Second International Symposium

Coma and Consciousness

Clinical, Societal and Ethical Implications

4-5 June 2009, Berlin

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Satellite to the 13th Annual Meeting of the
Association for the Scientific Studies of Consciousness

Université de Liège

COMA Science Group

cost EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

MIND SCIENCE FOUNDATION

BERLIN SCHOOL OF MIND AND BRAIN

HUMBOLDT-UNIVERSITÄT ZU BERLIN

James S. McDonnell Foundation

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Welcome Address

Dear colleagues,

Following the success of the first Coma and Consciousness Symposium held in Antwerp in 2004, satellite to the 8th Annual Meeting of the Association for the Scientific Studies of Consciousness (ASSC8), it is a pleasure to welcome you to Berlin for the Second International Symposium on Coma and Consciousness, satellite to ASSC13. We thank ASSC13 organizers John-Dylan Haynes, Michael Pauen, and Patrick Wilken.

This Symposium is a joint meeting of the European Cooperation in Science and Technology COST Action BM0605 "Consciousness: a transdisciplinary, integrated approach"; the Coma and Consciousness Consortium - McDonnell Foundation Initiative Grant "Recovery of consciousness after severe brain injury"; the EU Mindbridge STREP "Measuring Consciousness: Bridging the Mind-Brain Gap" and the DISCOS "Disorders & Coherence of the Embodied Self" Marie Curie Research Training Network. The Symposium is endorsed by the European Neurological Society and is co-funded by the Mind Science Foundation, the Berlin School of Mind and Brain and the University of Liège.

Advances in neuroimaging and neuroscience hold significant promise for improving understanding of disorders of consciousness arising from severe brain injuries. This meeting brings together a distinguished small group of neuroscientists and clinical investigators engaged in the investigation of coma and consciousness and mechanisms underlying large-scale cortical integration, state-of-the-art neuroimaging studies of sleep, anesthesia and patients with disorders of consciousness, and experts in the fields of the neurology of consciousness and ethics who addressed the larger context in which the emerging neuroscience will be received and integrated. The intended goal of this meeting aims at updating and advancing knowledge of diagnostic and prognostic methods, potential therapeutic strategies, and importantly identifying challenges for professionals engaged in the study of these patient populations.

Recent studies have underscored that recovery of consciousness after severe brain injury remains poorly understood. Although public interest is high, the broad needs for systematic research in this emerging area of knowledge are currently unmet. The challenges are surprisingly difficult with a degree of diagnostic uncertainty that may range at the bedside in some patients from unconscious to fully aware, even for patients with no evidence of behavioral responsiveness. As measurements improve, behaviorally defined states from vegetative state (no evidence of self or environmental awareness), minimally conscious state (at least some evidence of awareness), and up but not including patients in locked-in state (full consciousness with no motor control) will reveal subcategories of patients whose level of consciousness we cannot at present with confidence identify.

The contributions presented at the meeting are likely to help form the scientific foundations for frameworks to systematically organize information and approaches to future clinical assessments of consciousness. Equally important is that the strategies for measurement and definition of problems of these challenging disorders of consciousness will advance our basic understanding of human consciousness.

We look forward to a stimulating exchange of views and to fruitful discussions and hope that our joint efforts will ultimately improve the care and understanding of patients suffering from disorders of consciousness.

Steven Laureys	Nicholas Schiff	Adrian Owen
Liège	New York	Cambridge

PROGRAMME SCHEDULE
Thursday June 4

8:00 REGISTRATION

8:30 The need for a transdisciplinary study of coma and consciousness
Steven Laureys and Joseph Dial

9:00 The problem of unreportable awareness
Adam Zeman (Peninsula Medical School, UK)

9:30 (Un)consciousness through coherence
Andreas Engel (University Medical Centre Hamburg, Germany)

10:00 Sleep and consciousness: from theory to measurements
Marcello Massimini (University of Milano, Italy)

10:30 COFFEE

11:00 Why do seizures cause loss of consciousness?
Hal Blumenfeld (Yale University School of Medicine, New Haven, CT, USA)

11:30 Unexpected recovery from Minimally Conscious State : Lessons from Terry Wallis
Joseph Giacino (JFK Johnson Rehabilitation Institute, Edison, NJ, USA)

12:00 Awareness in the vegetative state?
Adrian M. Owen (Cambridge, UK)

12:30-14:30 LUNCH

14:30 The brain's default state and intrinsic functional connectivity
Michael Greicius (Stanford University School of Medicine, CA, USA)

15:00 PET and fMRI correlates of consciousness
Melanie Boly (University of Liège, Belgium)

15:30 The locked-in syndrome and brain computer interfaces
Andrea Kübler (University Wurzburg, Germany)

16:00 COFFEE

16:30 Improving consciousness using deep brain stimulation
Nicholas D. Schiff (Cornell University, NY, USA)

17:00 The neuroethics of measuring and modulating consciousness
Joseph J. Fins (Cornell University, NY, USA)

17:30 Closing remarks

18:00-20:00 Guided walking tour in Berlin's historic core

Friday June 5

8:00 - 9:00 COST BM0605 4th Management Committee Meeting (A. Cleeremans)

9:30 - 12:30 FREE COMMUNICATIONS

- The neural basis of consciousness
- Resting state connectivity during sedation involves key brainstem areas
- The role of frontal lobe in the lowest states of consciousness
- Neural correlates of preserved semantic processing in depressed consciousness
- Losing consciousness: falling asleep during a go/no-go task
- Brain oscillations shaping sensory awareness
- Nonlinear properties of cerebellar electrocortical activity in anesthesia
- Disentangling the automatic from the conscious brain: fMRI in VS
- Thalamic diffusion and volume and clinical correlates in VS & MCS
- Cognitive recovery of VS after EEG zero line: 8-y follow-up study
- VS and MCS: is a differential diagnosis possible in the long term?
- Neurobehavioral treatment in TBI: a randomized controlled trial
- Conditions of altered consciousness in childhood age
- Evaluation of subjective experience and self mechanisms in severe brain trauma
- The “Zombie argument” and disorders of consciousness

12:30 – 14:00 LUNCH

SEE ASSC13 Program (www.assc13.com)

14:00 – 19:00 McDonnell Consortium Management Committee Meeting

Lectures

The problem of unreportable awareness

Adam Zeman (Peninsula Medical School, UK)

We tend to regard consciousness as a fundamentally subjective phenomenon, yet we can only study it scientifically if it has objective, publically visible, manifestations. This creates a central, recurring, tension in consciousness science which remains unresolved. On one 'objectivist' view, consciousness is not merely revealed but endowed by the process of reporting which makes it publicly accessible. On the contrasting 'subjectivist' view, consciousness, per se, is and will always remain beyond the reach of observation - in which case consciousness science can never hope to do more than explore its correlates. I shall explore this tension with examples drawn from clinical neurology, cognitive neuroscience and philosophy. The underlying aim of the paper is to open up the simple but profoundly difficult question that lurks in the background of consciousness science: what is it that we are studying?

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(Un)consciousness through coherence

Consciousness-related changes of activity in deep brain structures - lessons from intraoperative microelectrode recordings

Andreas K. Engel, Andrew Sharott, Christian K.E. Moll (Dept. of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany)

Intraoperative microelectrode recordings from thalamic and basal ganglia (BG) nuclei have become an established diagnostic tool during stereotaxic surgery for deep brain stimulation (DBS), contributing to an improved definition of target sites through additional physiological information. Beyond their clinical relevance, such recordings provide a unique window onto the functioning of circuits in the human brain at a resolution of single cells or small cell ensembles.

This presentation will report intraoperative data (i) on attentional modulation of neuronal activity in thalamus and BG, (ii) on anesthesia-related changes of single-cell activity in thalamus and BG, and (iii) on behavioral and physiological arousal induced by microstimulation of BG structures under anesthesia.

(i) Attention-related data were recorded during performance of an auditory oddball task in awake patients with Parkinson's disease (PD). Single-cell activity was recorded along trajectories targeted at the STN from thalamus, striatum, subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr). In all structures, neuronal activity was found to discriminate between deviant and standard stimuli, suggesting an involvement of the BG loops in attentional stimulus selection.

(ii) Changes of neural activity were studied in PD patients who underwent micro-electrode guided implantation of DBS electrodes in the STN under general anesthesia with propofol and remifentanyl. Recording from thalamus and STN demonstrate profound alterations of neural firing rates and firing patterns compared to activity in awake patients. Under propofol, STN cells showed strongly reduced firing rate and an enhanced tendency for low-frequency bursting. Single spiking was found to be the predominant firing mode of thalamic neurons in the awake patient. In contrast, the firing of thalamic neurons under propofol was dominated by low threshold spike bursts. Interestingly, the firing pattern of neurons of the SNr, one of the BG output structures, did not show major differences to the awake state. However, their firing rate was considerably lower under propofol.

(iii) In several patients with dystonia who underwent implantation of DBS electrodes in the internal segment of the globus pallidus internus (GPi) under general anaesthesia, behavioural arousal could be elicited by microstimulation. Acute unilateral DBS of circumscribed sites within the subpallidal fiber-field with 130Hz caused a transient state of wakefulness with an increased responsiveness to external stimuli, opening and conjugated position of the eyes, but without detectable signs of conscious awareness. Behavioural arousal was accompanied by global cortical EEG activation in the gamma-frequency range and by autonomic activation. These findings suggest that the stimulated neural substrate, presumably pallidal outflow tracts and/or the nucleus basalis Meynert, is involved in the premotor control of lid and eye position and the control of the activation state of the human neocortex.

Taken together, these observations suggest that intraoperative recordings from deep brain structures can provide interesting data on consciousness-related changes in the human brain. Moreover, they suggest at least a partial involvement of BG circuits in selection of task-relevant sensory signals and the regulation of behavioral arousal.

Sleep and consciousness: from theory to measurements

Marcello Massimini (University of Milano, Italy)

Sleep reminds us everyday that consciousness is something that can come and go, grow and shrink, depending on how our brain is functioning. During deep NREM sleep consciousness fades, but cortical neurons remain active, keep receiving information from the periphery and can display patterns of synchronous activity. Why then consciousness fades? According to the Integrated Information Theory of Consciousness (Tononi 2004) what is critical for consciousness are not firing rates, sensory input or synchronization per se, but rather the ability of a system to integrate information. If consciousness is the capacity to integrate information, then the brain should be able to generate consciousness to the extent that it has a large repertoire of available states (information), yet it cannot be decomposed into a collection of causally independent subsystems (integration). A key prediction stemming from this hypothesis is that such ability should be greatly reduced in deep NREM sleep: the dreamless brain either breaks down into causally independent modules, shrinks its repertoire of possible responses, or both. To evaluate integrated information, it is not enough to observe activity levels or patterns of temporal correlations among distant brain regions (functional connectivity). Instead, the ability to integrate information among distributed cortical regions must be examined from a causal perspective: one must employ a perturbational approach and examine to what extent cortical regions can interact causally (integration) and produce differentiated responses (information).

I will report the results of a series of experiments (Massimini et al., Science 2005; Massimini et al., PNAS 2007) in which we employed a combination of transcranial magnetic stimulation and high-density electroencephalography (TMS/hd-EEG) to directly test this prediction in humans. TMS/hd-EEG measurements showed that during wakefulness, a direct cortical perturbation produced a long-range pattern of activation that was specific for the site of stimulation. During NREM, the same perturbation resulted either in a short-lasting local response or in a global and aspecific activation, suggesting a loss of integration and information, respectively. The ability of the thalamocortical system to react to TMS with long-range specific responses partially recovered during REM sleep, a state during which conscious report are more frequent and vivid, although the subject is paralyzed.

TMS/hd-EEG by-passes sensory pathways, subcortical structures and probes directly the thalamocortical system. Thus, at difference with peripherally evoked potentials and metabolic activations, it does not depend on the level of the subject's engagement or on the integrity of sensory and motor systems and can access any patient (unresponsive, deafferentated or locked-in) and any cortical area (including associative cortices). In addition, TMS/hd-EEG can be made portable and may prove a useful tool to assess disorders of consciousness at the patient's bedside.

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Why do seizures cause loss of consciousness?

Hal Blumenfeld (Yale University School of Medicine, New Haven, CT, USA)

Seizures are transient episodes of abnormal brain activity that often impair consciousness. Despite differences between seizures types, impaired consciousness in all seizures arises from dysfunction in a common cortical-subcortical network. Thus, absence seizures, generalized tonic–clonic seizures, and temporal lobe complex partial seizures differ dramatically in their cause, behavior, and electrophysiology. However, recent advances in neuroimaging and electrophysiology demonstrate that these seizures share a common pattern of disrupted activity in the consciousness system, involving the: (i) upper brainstem and medial thalamus, (ii) anterior and posterior interhemispheric regions (cingulate, medial frontal cortex, and precuneus), and (iii) lateral frontal and parietal association cortex. Additional work will be needed with real time behavioral testing of patients during seizures to refine the specific functions of these anatomical areas in impaired conscious arousal, attention, and awareness. Understanding the mechanisms for impaired consciousness in epilepsy has important practical applications for preventing patient injuries and social stigma, and may also shed light on mechanisms of normal consciousness.

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Unexpected recovery from the minimally conscious state: Lessons from Terry Wallis

Giacino, Joseph T. (JFK Johnson Rehabilitation Institute, Edison, NJ, USA)

At age 19, Terry Wallis suffered a severe traumatic brain injury in a motor vehicle accident. He emerged from coma within two weeks and subsequently recovered to a level of function consistent with the minimally conscious state (MCS). Over the course of the next 19 years, he received no formal therapy. Infrequently, he demonstrated simple command-following but developed severe contractures in all four extremities and remained unable to communicate through speech or gesture. At age 38, during a visit from his mother, he spoke his first word since the accident, “Mom,” and within 72 hours, regained conversational speech. Eight months after emerging from MCS, he underwent a series of neuropsychological and neuroimaging studies to investigate potential mechanisms to account for this unusual recovery. Neuropsychological testing revealed temporospatial disorientation, a dense amnestic syndrome and marked executive dysfunction. Although speech was markedly dysarthric, language assessment revealed no aphasic features. No active movement was noted in either lower extremity. MRI showed severe atrophic changes involving the brain stem, body of the corpus callosum and frontal lobes bilaterally. Diffusion tensor imaging showed a marked reduction in white matter tracts bilaterally, particularly within the medial corpus callosum, consistent with diffuse axonal injury. Curiously, well-defined regions of significantly-increased right-left anisotropy were also noted in the medial-parietal occipital (MPO) region, bilateral to the interhemispheric fissure, and contiguous with the splenium of the corpus callosum. On follow-up examination conducted eighteen months later, motor recovery was unexpectedly noted in both lower extremities, speech intelligibility was improved and cognitive performance on measures of attention, response persistence and behavioral regulation increased. On repeat DTI, anisotropy values in the MPO region had diminished and no longer differed from normal values. However, a new region of significantly increased right-left anisotropy was detected in the inferior portion of the cerebellar vermis, closely correlating with the recovery of lower extremity movement and speech intelligibility. FDG-PET images of resting metabolism provided converging evidence of relatively increased activity in the MPO area, at both assessment points. The late improvement in motor and cognitive functions noted over the 18 month assessment interval, occurring in temporal contiguity with the anisotropic changes, suggest that that Mr. Wallis’ functional recovery was mediated by ongoing neural reorganization.

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Awareness in the vegetative state?

Adrian M. Owen (Cambridge, UK)

How can we ever know, unequivocally, that another person is aware? Notwithstanding deeper philosophical considerations about the nature of consciousness itself, the only reliable method we have for detecting awareness in others is by eliciting a predicted response to an external prompt or command. Logically therefore, our ability to detect awareness in others is determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognized behavioral response. This problem exposes a central conundrum in the study of awareness in general, and in particular, how it relates to the vegetative state. From this perspective, I discuss various solutions to this problem using functional neuroimaging. In particular, I will contrast those circumstances in which fMRI data can be used to infer awareness in the absence of a reliable behavioral response, with those circumstances in which it cannot.

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The brain's default state and intrinsic functional connectivity

Michael Greicius (Stanford University School of Medicine, CA, USA)

Recent developments in functional MRI (fMRI) have allowed for the study of functional connectivity within brain networks detected as subjects rest quietly in the scanner. This has proven to be an important advance in allowing the use of fMRI in clinical scenarios (dementia, sedation, sleep, coma, etc…) in which subjects are unable to perform even simple tasks required for standard task-activation fMRI research. This talk will consider several intrinsic connectivity networks (ICNs) reproducibly detectable in resting-state fMRI studies. The focus will be on the default mode network but other ICNs and their putative functions will also be considered. The bulk of the talk will focus on the potential clinical relevance of ICNs in neuropsychiatric disorders generally and disorders of consciousness in particular.

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PET and fMRI correlates of consciousness

Melanie Boly (University of Liège, Belgium)

Patients in a vegetative state (VS) and minimally conscious state (MCS) continue to pose problems in terms of their diagnosis, prognosis and treatment. Consciousness is a subjective first-person experience which study has remained the field of philosophy for the past millennia. That time has finally changed and empirical evidence from functional neuroimaging is offering a genuine glimpse on the solution to the infamous mind-body conundrum. New technological and scientific advances offer the neurological community unique ways to improve our understanding and management of severely brain damaged patients.

Good medical management starts by making a correct diagnosis. There is an irreducible limitation in knowing for certain whether any other being is conscious. Vegetative patients can move extensively and clinical studies have shown how difficult it is to differentiate reflex or 'automatic' from voluntary or 'willed' movements. This results in an underestimation of behavioral signs of consciousness and hence a misdiagnosis, estimated to occur in about one third to nearly half of chronically vegetative patients.

PET and fMRI studies permitted to reject the ancient view that vegetative patients are neocortically dead or a-pallic. A succession of neuroimaging data has shown cerebral activation in isolated and disconnected islands of "lower level" cortices or "pallium" in response to auditory, visual, somatosensory and noxious stimuli. Functional neuroimaging studies have also provided scientific evidence that residual brain function in VS is very different from the brain's integrative capacity in MCS.

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The locked-in syndrome and brain computer interfaces

Andrea Kübler (University Wurzburg, Germany)

The main purpose of a brain-computer interface (BCI) ist to detect changes in brain activity related to human intention. An algorithm translates the brain signals to control a device such as a computer program or neuroprosthesis. A large proportion of BCI rely on neurofeedback to enable users to regulate their brain activity in a specific frequency band and location. Although BCI are developed for a range of clincal and non-clinical purposes, a large amount of effort is put in developing BCI for restoring motor output in patients who lost motor control or function, or both due to injury or disease. Despite an exploding research to improve detection of brain signals and to translate those in device commands, little is known about how the brain instantiates BCI control on the basis of neurofeedback and what limits such control. Sensorimotor rhythms (SMR) and slow cortical potentials (SCP) of the brain both look back on a long history of research about their origin, their neurophysiological basis, and their neuropsychological correlates. Those brain signals where intensively investigated in neurofeedback paradigms long before the idea of motor restoration was born. Both components of brain activity were subject to operant conditioning and could be brought under voluntary control. Such control lead to an improvment of motor and cognitive function, and e.g., in patients with epilepsy to a significant reduction of seizures. Psychological models of how the brain instantiates its own regulation comprised operant and motor learning. Generating SMR and SCP requires an intact brain stem – thalamic –cortical system. SMR synchronisation and desynchronisation can be understood as either the opening or closing of the thalamocortical gate that selectively enables or blocks information flow. Control of SMR and the improvement thereof may be a result of long-term potentiation with more effective transduction of the neural signal. SCP depend on sustained afferent intracortical or thalamocortical input into cortical Layers I and II and simulataneous depolarization of large pools of pyramidal neurons. SCP of negative polarity are indicative of depolarized cortical cell assemblies whereas positive SCP correspond to increased cortical excitation thresholds. To regulate SCP a circuit including the basal ganglia, thalamus and prefrontal cortical areas has to be selectively activated. Taken together, an intact attentional network is necessary for BCI control, but awareness of the mental strategies of BCI control is not necessary.

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Improving consciousness using deep brain stimulation

Nicholas D. Schiff (Cornell University, NY, USA)

We will here review the scientific rationale supporting the potential use of deep-brain electrical stimulation (DBS) in the central thalamus as a method to improve behavioral responsiveness following severe brain injury. Neurons within the central thalamus are selectively vulnerable to disconnection and dysfunction following severe brain injuries because of their unique geometry of cerebral connections. Because the central thalamus plays a key role in forebrain arousal regulation, impaired function of these cells has a broad impact. Prior clinical investigations, however, have targeted some components of the thalamus and related subcortical structures to improve behavioral responsiveness after severe brain injuries without providing evidence of sustained and clinically meaningful behavioral effects. Here important differences in conceptual framework, consideration of diagnostic categories for patient selection, and anticipated mechanisms of effect that distinguish earlier approaches and current studies are reviewed. As opposed to targeting chronically unresponsive patients, current efforts focus on identification of conscious patients with significant preservation of large-scale integrative cerebral networks. The potential mechanisms and limitations of this evolving strategy are discussed, including the need to develop frameworks to calibrate patient selection to potential clinical benefits, range of potential effect size, and other present unknowns.

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The neuroethics of measuring and modulating consciousness

Joseph J. Fins (Cornell University, NY, USA)

Until recently the measurement of consciousness was done by clinical examination and disorders of consciousness were beyond the therapeutic pale. With the advent of functional neuroimaging, deep brain stimulation and novel pharmacologic efforts it is now possible to both measure and modulate consciousness. In this session I will explore the relationship between the measurement of consciousness and its manipulation. I will focus on the import of rigorously distinguishing between inferred and actual evidence of consciousness by considering the discordance that can emerge between what is observed on neuroimaging studies and what is demonstrated behaviourally. To this end I will consider the liminal existence of those individuals who demonstrate the neural substrate capable of consciousness but remain unable to realize their full promise. I will stress the ethical import of rectifying these differences through the continued development of means and methods that can instrumentally harness residual cognitive abilities and yield functional communication which is the *sine qua non* of unimpeachable consciousness.

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Free communications

The neural basis of consciousness

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[2] National Institute for Laser, Plasma and Radiation Physics, Bucharest, Romania

Aim: The purpose of this paper is to show the role the two reticular systems (ascending reticular activating system - ARAS and ascending reticular inhibitory system - ARIS) may have in consciousness.

Methods: The consciousness processes belong to people who act by control mechanisms of psychological activities, generalization and abstractization mechanisms, by exploring and handling of mental images to solve all the problems man is facing with. The consciousness level depends on the complexity of the brain ontogenetic evolution. It must be a function of numerous interacting systems. Data based on authors' neurosurgery experience are shown to support this statement.

Results: The major structures supposed to play a key role in the neural correlates of consciousness are: the brainstem, the diencephalon (the hypothalamus and thalamus), the limbic system (especially the hippocampus and amygdala) and the cerebral cortex (1). The brainstem is the source of massive reticular formation pathways that activate or inhibit higher and lower brain centers. They are the core of the basic arousal and sleeping cycle. The hypothalamus, the thalamus and the cerebral cortex are likely closely intertwined with RF which plays a key role in consciousness. In general, there are an ascending reticular activating system (ARAS) and an ascending reticular inhibitory system (ARIS) (2).
However, ARAS which appears to be responsible for maintaining cortical arousal is not the same with consciousness.
Sleep is based on ascending reticular inhibitory system. The two reticular systems (ARAS and ARIS) are under the influence of the suprachiasmatic nucleus and of the awake and sleep centers in the hypothalamus. So, as much as awake is determined by ARAS, sleep considered the most profound natural alteration of consciousness, an active function, is determined by ARIS.
Lesions of the ascending reticular inhibitory system produced the logorrhea syndrome with hyperkinesia, hyperwakefulness and hyperprosexia.

Conclusion: This brief overview of the problem of consciousness indicates how thoughtful philosophers and brain scientists have struggled to clarify their views on this topic. And as the debate and the search goes on, neurosurgeons will make their unique contributions to this intriguing conundrum.

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Resting state connectivity during sedation involves key brainstem areas

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Aim: To identify neural correlates of consciousness by investigating whether the administration of propofol changes the connectivity of the default mode network (DMN), the set of areas active during "no task" fMRI.

Methods: Propofol was administered using a target controlled intravenous infusion to three target plasma levels - no drug (baseline), 0.6 mcg/ml (low sedation) and 1.2 mcg/ml (moderate sedation).We acquired resting state fMRI (150 volumes, TR=2s) from a group of 14 adults, 19-52 years old (mean=34.62) on a Siemens Trio 3T scanner (WBIC, Cambridge). We instructed volunteers to close their eyes and think about nothing in particular. fMRI images were corrected for slice-timing acquisition differences, spatially normalised to the MNI template and smoothed with an $8mm^3$ Gaussian kernel. We calculated DMN connectivity using time series from the posterior cingulate cortex (PCC) as the variable of interest in a linear regression model that also included global mean, global white matter and CSF signals as variables of no interest. We report clusters that survived a random field cluster threshold of $p \leq 0.05$ corrected for the entire brain. All processing was carried out with SPM5.

Results: At baseline the DMN primarily comprised the PCC and precuneus, medial prefrontal cortex (MPFC), bilateral parietal cortices and hippocampi (1). Bilateral parahippocampal, lingual, angular and postcentral gyri, calcarine sulci, and the R cerebellum were also involved. The DMN at low sedation additionally involved supplementary motor area and middle/anterior cingulate cortices (MCC, ACC). Further increases in DMN connectivity were observed during moderate sedation with more extensive ACC and pre/post central gyrus involvement. The observed increases in connectivity may represent the neural correlate of excitation during light anaesthesia. Statistically significant increases in connectivity from baseline to low sedation were found in the R putamen and R globus pallidus. Significant increases from baseline to moderate sedation were found in the ACC, L inferior parietal, L supramarginal, L pre/postcentral gyri, and in the reticular formation in the brainstem.

Conclusion: Increased resting state connectivity in cingulate and sensori-motor networks has been reported following sedation with midazolam (2,3). We report similar findings with propofol but importantly we also report a change in connectivity in the region of the reticular formation which has been implicated both in slow wave sleep (4) and consciousness (5).

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The role of frontal lobe in the lowest states of consciousness

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Aim: To analyze the role of frontal lobe in patients in low-level states of consciousness--vegetative state, minimal conscious state, and severe neurocognitive disorders--and to explore functional cortical connectivity differences using clinical psychological neuroimaging data.

Methods: The study included 16 TBI patients (7 MCS and 9 SND in non-acute phase, 14 male, 2 female, aged 18–49). Patients were selected from the Center for Brain Injury Rehabilitation (C.RE.CER.) in Seville, Spain. All participants underwent a three-scale assessment used by clinicians to evaluate low-level brain-injured patients. These scales include the Coma/Near Coma Scale, the Level of Cognitive Functioning Scale, and the Functional Independence Measure (FIM) + functional assessment measure (FAM), known as FIM + FAM. We used a 19-electrode (10-20 placement) system, with 256 Hz sampling frequency and bandwidth between 0.1 -- 100 Hz to explore coherence. The 19 electrode locations were divided into 5 regions: frontal, left temporal, central, right temporal and parietal-occipital. We applied standard coherence and Granger causality analyses.

Results: Our results indicate that SND subjects show more coherent activity -better connectivity patterns- between frontal and parietal-occipital and between temporal and parietal-occipital regions, with greater consistency in beta, alpha and theta bands.
Conclusion: The dysfunctions observed may be the result of deafferentation of the frontal lobe with the other cortical regions. The degree of preservation of the prefrontal parietal network may account for differences in awareness level between the lowest states of consciousness.

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Neural correlates of preserved semantic processing in depressed consciousness

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Aim: We aimed to investigate functional interactions between regions involved in semantic processing during depressed consciousness. These interactions were explored in a sedation model using the anesthetic agent propofol in healthy volunteers.

Methods: 17 right-handed, native English speakers were sedated with propofol using a target controlled infusion to three target plasma levels - no drug, 0.6µg/ml (light sedation), and 1.2µg/ml (moderate sedation). At each level subjects performed a semantic decision task on spoken concrete nouns while undergoing fMRI. Data were analysed with SPM5. Psycho-physiological interaction (PPI) analysis was used to model functional connectivity between the L inferior frontal gyrus (LIFG) and the rest of the brain during the semantic decision task at each sedation level. Time series were extracted from a spherical volume (6mm radius) of interest in the LIFG, the centre of which was derived from the peak activated voxel in the group analysis of spoken word stimuli vs. non-speech sounds. This was treated as the explanatory variable in a linear regression model, with activity from all other voxels treated as the response variable; this analysis was restricted to trials with correct semantic responses. We report clusters that survived a random field corrected cluster threshold of $p \leq 0.05$.

Results: Activity in the LIFG during the no drug condition positively correlated with activity in bilateral anterior and mid cingulate cortices, superior and middle temporal gyri, and in the left pars opercularis and pars triangularis, bilaterally in the putamen and in the right pallidum. This connectivity was absent during mild and moderate sedation. A direct assessment of the interaction between the connectivity pattern and sedation level revealed that sedation produced statistically significant decreases in connectivity between the LIFG and bilateral anterior and mid-cingulate cortices, and the R putamen.

Conclusion: Tasks involving semantic judgement are known to activate anterior cingulate cortex (ACC) (1); further, ACC and LIFG show coordinated activations during language comprehension (2,3). We show that activity in LIFG predicts ACC activity during correct semantic processing when awake. Propofol sedation decreases connectivity between LIFG and ACC, despite preserved semantic processing shown by behavioural responses. The ACC-LIFG interaction may not be crucial for successful semantic processing, and absence of this interaction does not predicate absent semantic processing in subjects unable to report responses.

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Losing consciousness: falling asleep during a go/no-go task

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Aim: To map the EEG-ERP and behavioral pattern changes from fully awake, to drowsy, to sleep stage 1 and 2 in a decision-making task.

Methods: We asked a group of subjects to press a button to a series of tones (go-left) and a different button to other tones (go-right). There were also tones that required the subjects to take no action (no-go trials).

Results: Preliminary analysis showed that reaction times got longer and more variable when going from full wakefulness to drowsiness. The evoked response to the tones became stronger in sleep stage 1, and the preparation/decision potential changed morphology but still showed differences between go and no-go trials. Stage 2 showed no button press responses but there were still some lateralized potentials to the left hand and right hand tones. The pre-trial signal predicted the subsequent motor response for most of the trials.

Conclusion: On the basis of these preliminary findings, we believe that decision making depends on conscious control and it is still, to a certain extent, spared in sleep Stage 1 but appears inconsistent and heavily dependent on the conscious microstate (pre-trial state). We believe there was a tone-hand association consolidated during wake and stage 1 showing no decision related processes in stage 2, nevertheless a memory trace was “on hold” since when the subjects emerged form sleep they reinitiated the task spontaneously.

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Brain oscillations shaping sensory awareness

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Incoming information from the outside world is sometimes consciously perceived but sometimes remains without conscious awareness even if the stimulus material is unchanged. Recent data suggests that oscillatory phenomena such as pre-stimulus alpha power or pre-stimulus phase-locking may determine the faith of the incoming information. We will shortly review this fascinating topic having implications for any study tackling the “neuronal correlates of consciousness”.

Hanslmayr and colleagues (1) revealed that the perception of a shortly presented stimulus is related to – or even predicted by – weak phase coupling in the alpha frequency (8-12 Hz) and high phase coupling in the beta/gamma frequency ranges (20-45 Hz). In another study using somatosensory stimuli Palva and colleagues (2) reported that conscious cortical processing is related to widespread cortical phase locking in somatosensory, frontal, and parietal regions as early as 30-70 ms from stimulus onset, whereas phase locking to unperceived stimuli remains weak and locally restricted. In addition, enhanced phase alignment was found to be present before subsequently perceived stimuli, indicating that the phase of ongoing cortical activities biases subsequent perception. Interestingly even for sleep there are reports that meaningful events can be detected (3). In a recent study using simultaneous EEG/fMRI we then wondered whether neurophysiological responses associated with auditory stimulation during deep sleep may not also depend on the phase of the slow oscillation in which a specific tone is occurring. Indeed preliminary results indicated that cortical responses to tones appear preferentially during pre-peak phases, whereas at the peak negativity subcortical activations are observed. The fact that stimuli presented during sleep are usually not consciously perceived may be simply explained by classical findings of Benjamin Libet demonstrating that at least 500ms of stable evoked activity is required for conscious sensory experience to emerge (4).

We conclude that the exact temporal window when a stimulus arrives determines the faith of that very material. During waking it are theta, alpha and higher brain oscillations which indicate the attentional state of an organism and thereby determine whether sensory awareness will occur. During sleep on the other hand the phase of the slow oscillation shapes the short discrete temporal windows during which the brain remains open to external stimuli.

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Nonlinear properties of cerebellar electrocortical activity in anesthesia

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Aim: Our intention was to analyze by nonlinear methods the rat cerebellar electrocortical activity in various states from anesthesia to alertness as there is a considerable interest regarding the contributions of cerebellum to various aspects of cognition.

Methods: Electrocortical activity (ECoG) of cerebellar vermis and parietal lobe were recorded in adult Wistar rats in accordance with the European Council Directive (86/609/EEC) for the care and use of laboratory animals. For chronic recordings, the stainless steel screw electrodes were implanted (under general anesthesia with ketamine 75 mg/kg, ip) in the skull towards target areas: anterior and posterior left/right parietal cortex (stereotaxic coordinates: 2.5 and 6.0 mm caudal to bregma, 2.0 mm left/right of the midline) and paravermal cerebellar cortex (10.5 mm posterior to bregma and 1.5 mm left/right of the midline). Chronic recordings were carried out between 7-10 days after the electrode implantation, inside a custom-made cage where the animal could move freely, be quiet or sleep. For acute experiments the electrodes were positioned at the same target cerebral and cerebellar areas but the recording procedure was performed under anesthesia (Nembutal - 40mg/kg or Zoletil – 60mg/kg) while the animal was fixed in a stereotaxic frame. Simultaneously, 4 biosignals (cerebellar and cerebral ECoGs) were sequentially acquired and digitized at the sampling rate of 256 Hz, in various states (awake, anesthetized ...). The nonlinear measures of biosignals - values of fractal dimension (FD, according to Higuchi, 1988) and Hurst exponent (HE, Martinis et al, 2004), were calculated.

Results: We have found that the mean values of fractal dimension of cerebellar activity are greater than the mean FDs of cerebral in wakefulness as well as in anesthesia. The mean values of FD at cerebellar level in wakefulness could be higher than in anaesthetized state, what is in accordance with the values of HE, where HE<0.5 might indicate absence of long memory effects.

Conclusion: The nonlinear measures, such as HE and FD can be successfully applied to describe not only cerebral activity but also the cerebellar activity in various states of consciousness and could be useful for improving diagnostic methodology.

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Disentangling the automatic from the conscious brain: fMRI of the vegetative state

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Recent evidence has suggested that functional neuroimaging may play a crucial role in assessing residual cognition, and awareness, in brain injury survivors. In particular, brain insults that compromise the ability of patients to produce motor output may render standard clinical testing ineffective. It is in these situations that functional neuroimaging may provide a window on brain function without requiring any behavioral response by the patient. Using brain activity data to assess residual cognition, and especially awareness, however, presents many of the same complexities of teasing apart reflexive from voluntary behavior faced by bedside testing. Can automatic brain responses be separated from willful mental effort?

To address this problem, we propose and present data from a hierarchical approach to patient assessment, based on fMRI. In this methodology, different sensory modalities are tested at increasing levels of complexity. At the lowest level basic sensory perception is probed (e.g. sound perception, presence or absence of light). In a series of tasks we then follow neuro-cognitive systems along their processing stream, testing increasingly complex stimuli. In the case of vision, for example, color perception, motion, and object recognition are sequentially tested. At the highest level of the hierarchy, this approach probes for the ability to willfully modulate brain activity (e.g. top-down allocation of attention).

From a methodological standpoint, we argue that careful methodology may suffice to enable interpretation of brain activation, particularly for what pertains tests of volitional activity. In this latter case, when 'task' and 'baseline' epochs are perceptually identical, and only differ for their respective instructions, it becomes difficult to interpret differential brain activation without assuming a willfully different "mind-set" across the two conditions.

Thalamic diffusion and volume and clinical correlates in VS & MCS

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Introduction: Vegetative state (VS) is a clinical condition characterized by the maintenance of the arousal in absence of awareness. The minimally conscious state (MCS) represents a progression from the vegetative state in which the patient demonstrates inconsistent but reproducible evidence of awareness of self or the environment. In patients who had suffered traumatic brain injury (TBI) leading to a VS or MCS, post-mortem works have demonstrated that one of the most striking neuropathological finding is damage in the thalamus.

Aim: We aimed to study *in-vivo* the integrity and volume of the thalami in a group of patients in VS or MCS following severe TBI.

Methods: We acquired diffusion tensor imaging (DTI) data from a sample of patients in VS (n=3) or MCS (n=9) and 19 healthy voluntary controls with a 3T scanner (Magnetom Trio Tim, Siemens Medical Systems, Germany). DTI data were preprocessed using FMRIB Software Library [FSL, version 4.1.0; Oxford Centre for Functional MRI of the Brain, UK; http://www.fmrib.ox.ac.uk/fsl/] to obtain mean diffusivity (MD) maps. We manually defined the thalami for each subject in native space. The internal boundary was defined by the third ventricle and the external boundary by the internal capsule. MD mean values and volume were obtained from each thalamic ROI and analyzed using SPSS v.16. We used non parametric Mann-Whitney *U* to compare patient and control groups and Spearman's rho to correlate the thalamic measures with the score in the Disability Rating Scale (DRS) in the patients group.

Results: Both thalamic MD and volume were significantly reduced in the patients group compared to controls (U = 20, $p<0.001$; U = 30, $p=0.001$ respectively). We found a negative correlation between the thalamic volume and the DRS score in the patients group (*rho* =-0.68; p = 0.023).

Conclusion: These findings demonstrate that the analysis of DTI images is a feasible approach for *in-vivo* identification of changes in the thalami that might be partially explaining the clinical profile in VS and MCS patients.

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Cognitive recovery of VS after EEG zero line: 8-y follow-up study

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Aim: The vegetative state describes a unique disorder in which patients who emerge from coma appear to be awake but show no signs of awareness. Patients with non-traumatic brain-injury who remain more than 3 months in the vegetative state are classified as "persistent" vegetative (1). The aim of the present study was to assess the cortical functions in a patient who was diagnosed as persistent vegetative since seven years. Shortly after he suffered from a severe hypoxia his EEG showed a zero line and no evoked potentials could be obtained.

Methods: In 2001 a 51-year-old man sustained a severe hypoxia as a result of an epileptic seizure. No evoked potentials were recorded at this time and he showed an EEG zero line. Seven years later no signs of awareness were present and the patient remained unresponsive. According to the international guidelines he fulfilled the criteria for the diagnosis of persistent vegetative state. In 2008 and 2009 we used an electrophysiological test battery to measure his cognitive functions. The test battery contained the following paradigms: a) cortical learning was assessed by using a series of 10 runs of 800 Hz sine tones and an 11th run which contained tones of 1500 Hz; b) attentional and memory processes were assessed by using an active and passive oddball paradigm; c) language processing was examined by using word pairs.

Results: We found in both sessions evidence of the N100 and P200 in response to tones. In addition, we found evidence of cortical learning. Moreover, signs of higher awareness were observed, reflected in the P300 to targets in the oddball paradigms, which was larger by trend in the active oddball compared to the passive oddball paradigm. Also, we found larger N400 to unprimed words than to primed words in the word pair paradigm.

Conclusion: The results confirm that, despite fulfilling the clinical criteria for a diagnosis of persistent vegetative state, this patient retained cortical recovery and even the ability to respond to verbal stimuli through his brain activity, rather than through speech or movement. This case study clearly demonstrates that cortical recovery is possible even after seven years from a condition in which no evoked potentials were recorded immediately after the brain injury and the patient showed an EEG zero line. The results are very important regarding the ongoing discussion about the euthanasia.

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VS and MCS: is a differential diagnosis possible in the long term?

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The differential diagnosis among Vegetative State (VS), Minimally Conscious State (MCS) and Locked-in Syndrome (LIS) is not as simple as reported in the international literature. In fact, the recovery of visual fixation and pursuit, which is not universally considered as equivalent to obeying commands, is, nevertheless, a fluctuating interactive behaviour with the environment. Likewise, psychomotor agitation is frequently observed in patients with severe brain injury who may not yet be able to follow simple orders. Agitated patients often show intentional aggressive behaviours against themselves or others; however, also in these cases the extreme attentive exhaustibility or oppositive behaviours rarely make these patients able to obey simple commands. According to the definition of VS as the “lack of any understandable behaviour in response to external stimulus or inner need”, aggressiveness may be interpreted as the manifestation of physical or emotional discomfort or of mental confusion that the patient is unable to express otherwise. Therefore, rather than a syndrome “in search of a name”, as reported by Jennett, VS can be defined as a name in search of a universally accepted definition. Clinical misdiagnosis between VS and MCS is indeed reported in percentages from one third to half of the chronic VS patients. The differential diagnosis between VS and MCS and LIS is not always obvious. It is reported that some LIS patients are unable to communicate by eyelid movements because of palsy that extends also to ocular motility (1). In such cases, the clinical differentiation between VS and LIS may be very difficult. Indeed, this could be the case in the Owen et al case study, where one patient diagnosed as VS was able to perform a complex mental imagery task, as demonstrated by fMRI. In our clinical experience some VS patients pass through LIS during recovery of consciousness. This process does not always occur in the presence of structural brain stem lesions, but is often associated with diffuse axonal injury with a functional disconnection syndrome (2). We conclude that behavioural lack of interaction with the environment does not always lead to the exclusion of awareness, even in some chronic VS or MCS patients. The video recordings of some patients will here be presented, in order to discuss if visual fixation or pursuit as well as functional use of objects, pain reactions or even simple command following may be sufficient to establish the presence or the absence of conscious interaction with the environment.

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Neurobehavioral treatment in moderate to severe TBI: a randomized controlled trial

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Aim: To determine the effects of a systematic neurobehavioral treatment therapy approach on neuropsychological and functional performance in patients with traumatic brain injury (TBI).

*Methods***:** All subjects with TBI were enrolled in comprehensive post-acute rehabilitation after sustaining a moderate-severe injury resulting in significant loss of consciousness. Two groups of ss with moderate-severe TBI (experimental n = 21, and control n = 14) and one group of non-injured normal ss participated, n = 16. TBI ss were randomly assigned into the experimental or the control group and were matched on critical variables and severity indices. There was no difference between TBI participants in pre-tx performance on dependent measures such as the MPAI-3, CIQ, or any of the neuropsychological measures. The experimental TBI group received systematic neurobehavioral training as part of a clinical trials project testing the effects of the Categorization Program (Constantinidou et al., 2001). TBI subjects in the control group did not receive the CP training; instead they received cognitive tasks traditionally used in their facility. Subjects were monitored in order to receive similar amounts of cognitive treatment. Subjects received about 12 weeks of post-acute rehabilitation. Ss were assessed before rehabilitation and at the end of their treatment.

*Results***:** MANOVA yielded significant gains ($p < .05$) on 12 neuropsychological measures for the TBI experimental group in the areas of processing speed, reasoning, concept formation, visual memory, and executive functioning. The control group improved on 6 of the neuropsychological measures. In terms of functional gains, MANOVA yielded significant gains on total post CIQ for both groups ($p = .0001$). Pairwise t-tests showed significant changes on the 3 subscales for the experimental group. TBI controls only improved in Productivity subscale. MANOVA on the MPAI-3 resulted in significant improvement for both groups on all subscales.

*Conclusion***:** Neurobehavioral treatment is beneficial to patients with TBI. However, patients enrolled in a systematic categorization training demonstrate a greater degree of neuropsychological and functional improvement than patients who receive conventional cognitive rehabilitation. Future studies need to determine the long-term effects of such treatment.

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Conditions of altered consciousness in childhood age

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Aim: Many acutely ill children are not fully conscious. Most make a full neurological recovery as the underlying cause is treated, but considerable skill is required to distinguish the group at high risk of further deterioration, potentially leading either to death or to severe handicap. This article is an attempt to guide the worried pediatrician in casualty or on the ward faced with a child in non-traumatic coma who may need intensive care. The most effective method of deciding the order of priorities in this emergency situation is to ask oneself a series of questions which will be evaluated in this article. Of utmost importance in the practice of neurological critical care is the treatment of cerebral edema, when possible, and the control of life-threatening seizures. In this regard, severe traumatic and non-traumatic head injury and refractory status epilepticus are useful clinical therapeutic paradigms. Evidence-based treatment established for these conditions has, by necessity, a wider application to other much less frequent causes of coma and acute neurological illness managed in the intensive care therapy unit.

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Evaluation of subjective experience and self mechanisms in severe brain trauma

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Aim: Our experience with severely brain-injured patients at various levels of (un)consciousness reveals a broad spectrum of emotional states and behaviors, both of patients and their families, and of hospital staff. This emotional communication has often been discarded as minor phenomena, compared to motor, cognitive and language skills.
The aim of this study was to arrange the systematic observation of the basic emotional and behavioral events of the brain injured patients in low awareness states. We assumed that our data might be a clue to a better understanding of the subjective experience and the "core self" mechanisms even in the absence of overt verbal communication.

Methods: Observational pilot study. For evaluation of emotional events in very severe brain injured non-verbal patients we applied the modified Ester Bick's psychoanalytically oriented method of infant observation from early-child-development research. We organized a seminar led by a clinical psychologist trained in the field of infant observation. The seven members of the observational group were all professionals working with brain- injured patients and their families in various contexts (physiotherapy, occupational therapy, speech therapy, nursing, psychology, social work, etc.); Each participant was asked to have an continuous observation of one patient while instructed to listen, to observe, and to document each session in full detail. In the course of the observation in different daily regular situations the observer focused on the patient, the family, and the surroundings, including staff members. Each presentation was discussed on the team meeting. Analysis of the emotional reactions of observers was an integral part of discussion.

Results: Variable reactions were observed among patients according to their arousal status, changes in their environment and during interactions with family members, staff, and the regular therapists. We have observed changes in facial expression, sometimes voluntary body movements, involuntary reflective movements, increasing tonus, appearance of dystonic movements, and prominent autonomic reactions, i.e. acceleration of heart beat, entering a "vegetative storm". The observation also reveals the high levels of anxiety among family members and the different defensive mechanisms of staff within the rehabilitation unit.

Conclusion: Our conclusion is that it is possible to use this methodology in order to approach the understanding of the emotional reactions and “self” manifestations of the patients in low awareness state. The observation facilitates the understanding of family reactions and the defense mechanisms of the staff. This could open possibilities of applications in institutional facilities.

The "Zombie argument" and disorders of consciousness

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A spectre is haunting Europe—the spectre of Communism.
K. Marx & F. Engels, The Communist Manifesto (London, 1848)

Likewise, a spectre of the philosophical Zombie is haunting the modern philosophy of mind and parasitises over the issue of consciousness. In contrast to its non-philosophical brethren, this being looks and behaves exactly like each of us but is presumed to have no "inner world", no conscious experience. Regarding clinical applications, the Zombie argument inter alia results in the apparent "other minds problem", implying our principal inability to know anything but indirect hints about the presence of consciousness in a neurological patient.

In the present talk the roots of Zombie argument are followed to classical rationalist philosophy of 17th-18th centuries on the one hand, to the computer metaphor on the other hand. It is shown that on the basis of both philosophy (Dewey, Heidegger, Wittgenstein, Ryle) and natural science (e.g., Plessner, Prigogine, J.J.Gibson, Rosen, Kaufman) of the 20th century, Zombie argument does not sound. Very briefly, the very condition of life is a self-sustaining process entailing an inner constituent ("organism") and an external constituent ("environment"), and the organism can only exist through continuous inclusion in its body ("embodiment") of elements from the environment. The organism becomes itself "about" the environment, and the environment becomes "the content" of a living body. If this primary aboutness as the attribute of life can be regarded as a basis of sentience and, finally, of consciousness, then no living being can ever be Zombie, as none can exist without including its environment in its content, i.e., without having intentional relationship to external "things". In other words, each living being must possess something like proto-consciousness.

Turning now to clinical issues, this approach removes the dualism between "first-person" and "third-person" processes, thus making obsolete the "other minds problem". Consciousness manifests itself in "transactions" (Dewey) between organism and world. From neuroscience we learn that these obvious manifestations are related to other, less obvious ones (e.g., if I cry for pain, my insula and ACC are activated). If the former do not work as diagnostic signs in a patient, the latter can be used instead. The other minds problem, as a philosophical issue, is either equally valid for coma patients and for any healthy fellow, or it is invalid altogether. If you can never "exactly" know whether a patient has consciousness, you cannot know whether I have either. What remains when this problem is removed is a technical diagnostic problem, which can albeit be very difficult but remains completely within empirical neuroscience and is not more philosophical than any other difficult diagnostics in medicine (e.g., pancreas tumor).

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Participants Abstracts

Automated quantification of fMRI "resting state" brain connectivity in VS

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Aim: The aim of this study is to assess fMRI resting-state cerebral connectivity in vegetative state patients by means of a user-independent method. Resting baseline (or "default mode") activity is thought to be related to awareness of the internal world (i.e., mind wandering, daydreaming, mental imagery, inner speech etc) and encompasses posterior-cingulate/precuneal, anterior cingulate/mesiofrontal and temporoparietal junction cortices.

Methods: We here present a novel clinical application for a user-independent "default mode" network analysis. Resting state data were acquired on 12 vegetative state (age range 27-87 y) and 26 healthy subjects (21-60 y). Patients' diagnosis was based on Coma Recovery-Scale assessment prior and following scanning. Data were pre-processed and analyzed using independent component analysis ICA as implemented in Brain Voyager. Connectivity studies employed 13 target regions of interest (10x10x10 mm) defined on an average "default mode" map calculated in controls. Resting state connectivity was assessed by calculating the number of functional connections within the "default mode" map for each subject. Next, student-T tests compared patients to controls at the group-level ($p<0.05$).

Results: Compared to controls, vegetative patients showed a lower total number of edges (i.e., connections; 46 +/- 15 and 24+/-9, p=5*10^-6) and less functional connections with the precuneus (9+/-2 and 4+/-3; p=7*10^-4). The "default mode" network shows a reduced connectivity in vegetative patients as compared with controls mainly in posterior brain areas encompassing the precuneus and posterior parietal cortices.

Conclusions: The presented connectivity ICA method permits a user-independent identification of the "default mode" network connectivity in the vegetative state. Comparison with healthy control data emphasizes the importance of precuneal and posterior parietal functional disconnections in pathological loss of consciousness.

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Behavioral quantification of the "Resting State"

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Aim: Despite neuroimaging evidence that awareness of environment (external) and of self (internal) are anticorrelated, switching their activation at an average rate of 0.06 Hz (Boly et al., 2008, Soddu unpublished data), little is known about the behavioural quantification of the resting state. The present study provides behavioural data on the relationship between external and internal awareness.

Methods: 31 healthy volunteers were in a resting condition (i.e. sitting with eyes closed), avoiding structural thinking (e.g. counting). 66 auditory prompts were presented at random intervals via headphones. The participants' task was to rate on a keyboard their external and internal awareness state as it was before the presentation of the prompt on a 4-point scale (0 = absent; 1 = mild; 2 = moderate 3 = maximal). The content of awareness was indentified via thought sampling.

Results: At the individual level, 24/31 subjects showed significant anticorrelation between internal and external awareness (1/31 positive correlation, 6/31 no significant correlation, $p < .05$). At the group level, Spearman's r was calculated at -.44, ($p < 0.02$ two-tailed). On average, the switching from internal to external occurred at 0.05Hz (range: 0.01-0.1Hz).
Self-reports for external awareness included auditory (100% subjects), somesthetic (90%), olfactory (20%) and visual (10%). Self-reports for internal awareness included experiment-related thoughts (80% subjects), autobiographical (65%) and inner speech (20%).

Conclusion: Our results confirm the predicted anticorrelation between internal and external awareness at the behavioural level. The temporal dynamics of external to internal switch is in line with previous neuroimaging data. Our study bridges the cognitive and physiological characteristics of the brain 'default' resting state activity.

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Cerebral activation to patients' own name uttered in the vegetative state

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Aim: To evaluate the differences in brain activation in response to presentation of the patients' own name spoken by a familiar voice (SON-FV) in VS and MCS patients.

Methods: By using fMRI, we prospectively studied residual cerebral activation to SON-FV in 10 VS and 1 MCS patients. Standardized behavioral evaluation was performed after fMRI.

Results: 5 VS patients and the 1 MCS patient failed to show any significant cerebral activation. 1 VS patient showed SON-FV induced activation in auditory cortices involving Heschl's gyrus (HG) and Brodmann's areas (BA) 41-42. Finally, 4 VS patients not only showed activation in HG and BA 41-42 but also in hierarchically higher order associative temporal areas involving BA 21-22. 3 VS patients showing no activation and 1 VS patients showing primary activation show no further recovery. All the 4 VS patients showing the most widespread activation subsequently showed clinical improvement. Other 2 VS patients who failed to show any significant cerebral activation also showed clinical improvement, among them, 1 patients showed wider activation after conscious recovery while scanning one more time. The 1 MCS patient show activation to other audory task while scaning.

Conclusion: It is suggested that the cerebral responses to the SON-FV as measured by fMRI might be a useful tool to predict or reflect the conscious recovery of the VS patients.

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Distinctions between disorders and enhancements of consciousness
Towards a comparison of MCS/VS patients and meditation experts.

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Disorders of consciousness in minimally conscious state (MCS) and vegetative state (VS) patients (Bernat, 2009; Demertzi, Laureys & Boly, 2009) have important parallels to maps of changes in consciousness derived from Indo-Tibetan models of meditative expertise development as described in classical yoga texts such as Patanjali's Yoga Sutras circa 200 BCE. These models of meditative stages involve a series of conscious (Samprajanata) and nonconscious states (Asamprajanata) that are marked by both the cessation and transformation of various cognitive and autonomic functions. The progression of these higher meditation stages is marked by decreases in awareness of time, space, environment and self. However these decreases are not permanent or irreversible, and lead to paradoxical intensifications of awareness, equanimity and well-being, culminating in a nonconscious dissolution of self-object duality. The neural correlates of experiences in meditation experts during highest yogic meditation states are as yet undetermined (Cahn & Polich, 2006; Newberg & d'Aquili, 2000; Lutz et al., 2008; Newberg & Iversen, 2003; Vaitl et al., 2005) but thus far suggest the involvement of various processes including the deafferentation of superior parietal regions associated with dissolution of bodily self-schema, as well as changes in function and connectivity of fronto-parietal, limbic, resting, and sensori-motor networks. Similarly, MCS, VS, and comatose patients can be distinguished by progressively decreasing glucose metabolism in parietal regions, and fragmented attentional and self-relevance functions. Neuroimaging assessment paradigms that involve passive viewing of attention-demanding self-referential stimuli such as first names or one's own face, or that involve the evaluation of emotional stimuli or errors, may be applicable to understanding similarities and differences in the function of brain networks in both MCS/VS patients and individuals experiencing highest meditative states. For example, the dropping out of self-awareness at highest stages of meditation may be akin to the lack of reactivity to self-relevant stimuli in VS as compared to MCS patients. The direct examination of coma patients with disorders of consciousness and meditation experts with enhancements of consciousness may help us to parse consciousness with greater accuracy. Other questions include: how is the reorganization or disconnection between fronto-parietal and sensory networks achieved voluntarily by meditation experts and how is it different from the disorganization evidenced in MCS/VS patients ? Further, how do meditation experts turn off or permanently modify the mechanisms of evaluation and self-awareness ? The outstanding possibility is that meditation experts volitionally induce a set of states that overlap with some of the non-volitionally induced characteristics of disordered consciousness currently known to exist in MCS and VS patients.

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Consciousness & autonomic dysfunction in absence seizures

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Aim: The purpose of this presentation is to show bilateral, symmetric spike-wave (S-W) discharges of 3-4Hz arising from talamocortical networks and correlate them with the clinical picture of impaired consciousness and paroxysmal autonomic dysfunction in idiopathic generalized epilepsy with non-convulsive absence status epilepticus in adults.

Methods: EEG and wake-sleep EEG after sleep deprivation were performed in 21 year old female patient with episodes of impaired consciousness and 24 year old male patient with episodes of mild cognitive impairment and predominant autonomic dysfunction. Somatoneurological status was normal in both patients as well as brain MRI. findings.

Results: Episodes of impaired consciousness with erroneous behavior lasting for hours and usually finishing with generalized tonic-clonic seizures (GTCS) were reported in female patient history starting at her age of 14 years. Antiepileptic drug (AED) treatment was started with carbamazepine with seizure aggravation of GTCS. Episodes of paroxysmal autonomic dysfunction with palpitation, nausea, confirmed ECG signs of tachycardia, bradycardia, arrhythmia, high blood pressure lasting for hours repeating once or twice per year were reported in male patient history starting at his age of 17 years. These events appeared usually on awakening, after partial sleep deprivation, the patient manifested a mild cognitive impairment as being slow, but responsive, without amnesia for the events. These events were unrecognized as seizures for years. Epilepsy was not suspected and AED was not introduced. His father had rare GTCS, incompliant, died unexpectedly at the age of 55, when SUDEP was suspected. EEG performed during such long lasting episodes of impaired consciousness in both patients showed series of bilateral, symmetric spike-wave (S-W) discharges of 3-4Hz lasting from 1 to 4 seconds each, arising from a normal background activity, confirming the epileptogenic nature of these episodes. Diagnoses of idiopathic generalized epilepsy (IGE) with phantom absences and absence non convulsive status epilepticus (SE) were established in both patients and with GTCS in female patients with therapeutic and prognostic implications. Complete seizure control is achieved in the follow up period with valproate administration.

Conclusion: EEG could confirm the epileptic nature of impaired consciousness in non convulsive absence status epilepticus in adults. Different clinical manifestations even in a unique epilepsy syndrome of IGE with generalized S-W discharges suggest specific neural network engagement and propagation, affecting the talamocortical neural networks and brain stem region.

Numerical simulations of respiratory rhythms and brain spirography in coma

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Aim: To outline levels of Na+, K+, Ca++ ions and neurosynaptic peptides influencing brain rhythms dynamics allowing to simulate respiratory rhythms comparable with those obtained with brain spirography diagnostic routine from heavy stroke patients (NIHSS>20 pts) with consciousness disturbances. To modify existing stroke clinimetric scales with factors obtained from simulations of breathing patterns.

Methods: We studied model of neural rhythm generators controlling the breathing patterns. This network consists of three interconnected groups of neurons in the dorsomedial brain stem: the Pontine Respiratory Group (PRG), Dorsal Respiratory Group (DRG) and the Ventral Respiratory Group (VRG) with inspiratory and expiratory neurons. The multilevel dynamics of neural networks creating rhythmic activations was studied in dependence of clinical and biochemical parameters. Different types of breathing patterns generated by the model were compared with those obtained from ischemic unconscious patients. Simulated patterns were compared with clinical data using global numerical parameters describing nonlinear characteristics of physiological systems: Fractal Dimension and Kolmogorov-Sinai entropy.

Results: Comparison of the results of the breath rhythms simulations with clinical data. Description of the correlation of nonlinear parameters of ionic streams with patients' clinical status.

Conclusion: We described and analyzed correlations between clinimetric parameters of neuronal dynamics. Differences which could be used for differential diagnosis of vegetative state and other consciousness disturbances were outlined. Modifications of existing clinimetric scales basing on parametrical correlations of the clinical data and computer simulations.

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Consciousness & non-linear analysis of brain spirography in ischemic stroke

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Aim: Breath rhythms originate from regulation loops considered as coupled oscillation systems. The model of respiratory control system described by Kollar presents a nonlinear behavior of respiratory-control-system chaotic properties. The observations of patients with strokes and transient ischemic attacks (TIAs) suggest aggravation of breath-rhythms changes. The aim of the study was to find possible correlations between clinical status of heavy ischemic stroke patients with consciousness disturbances diagnosed with brain spirography, assessed with numerous clinimetric scales, and numerical values of nonlinear data analysis methods for investigating properties of human respiration rhythms - Fractal Dimension and Kolmogorow-Sinai entropy.

Methods: A group of 22 ischemic stroke patients (NIHSS>20pts, GCS<7pts.), aged 73.3+/-2.29, 11men and 11 women were analyzed. Respiration disturbances were investigated with experimental device - brain spirograph - 3 times a day for minimum 5 first days of stroke. Nonlinear data analysis methods for investigating properties of human respiration rhythms were applied.

Results: There was deep correlation between the degree of consciuosness disturbances assessed with Glasgow Coma Scale and Insuffitientia Trunci Cerebri scale and numerical parameters of non-linear analyses of breath rhythms. The mean value of FD was 1.944+/-0.031 was significantly different (p=0.005). The values of entropy appeared to be vice-versa proportional.

Conclusions: Mutual correlations of non-linear parameters could be the basis of a new, dynamic clinimetric scale for ischemic patients with consciousness disturbances.

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fMRI findings in recovery of consciousness: a case report

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Aim: To evaluate the differences in brain activation in response to presentation of the patients' own name spoken by a familiar voice (SON-FV) in VS and after conscious recovery.

Methods and Results: A 26-year-old man with bilateral frontal and temporal cerebral injury was admitted to the Rehabilitation Centre. CRS-R scale 8/23 indicate vegetative state. fMRI using own name indicate no brain activation. One month after fMRI scanning, the patient suddenly emergent to good recovery with CRS-R scale 23/23. Half month later own name fMRI indicate activation in bilateral primary and secondery auditory cortex.

Conclusion: This one case study describes that fMRI findings by using subject's own name might be useful as an index for the recovery of consciousness.

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Consciousness and Attention in Autism Spectrum Disorders

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Aim: Understanding Autism Spectrum Disorders (ASD) (1,2) at the level of neural information processing using computational modeling, linking genetic, molecular, neural and behavioral levels, including the role of attention and consciousness.

Methods: The ability to shift attention between objects in computational neural model depends on properties of ion channels. Neural dynamics may serve as a bridge between genetic and molecular level on the one hand and behavioral level on the other.

Results: ASD may be treated as a whole family of developmental disorders leading to a broad spectrum of behavioral deficits emerging from neural dynamics that is a result of abnormal properties of neurons and synapses. Autism has been linked to many genetic and environmental factors that influence metabolic processes in cells and change biophysical properties of neurons, creating dysfunctional membranes, ion channels and synapses, even whole cortical minicolumns (2). Correlation of ASD with epilepsy (40%) and metabolic problems is an obvious result of this aetiology. In this study the influence of leaky ion channels on neural fatigue in a model of visual attention shift is studied. The model includes LGN, V1, V2, V4/IT, and V5/MT visual areas with 9 layers that contain almost 1000 neurons; it has been implemented using Emergent simulator (3) that includes biologically plausible learning mechanisms combining Hebbian and error-driven learning with k-winners-take-all inhibition and bidirectional activation propagation. The key element that is necessary for recognition of multiple objects that are shown to such system as input is the coupling between MT and IT areas that allows first to localized and then to synchronize (focus attention) neural activity on one of the objects. Fatigue of neurons results from inhibitory leaky ion currents and allows for desynchronization of neurons and attention shifts to other objects. Various channelopathies (CASPR2 genes influencing calcium, or SCN2A sodium channels) slow down this process and as a result the system stays in one attractor unable to focus on other stimuli or reach an attractor for quickly changing stimuli.

Conclusion: Wide range of ASD symptoms may be generated from the model, from simple absorption while staring at object, repetitive movements, inability to generalize and form invariant recognition of object categories, to lack of social communication. Computational models of this sort link molecular and behavioral levels through neural dynamics.

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Imagery Agnosia: what goes on in my head?

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Aim: Imagery agnosia is an important but yet little explored condition showing that even higher cognitive functions are mostly processed in unconscious way.

Methods: Neuropsychological case study. Agnosia is usually associated with the bottom-up processing stream, inability to extract relevant information from the sensory data. Top-down processes help to establish conscious percepts that need sensory cortex to re-create qualia in various modalities. The Vividness of Visual Imagery Questionnaire (VVIQ) measures the ability to re-create visual experiences, but similar questionnaires for other sensory modalities have not been developed. Statistics on how many people are visual non-imagers is still controversial. The vividness of imagery for sounds, tastes or tactile experiences should be positively correlated with the strength of top-down projections in the brain. Significant number of people have no conscious access to visual or auditory details of their experiences, although rich perceptual information may be encoded in their memory. This general condition may be called “imagery agnosia”, as subjects may show all kinds of symptoms typical for agnosia when required to perform some tasks based on imagery.

Results: This study is focused on auditory imagery agnosia, or imagery amusia, the inability to consciously imagine sounds, including pitch, timbre and melody. This condition seems to be different from associative auditory agnosia (1). People with vivid auditory imagery show Evoked Response Potentials (ERPs) and BOLD fMRI activation in the auditory cortex for imagined sounds, filling in the missing sounds in well-known melody using their imagination. In people with imagery amusia no auditory ERP response should be expected, the only way to know that a melody runs in their head is by humming or playing. A case study of subject WD (male, 55) with sensory agnosia (auditory and visual) is reported. He describes his experiences with playing music to be similar to the experiences of people suffering from blindsight, maneuvering blindly in the auditory space, without the ability to imagine results of next move (hitting piano key). Yet after a long period of learning WD is able to improvise, surprising himself with correct cadencies, with no conscious influence on what he is playing. For him the only way to know what goes on in his brain is to act it out.

Conclusion: Imagery agnosia may be rather common, but rarely acknowledged situation, of great importance to education. Tests for different type of talent in architecture, design or music should include evaluation of imagery agnosia. Investigation of people with this condition may elucidate relations between conscious and unconscious processes in implementation of higher cognitive functions.

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