragenual anterior cingulate cortex; and VMPFC/DMPFC, ventro- and dorsomedial prefrontal cortex.

conditions of possible consciousness, that is, neural predisposition of (the level of) consciousness (NPC).

The distinction between NCC, preNCC, and NPC may serve as clinical marker for diagnosis. Both coma and VS/UWS seem to be characterized by deficits in the NPC exhibiting global reductions in both GABA-A receptors and energetic metabolism entailing rather bad prognosis. In contrast, MCS shows better preservation in NPC, that is, GABA-A receptors and energetic metabolism suggesting better prognosis, whereas its preNCC, that is, the resting state's spontaneous fluctuations and variability, seem to be still deficient. Prognostically, only those MCS patients may revert to full consciousness who show high activity change in response to for instance self-related stimuli mirroring the NCC.

## Conclusions

PET in patients with coma or VS is useful to assess the degree and extent of functional disturbance (by measuring glucose metabolism) and to identify structural, that is, neuronal damage (by imaging benzodiazepine receptor density). Residual or regained cortical functions can be detected by studies recording the activation to external stimuli. The validity of these findings for estimation of clinical cause and outcome, however, must still be demonstrated in larger follow-up and long-term studies in patients with impairment of consciousness.

Energetic metabolic deficits and structural damage may, in turn, impair the functional level, that is, neural activity as observed during either resting state activity or task-evoked activity. fMRI resting state studies demonstrate a specific role of the midline regions as part of the DMN in VS/UWS showing reduced functional connectivity and variability, that is, temporal variance in these regions. Stimulus-induced activity as probed by cognitive tasks and self-related stimuli is still present in VS/UWS although reduced. Most interestingly, especially, the degree of neuronal self–nonself differentiation in the midline regions predicts the level of consciousness.

Taken together, the findings demonstrate energetic metabolic deficits and structural damage, as well as impairments in both resting state and stimulus-induced activity. Thereby, a particular focus seems to be cortically on the midline regions (and the DMN) and related subcortical deficits. The relation of these different measures and the midline regions to the loss of the level of consciousness in VS/UWS remains unclear at this point in time though. Future investigation will most probably reveal further differentiation of different neural measures contributing in different ways (as neural predispositions or neural correlates) to the level of consciousness and its loss in VS/UWS. Differential and more sophisticated neuronal measures will also allow their use as diagnostic indexes and therapeutic predictors, thus being clinically relevant.

Most importantly, the findings suggest deficits at different levels in VS/UWS and MCS. Coma and VS/UWS show major global deficits in GABA-A receptors and energetic metabolism that may be considered NPC. In contrast, these NPC seem to remain more or less intact in MCS where although the resting state's spontaneous fluctuations and its variability seem to be impaired thus reflecting a deficit in the neural preNCC. Both must be distinguished from the neural correlates of the actual level of consciousness (NCC) that may be related to the degree of activity change as induced either internally or externally; the degree of NCC may serve for predicting conversion to full consciousness in MCS. Hence, if confirmed, the differentiation between NPC, preNCC, and NCC is clinically highly relevant for diagnosis and therapeutic prediction with deficits in NPC having the worst prognosis.

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None.

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