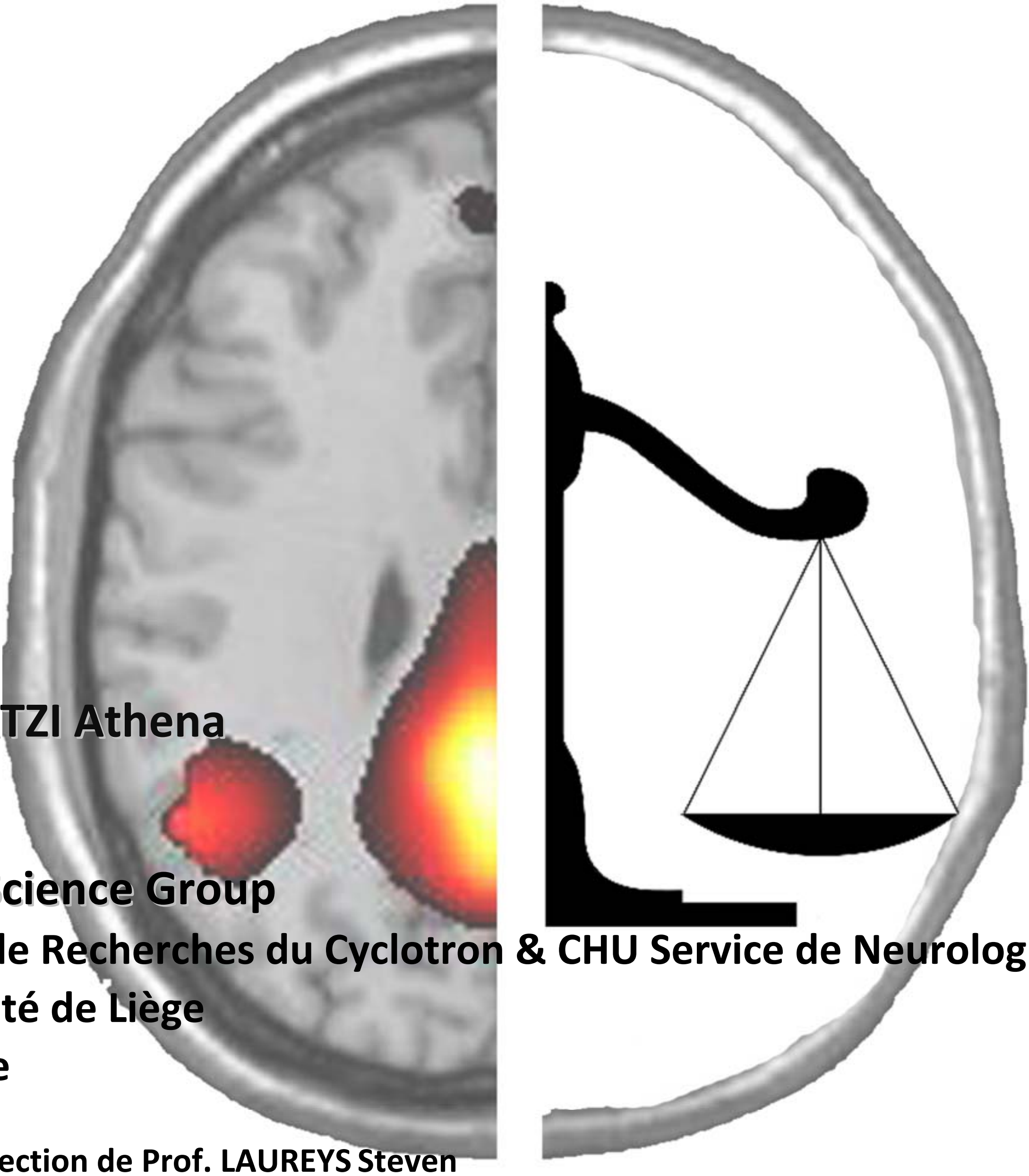
UNIVERSITÉ DE LIÈGE
Faculté de Médecine

AIN'T NO REST FOR THE BRAIN

Neuroimaging and neuroethics in dialogue for patients with disorders of consciousness



DEMERTZI Athena

Coma Science Group
Centre de Recherches du Cyclotron & CHU Service de Neurologie
Université de Liège
Belgique

Sous la direction de Prof. LAUREYS Steven

Thèse présentée en vue de l'obtention du grade de Docteur en Sciences Médicales
Année Académique 2011-2012

To those
for whom I wish I had been more present

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Summary

The sheer amount of different opinions about what consciousness is highlights its multifaceted character. The clinical study of consciousness in coma survivors provides unique opportunities, not only to better comprehend normal conscious functions, but also to confront clinical and medico-ethical challenges. For example, pain in vegetative state/unresponsive wakefulness syndrome patients (VS/UWS; i.e. awaken, but unconscious) and patients in minimally conscious states (MCS; awaken, with fluctuating signs of awareness) cannot be communicated and needs to be inferred. Behaviorally, we developed the Nociception Coma Scale, a clinical tool which measures patients' motor, verbal, visual, and facial responsiveness to noxious stimulation. Importantly, the absence of proof of a behavioral response cannot be taken as proof of absence of pain. Functional neuroimaging studies show that patients in VS/UWS exhibit no evidence of control-like brain activity, when painfully stimulated, in contrast to patients in MCS. Similarly, the majority of clinicians ascribe pain perception in MCS patients. Interestingly, their opinions appear less congruent with regards to pain perception in VS/UWS patients, due to personal and cultural differences. The imminent bias in clinical practice due to personal beliefs becomes more ethically salient in complex clinical scenarios, such as end-of-life decisions. Surveys among clinicians show that the majority agrees with treatment withdrawal for VS/UWS, but fewer respondents would do so for MCS patients. For the issue of pain in patients with disorders of consciousness, the more the respondents ascribed pain perception in these states the less they supported treatment withdraw from these patients. Such medico-ethical controversies require an objective and valid assessment of pain (and eventually of consciousness) in non-communicating patients.

Functional neuroimaging during "resting state" (eyes closed, no task performance) is an ideal paradigm to investigate residual cognition in non-communicating patients, because it does not require sophisticated technical support or subjective input on patients' behalf. With the ultimate intention to use this paradigm in patients, we first aimed to validate it in controls. We initially found that, in controls, fMRI "resting state" activity correlated with subjective reports of "external" (perception of the environment through the senses) or "internal" awareness (self-related mental processes). Then, using hypnosis, we showed that there was reduced fMRI connectivity in the "external network", reflecting decreased sensory awareness. When more cerebral networks were tested, increased functional connectivity was observed for most of the studied networks (except the visual). These results indicate that resign state fMRI activity reflects, at least partially, ongoing conscious cognition, which changes under different conditions. Using the resting state paradigm in patients with disorders of consciousness, we

showed intra- and inter-network connectivity breakdown in sensory-sensorimotor and “higher-order” networks, possibly accounting for patients’ limited capacities for conscious cognition. We have further observed positive correlation between the Nociception Coma Scale scores and the pain-related (salience) network connectivity, potentially reflecting nociception-related processes in these patients, measured in the absence of an external stimulus.

These results highlight the utility of resting state analyses in clinical settings, where short and simple setups are preferable to activation protocols with somatosensory, visual, and auditory stimulation devices. Especially for neuroimaging studies, it should be stressed that such experimental investigations tackle the necessary conditions supporting conscious processing. The sufficiency of the identified neural correlates accounting for conscious awareness remains to be identified via dynamic and causal information flow investigations. Importantly, the quest of subjectivity in non-communicating patients can be better understood by adopting an interdisciplinary biopsychosocial approach, combining basic neuroscience (bio), psychological-cognitive-emotional processing (psycho), and the influence of different socioeconomic, cultural, and technological factors (social).

Résumé

L’abondance d'opinions sur la définition scientifique de la conscience met en évidence son caractère multiforme. C’est la raison pour laquelle l’étude clinique de la conscience chez les patients qui survivent à un accident cérébral sévère procure d’une part une opportunité unique de comprendre le fonctionnement « normal » et « pathologique » de la conscience, mais également de confronter les données cliniques obtenues lors des différentes recherches avec les questions socio-éthiques omniprésentes au sein de notre société. Un exemple marquant peut être mis en évidence lors de l’étude de la douleur chez les patients qui ne peuvent communiquer leurs ressentis tels que les patients en état végétatif/syndrome d’éveil non répondant (EV/SEN) et en état de conscience minimale (ECM ; patients éveillés présentant des signes clairs mais fluctuants de conscience). Afin de pallier ce problème, nous avons mis en au point la « Nociception Coma Scale », un outil clinique qui permet de mesurer et d’évaluer les réponses motrices, verbales, visuelles et faciales des patients en réponses à diverses stimulations nociceptives. Toutefois, il est important de signaler que l’absence de réponse comportementale ne doit pas être interprétée comme une absence de preuve de douleur. Des études en neuroimagerie fonctionnelle chez des patients EV/SEN démontrent une absence de réactions cérébrales en réponse aux stimulations nociceptives, en opposition aux réponses observées auprès des patients en ECM. Compte tenu de ces informations, il a été mis en évidence que la majorité des cliniciens mettent en place un traitement de la douleur chez ces derniers. Des études ont toutefois démontré que l’opinion des cliniciens concernant la perception de la douleur chez les patients EV/SEN est influencée par leurs traits de personnalité ou encore leur culture. La présence et l’influence de ces différents biais lors des prises de décisions éthiques deviennent encore plus importantes lors de la prise de décisions de fin de vie chez certain patient. Des études menées auprès de cliniciens montrent que la majorité d’entre-eux sont d’accord avec l’idée d’arrêter l’hydratation et la nutrition chez les patients EV/SEN mais que cette majorité n’est plus d’actualité lorsque l’arrêt de fin de vie concerne les patients en ECM. De plus, il a été mis en évidence que l’attribution de la douleur chez les patients en état de conscience altérée était en lien avec les décisions de fin de vie. En effet, les participants à cette enquête refusaient d’envisager un arrêt de traitement chez les patients pouvant ressentir la douleur. De telles controverses socio-éthiques nécessitent une évaluation objective et valide de la douleur (et éventuellement de la conscience) chez les patients non-communicants.

La neuro-imagerie fonctionnelle durant l’état « resting state » (« état de repos », yeux fermés, absence de réalisation de tâche) est un paradigme idéal qui permet d’investiguer l’activité cognitive résiduelle des patients non-communicants car ce dernier ne nécessite pas de support technique

sophistiqué ou un apport volontaire de la part du sujet. Avant d'utiliser ce paradigme chez les patients, nous nous sommes tout d'abord attelés à valider cette technique auprès de sujets contrôles. Nous avons tout d'abord pu mettre en évidence que l'activité « au repos » des sujets contrôles était en corrélation avec la perception subjective des pensées « externes » (perceptions de l'environnement à travers les différents canaux sensoriels ») et des pensées « internes » (processus mentaux personnels). Nous avons ensuite utilisé la technique de l'hypnose afin de mettre en évidence que durant cet état particulier, il existe une réduction de la connectivité cérébrale mesurée en IRMf au sein des réseaux externes, reflétant une diminution de la conscience sensorielle. Toutefois, lorsque d'autres réseaux cérébraux ont été évalués, nous avons noté une augmentation de la connectivité fonctionnelle dans la plupart des réseaux étudiés (excepté le réseau visuel). Ces résultats indiquent que l'étude de « l'état de repos » en IRMf reflète, au moins en partie, la conscience cognitive qui se modifie en fonction des différents états de conscience (état normal versus hypnose). Enfin, nous avons étudié ce paradigme chez les patients présentant un état altéré de conscience. Nous avons pu mettre en évidence une diminution de la connectivité intra- et inter- réseau au sein des réseaux sensori-moteur et de haut-niveaux traduisant une limitation des capacités cognitives des patients. Nous avons ensuite observé une corrélation positive entre la « Nociception Coma Scale » et le réseau douleur, reflétant potentiellement le traitement cérébral de la douleur chez ces patients en l'absence d'un stimulus externe.

Ces résultats soulignent intérêt de l'utilisation de ces paradigmes « resting state » dans des situations cliniques extrêmes où des paradigmes simples et courts sont préférables aux paradigmes d'activation somato-sensoriels, visuels et auditifs. En ce qui concerne les études en neuroimagerie, il convient de souligner que de telles investigations expérimentales permettent de mettre en place les conditions nécessaires à l'étude de la conscience. Notons toutefois que les corrélats neuronaux de la conscience restent à être identifiés par l'intermédiaire d'investigation dynamique et causale (dynamic and causal information flow investigations). Enfin, la quête de la subjectivité chez les patients non communicants peut être mieux comprise par le biais d'une approche interdisciplinaire biopsychosocial, combinant neurosciences fondamentales (bio), les sciences psycho-cognitive et de traitement émotionnel (psycho), ainsi que l'influence de différents facteurs socio-économiques, culturels et technologiques (social).

Acknowledgements

When I contemplate on the last four years' work, I realize how grateful I feel to so many people who surrounded my way towards the doctoral degree. Each of them has assisted me in her/his own unique way leading to my today's accomplishments. I thank you all deeply and I wish to dedicate some words for each of you separately.

I will be eternally grateful to my PhD thesis supervisor, Prof. Steven Laureys. Steven, the past four years you had been an inspiring motivating force in my life, gladly enough not only in academic terms. Your scientific insights provided me with unique opportunities to confidently open up to the academic world. You have been a great teacher whose warmth and positive attitude will keep reminding me of our moral duty to optimism. I feel profoundly honored having worked by your side and I am looking forward to the upcoming clinical and academic challenges.

A special thanks is meant for Dr. Andrea Soddu. Andrea, you have been an irreplaceable colleague to me. Your kind patience (indeed too kind sometimes) with teaching me the secrets of methodological analysis provided me with priceless supplies to now boldly explore new horizons. Your friendship will always be precious to me.

Next I would like to address my gratitude to the exceptional ladies of the Coma Science Group's clinical team (10 neuropsychologists and our physiotherapist!). Referring to them in a chronological order according to their entrance in the group, Caroline Schnakers, Audrey Vanhaudenhuyse, Marie-Aurélie Bruno, Olivia Gosseries, Camille Chatelle, Marie Thonnard, Aurore Thibaut, Vanessa Charland-Verville, Ithabi Gantner, Dina Habbal and Lizette Heine. Ladies, you are the core of this wonderful team. I have learned so much from you in terms of clinical assessment (yes, in French too!), organizational skills and of course sincere patient care. I would like to thank each of you for sharing my happy moments and providing me with limitless support when the times required it.

I cannot miss of course the rest of the Coma Science Group people without whom this work could not have been possible. Exceptional thanks to Quentin Noirhomme, Francisco Gomez (also known as Pacho), Didier Ledoux, Audrey Maudoux, Mélanie Boly, Jean-Flory Tshibanda, Pierre Boveroux, Rèmy Lehembre, Anne-Nora Mergam, Pieter Guldenmund, Muriel Kirsch, Damien Lesenfants and Zulay Lugo.

I will be always grateful to the special support of Marie-Elisabeth Faymonville without whom hypnosis would have remained a mystery to me. Thank you all in the CHU Neurology Department, especially Prof. Moonen and the assistant doctors. Also Tahar Bakay and the nursing team and of course Lucienne Arena.

Many thanks to all people of the Cyclotron Research Center, especially to André Luxen, Pierre Maquet, Christophe Phillips, Eric Salmon, Mohamed Bahri, Christian Degueldre, Gaëtan Garraux, Evelyne Balteau, Fabienne Colette, Christine Bastin, Jessica Schrouff, Caroline Kussé, the Jedidi brothers, Ariane Foret, Laura Mascetti, Dorothée Feyers, Luca Matarazzo, Vincenzo Muto, Anahita Shaffii, Erik Ziegler, Sarah Genon, Kevin D'Ostilio, Julien Grandjean, Elodie André, Geoffroy Kaisin, Marine Manard, Gilles Vandewalle, Roman Wesolowski, Joël Aerts, Benjamin Deville and Erik Lambot. And I will always remember the assistance of the two wonderful CRC secretaries, Claes Annick and Brigitte Herbillon. Finally, I would like to sincerely acknowledge the aid of Serge Brédart, Arnaud D’Argembeau and Steve Majerus.

A particular thanks to all external and international collaborators for their trust and support. From the Erasme Hospital, Serge Goldman, Xavier de Tiège, Marc op de Beeck, Mathieu Bourguignon and the nurses Martine Lemaire and Mohamed Tahere. Last but not least, I would like to thank Prof. Eric Racine (University of Montreal & McGill University, Canada), Dr. Ralf Jox and Dr. Katja Kuehlmeyer (University of Munich, Germany).

In this last part I would like to deeply thank my parents, my sisters and the rest of the “big fat Greek” family who believed in and unquestionably supported all my efforts in the past years. And my friends Tasoula, Persa, Stelios and Christos for their priceless friendship, giving me courage, energy and perspective in every thing I attempt in my life.

Dave, you know that your unconditional love and support keep me up pursuing my dreams. Your integrity and your profound philosophical concerns about what makes us be, have contributed in re-evaluating many of my personal values, making me a better person. I feel extremely blessed to have you by my side as life partner, looking forward to our next unexplored steps.

Αλεξανδράκι μου, you could not have been a better kid than you already are. Believe it or not, you saved my thesis! Mom is very proud of you. I promise that I will show you the world to the best of my possibilities. I will love you eternally!

Liège, April 2012

1

Introduction

“Γνῶθι σαυτὸν”

(Know thyself)

Carved at the entrance of the Delfi temple
Peloponnesos, Greece

Attributed to Socrates

Based on:

Demertzi, A., Vanhaudenhuyse, A., Bruno, M.-A., Schnakers, C., Boly, M., Boveroux, P., Maquet, P., Moonen, G., Laureys, S., **2008**. Is there anybody in there? Detecting awareness in disorders of consciousness. Expert Rev Neurother. 8, 1719-30.

Gosseries, O., **Demertzi**, A., Noirhomme, Q., Tshibanda, J., Boly, M., de Beeck, M.O., Hustinx, R., Maquet, P., Salmon, E., Moonen, G., Luxen, A., Laureys, S., De Tiege, X., **2008**. [Functional neuroimaging (fMRI, PET and MEG): what do we measure?]. Rev Med Liege. 63, 231-7.

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Demertzi, A., Liew, C., Ledoux, D., Bruno, M.-A., Sharpe, M., Laureys, S., Zeman, A., **2009**. Dualism persists in the science of mind. Ann N Y Acad Sci. 1157, 1-9.

Demertzi, A., Schnakers, C., Soddu, A., Bruno, M.-A., Gosseries, O., Vanhaudenhuyse, A., Laureys, S., **2011**. Neural plasticity lessons from disorders of consciousness. Front Psychol. 1, 1-7.

1.1 Consciousness

An operational definition of consciousness

Consciousness is a multifaceted term for which there is no universal definition (Zeman, 2001). Clinical experience teaches that we can define consciousness operationally, by reducing it to two components: wakefulness and awareness (Posner et al., 2007). Wakefulness refers to the level of alertness and it is supported by the function of the subcortical arousal systems in the brainstem, the midbrain and the thalamus (Steriade et al., 1997). Clinically, it is indicated by eyes opening. Awareness refers to the content of consciousness and is thought to be supported by the functional integrity of the cerebral cortex and its subcortical connections. Awareness can be further reduced to awareness of environment and of self (James, 1890). Clinically, awareness of environment is assessed by evaluating command following and observing non-reflex motor behavior, such as eye tracking and localized responses to pain. Awareness of self, a more ill-defined concept, can be assessed by the patients' response to self-referential stimuli, such as the patients' own face in the mirror (Vanhaudenhuyse et al., 2008).

An illustrative example of the relationship between the two components of consciousness is the transition from full wakefulness to deep sleep: the less aroused we get, the less aware we become of our surroundings (Figure 1.1).

Attitudes towards consciousness

The scientific study of consciousness indicates that there is an intimate relationship between mind and brain (Tononi & Laureys, 2009). **Functional neuroimaging** technologies have contributed significantly to unraveling the neural correlates of (un)conscious states (e.g., Laureys & Boly, 2008). As a consequence, nowadays one could expect less support of the separateness between mind and brain, classically held by the philosophical position of **dualism.** Nonetheless, a survey among U.S.

Functional neuroimaging techniques allow the in vivo study of human cognitive and sensorimotor functions in physiological or pathological conditions. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) measure haemodynamic changes induced by regional changes in neuronal activity with high spatial resolution (i.e. a few millimeters). Electroencephalography (EEG) and magnetoencephalography (MEG) measure respectively the neuronal electrical or magnetic activity with high temporal resolution (i.e. milliseconds).

Dualism represents the view that mind and matter involve different kinds of "substance," a view now known as "substance" or "Cartesian" dualism. In this view, the brain belongs to the physical world, the mind to the nonphysical, yet they are closely related to each other (Descartes, 1968). Physical events can cause mental events and vice versa. Dualism, however, notoriously fails to explain how physical and mental entities can interact.

scientists shows that about 40% of the sample believes in a personal God or in life after death (Larson & Witham, 1997), a similar figure to that obtained almost a hundred years ago (Leuba, 1916). Indeed, "dualistic" views are often reflected in religious convictions which typically endorse the existence of a soul independent of the body and/or the idea of an afterlife.

The clinical and theoretical implications of endorsing dualistic attitudes have been stressed in a questionnaire survey. Students from various disciplines reported that different perspectives on the mind–brain problem were likely to influence doctors' and psychologists' choice of research methods, treatment options, and their behavior toward patients (Fahrenberg & Cheetham, 2000).

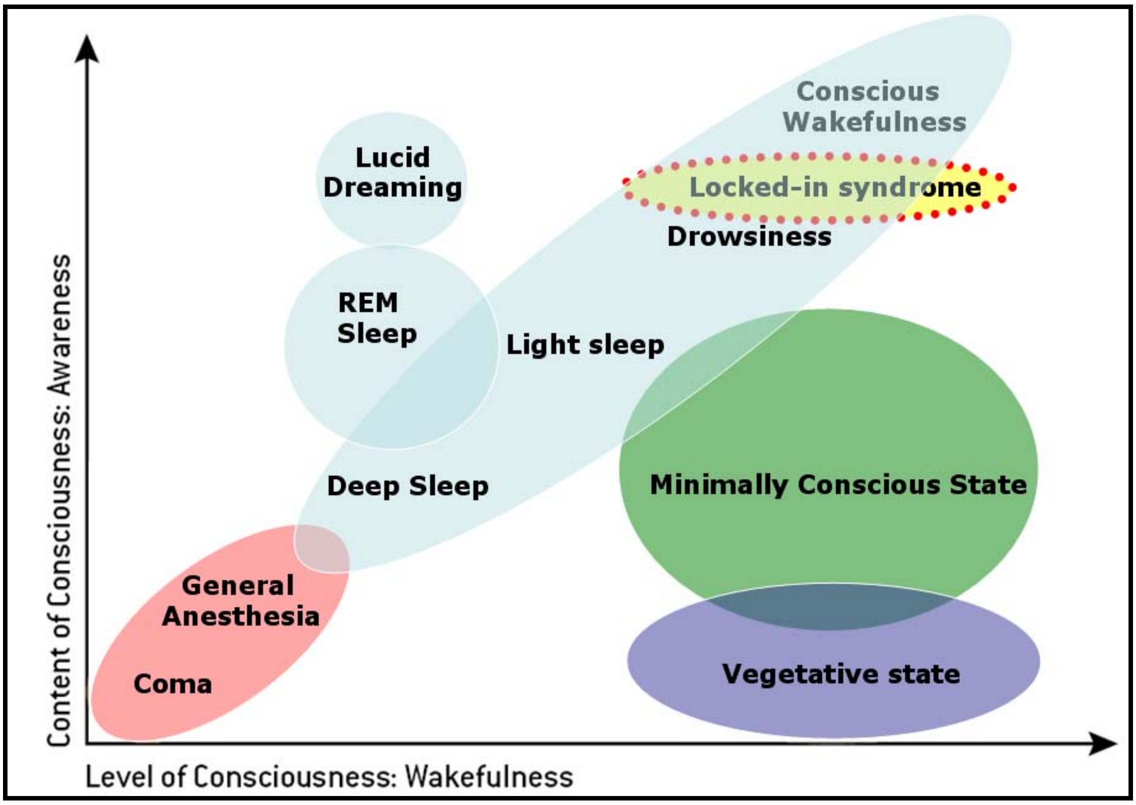

Figure 1.1 *Simplified illustration of the two major components of consciousness and the way they correlate within the different physiological, pharmacological and pathological modulations of consciousness. From Demertzi et al, "Encyclopedia of Consciousness" (2009a) (reproduced from Laureys, Trends in Cognitive Sciences 2005)*

Considering the relevance of personal attitudes to clinical practice, we aimed to update attitudes towards the mind-brain relationship and determine the variables that account for differences in views. Two closely-related surveys were conducted: the first by the University of Edinburgh (UK) including students of various disciplines; and the second by the University of Liège (Belgium) including attendees (i.e. healthcare workers, academics) of public or scientific meetings on consciousness. By including both students and healthcare professionals, the variance of educational level was better controlled. The two surveys shared four key questions asking participants to state their views on whether (a) the mind and brain are two separate things; b) the mind is fundamentally physical; (c) some spiritual part of us survives after death; (d) each of us has a soul that is separate from the body (see Methods box for more details).

We found that the majority of undergraduates sampled in the Edinburgh survey endorsed that "mind and brain are separate" and hence they held dualistic views on the relationship between mind and brain. The majority disagreed that the mind is a purely physical entity by agreeing on the existence of a soul that is separate from the body and survives death. The views of a wider group of seniors sampled in the Liège survey were found less dualistic compared to the undergraduates (Figure 1.2). Nevertheless, over a third of the healthcare workers expressed dualistic opinions; also, half of the sample reported being religious (independent of practicing). Religious respondents, younger participants, and women, were more likely to endorse the dualistic statements compared to non-religious, older respondents, and men respectively (for more details, see Demertzi et al., 2009b).

Our results corroborate previous surveys with higher-educated samples (i.e. scientists). At the beginning of the twentieth century, 40% of scientists held religious convictions as reflected by their beliefs in a personal God and in afterlife (Leuba, 1916). Eighty years later, these figures had not considerably changed and seemed to characterize one third of U.S. scientists (Larson & Witham, 1997). Nevertheless, when the survey was restricted to "leading" scientists-members of the National Academy of Science, the majority (72%) of respondents were found to "reject God". In that respect, dualistic views have been reduced in this target group since the 1900's, when only 53% of the "leading" scientists did not believe in a God (Larson & Witham, 1998).

We need to stress that our findings must be considered in the context of the groups we have surveyed and the approach we have taken. A larger survey, including participants from a broader range of educational and cultural background, could shed more light on expressed opinions. Additionally, the closed "agree-disagree" statements used in the survey forced participants to endorse attitudes that they might have wished to further qualify. For example, a majority of the Liège survey did not support the **materialistic** view that mind is fundamentally physical. Yet the group's perspective was not consistently dualistic, as a majority also endorsed the statement that the mind is not separable from the brain.

Reductive Materialism (or "Identity Theory") holds that there are no "hard questions" to be answered and no "gaps" to be explained. The mind cannot be separated from the brain. It is the brain. Experience can be explained simply by revealing what happens within the brain, just as heat is explained by the motion of atoms. The difficulty with this perspective is that it seems to give no account of the subjective qualities of experience. In other words, it does not explain why an experience should be "like something". This view, albeit convenient for neuroscience, has been accused of "leaving out the mind" (Searle, 1992).

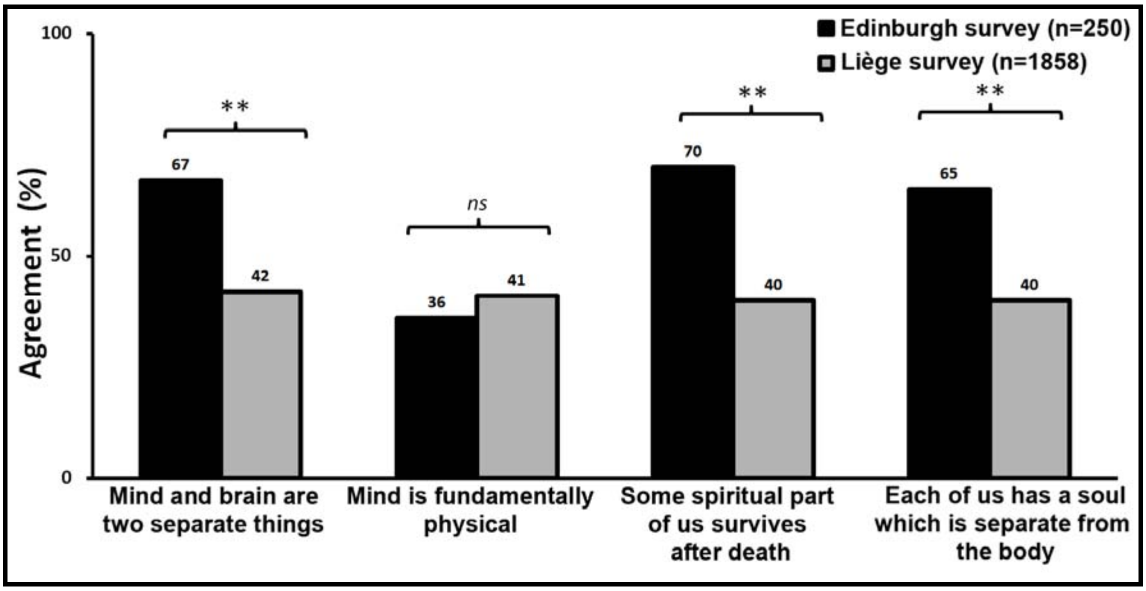

Figure 1.2 *Survey results on attitudes towards the mind-brain relationship. From Demertzi et al., Ann N Y Acad Sci. (2009b)*

Such figures may reflect the complexities of the concept of mind or the understandable confusions about its nature, which remain controversial among philosophers. Finally, it can be argued that the dichotomous “agree-disagree” way that the respondents were asked to answer did not allow them to doubt the statements by providing, for example, an “I don’t know” response. In that respect, one could expect the respondents to leave the questions unanswered if they felt that did not represent their views. Considering, however, the small number of missing values in our data (for Liège survey statement a: 5%; b: 5%; c: 7%, d: 6%), we can conclude that participants were able to express their attitudes in a good and representative way.

Discussion

The persistence of dualistic attitudes toward mind and brain has both scientific and clinical implications. At the scientific level, we suggest that dualism is at work in neuroscientific thinking about consciousness. Talk of consciousness being “generated by” or “conjured from” the brain is reminiscent of the Cartesian view that our mental lives interact with our physical being, while being radically separate from it. Some contemporary philosophers of mind regard dualism of this kind as being theoretically appropriate (Chalmers, 1996). Here, we simply draw attention to the fact that the widespread dualism revealed by our survey continues to exert an influence on scientific thought. Dualistic preconceptions about mind and brain may also influence the reception of scientific theories of consciousness by the general public. If such views remain alive among scientists who formulate and try to answer questions within the science of consciousness, they are likely to be all the more influential among the wider public. In any case, whether or not dualistic views are correct, their continuing influence should be acknowledged.

At the clinical level, the mind–brain dichotomy may be utilized to reason about patients' responsibility for their condition: when a problem is considered of a psychological-behavioral origin, the patients are more often thought to be responsible for their condition. In contrast, when a problem is thought to have a neurobiological cause, the patients are considered less blameworthy (Miresco & Kirmayer, 2006). Similarly, dualistic models about pain support that pain is either psychological or physical (Nicholson et al., 2002). Dualistic attitudes towards pain are likely to support biases in clinical practice, in the sense that clinicians will only treat the physical pathology (considering that pain will eventually subside, e.g., tissue damage) or the emotional distress (considering that pain is "in patients' heads", e.g., depression). Especially the issue of pain (see Chapter 2, this Thesis) becomes more ethically challenging in cases of patients who are not able to communicate and express their feelings, such as patients with disorders of consciousness.

Methods

The Edinburgh survey included *n* = 250 students from the University of Edinburgh, of eight academic disciplines: anthropology (33), astrophysics (19), civil engineering (32), computer science (30), divinity (36), medicine (30), mechanical engineering (34), and physics (36). The students were addressed as a class after their lectures and then asked to complete and return the questionnaire within the next 15 minutes. Participants' views were expressed on a 4-point Likert scale (Agree- Somewhat agree- Somewhat disagree- Disagree), which was collapsed into two categories ("agree" vs. "disagree") for further analysis. The participants were also asked to provide information about possible belief in the existence of a God or Gods.

The Liège survey included *n* = 1858 attendees of public or scientific meetings on consciousness. The sample was comprised of medical professionals (782/1858); paramedical healthcare workers (nurses, psychologists, physiotherapists (290/1858)) and other professional backgrounds (455/1858; 331 missing data on profession). The administration was oral and it took approximately 15 minutes for the completion of the questionnaire. The answers were expressed dichotomously ("agree–disagree"). Information about belief in a personal God was also collected. The data were analyzed using SPSS 14.0 for Windows (SPSS, Inc., Chicago, IL, USA). Internal consistency was assessed by calculating inter-item correlations. Chi-square tests for categorical data were used to test the differences in responses between groups. Logistic Regression analyses (method: backward stepwise) were ordered to describe the relationship between agreement on the four statements and a set of explanatory variables (i.e. age, gender, profession, and religiosity, tests thresholded at p=.05).

1.2 Disorders of consciousness

A short history

About 50 years ago, before the era of neurocritical care, things were relatively simple. After a severe brain damage, patients who were in **coma** either died or, more rarely, recovered with more or less cognitive deficits. This picture changed after the invention of the positive pressure mechanical ventilator by Bjorn Ibsen in the 1950s, and the widespread use of intensive care in the 1960s in the industrialized world, changed the picture. Severely brain- damaged patients could now have their heartbeat and systemic circulation sustained by artificial respiratory support. Nevertheless, they could end-up unconscious. Such profound unconscious states had never been encountered before as, until that time, all these patients had died instantly from apnea. As a consequence, medicine was forced to redefine death, using a neurological definition, that of **brain death** (Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, 1968). In the meantime, Fred Plum and Jerome Posner described for the first time the **locked-in syndrome (LIS)**, to refer to fully conscious coma survivors who are unable to communicate due to physical paralysis (Plum & Posner, 1966). In 1972, Bryan Jennet and Fred Plum published the clinical criteria of another artifact of modern intensive care, the **vegetative state (VS)**, a state of "wakefulness without awareness" (Jennett & Plum, 1972). In 2002, the Aspen

Coma is a time-limited condition leading to death, recovery of consciousness, or transition to vegetative state (Laureys, 2007). It can result from bihemispheric diffuse cortical or white matter damage or brainstem lesions bilaterally, affecting the subcortical reticular arousing systems. After three days of observation, bad outcome is heralded by absence of pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, bilateral absent cortical responses of somatosensory evoked potentials, and, for anoxic coma, biochemical markers (i.e. high levels of serum neuron-specific enolase) (Wijdicks et al., 2006).

Neurobehavioral Conference Workgroup realized that the clinical reality was yet more complicated. Some patients showed signs of voluntary behavior, and were therefore no longer vegetative, but still remained unable to functionally communicate. Based on these observations, they published the diagnostic criteria of a new clinical entity, the **minimally conscious state (MCS)** (Giacino, et al., 2002).

Brain death is death based on neurological criteria. Classically, it is caused by a massive brain lesion, (trauma, intracranial hemorrhage, anoxia). According to the American Academy of Neurology (1995) the diagnostic guidelines for brain death are:

1. demonstration of coma
2. evidence for the cause of coma
3. absence of confounding factors (hypothermia, drugs, electrolyte, endocrine disturbances)
4. absence of brainstem reflexes
5. absent motor responses
6. positive apnea testing
7. a repeat evaluation in six hours is advised, but the time period is considered arbitrary and confirmatory laboratory tests are only required when specific components of the clinical testing cannot be reliably evaluated.

According to these criteria, no recovery from brain death has ever been reported over the last 50 years (Laureys, 2005b).

Vegetative state (VS) is caused by diffuse grey and white matter lesions. The diagnostic criteria are:

1. no evidence of awareness of self or environment; inability to interact with others

More recently, it has been recognized that part of the healthcare, media and lay public feels uncomfortable using the unintended denigrating “vegetable-like” connotation (seemingly intrinsic to the term VS). Hence, the European Task Force on Disorders of Consciousness proposed the alternative name *“unresponsive wakefulness syndrome”* (UWS), a more neutral and descriptive term, pertaining to patients showing a number of clinical signs (i.e. syndrome) of unresponsiveness (i.e. without response to commands or oriented voluntary movements) in the presence of wakefulness (Laureys et al., 2010). With regards to MCS, it has been proposed to subcategorize this entity into MCS+ and MCS- based on the distinct behavioral and neuroanatomical pattern observed in these patients (Bruno et al., in press). More particularly, MCS+ patients exhibit high-level behavioural responses, such as command following, intelligible verbalization or non-functional communication. On the other hand, MCS- patients show low-level behavioural responses, such as visual pursuit, localization of noxious stimulation or contingent behaviors like appropriate smiling or crying to emotional stimuli (Bruno et al., 2011b). Finally, patients whose non-behavioural evidence of consciousness or communication is only measurable via assisting technologies (i.e. functional MRI, positron emission tomography, EEG or evoked potentials) have been suggested to be in a functional LIS (Bruno, et al., 2011b).

Clinical assessment

The objective assessment of consciousness is difficult due to its first-person nature. For that reason, clinicians need to infer awareness via the evaluation of motor activity and command following. This is extremely challenging for patients with disorders of consciousness and LIS because these patients are usually deprived of the capacity to make normal physical movements. In addition, they often show limited attentional capacities, aphasia, apraxia and cortical deafness or blindness which are possible confounders in the clinical assessment. As a result, incorrect diagnosis in these patients is not a rare phenomenon. It has been estimated that around 40% of VS/UWS patients are misdiagnosed (Andrews et al., 1996; Childs et al., 1993). We recently showed that, despite the introduction of the clinical criteria for the MCS, this diagnostic error rate has not substantially changed since the 1990's, which can be partially attributed to the scales used for clinical evaluation (Schnakers et al., 2009).

Standardized behavioral evaluation

The most common and most widely used tool, mainly thanks to its short and simple administration, is the *Glasgow Coma Scale* (GCS) (Teasdale & Jennett, 1974). The GCS measures eye, verbal and motor responsiveness. However, there may be some concern as to which extent eye-opening is sufficient evidence for assessing brainstem function (Laureys et al., 2002b). Additionally, the verbal responses are impossible to be measured in cases of intubation and tracheostomy. The scale requires the clinician to arrive at a certain judgment (e.g. "the patient follows commands") without any formal guidance on how to arrive at that judgment (i.e. what and how many commands to use, how to assess confounds such as motor or sensory or spontaneous movements, etc.). Finally, the GCS is not sensitive to detect transition from VS/UWS to MCS (Schnakers et al., 2006).

A recently proposed alternative to the GCS is the *Full Outline of Unresponsiveness* (FOUR) (Wijdicks et al., 2005). The scale is named after the number of subscales it contains (eye, motor, brainstem, and respiratory functioning) as well as after the maximum score that each subscale can take (four). The advantage of the FOUR is that it does not need a verbal response and, hence, can be employed in intubated patients. The FOUR can discriminate between VS/UWS and MCS patients

2. no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli
3. no evidence of language comprehension or expression
4. intermittent wakefulness manifested by the presence of sleep-wake cycles
5. sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care
6. bowel and bladder incontinence
7. variably preserved cranial-nerve and spinal reflexes (The Multi-Society Task Force on PVS, 1994a).

VS can be a transition to further recovery, or it may be permanent. 'Permanent' VS (>1 year after traumatic or 3 months after non-traumatic injury) refers to patients whose chances for recovery are close to zero (The Multi-Society Task Force on PVS, 1994b).

Minimally conscious state (MCS) describes patients showing at least one of the following:

1. purposeful behavior including movements

or affective behavior contingent to relevant environment stimuli (i.e. visual pursuit, sustained fixation, reaching for objects, touching or holding objects, vocalizations)

2. following simple commands
3. gestural or verbal yes/no responses, regardless of accuracy
4. intelligible verbalization

(Giacino et al., 2002). Emergence from MCS is defined by the ability to exhibit functional interactive communication or functional use of objects. Similarly to the VS, traumatic etiology has a better prognosis than non-traumatic anoxic brain injuries (Giacino & Kalmar, 1997).

Locked-in syndrome (LIS) can result from a bilateral ventral pontine or mesencephalic lesions (Laureys, et al., 2005). According to the American Congress of Rehabilitation Medicine (1995), LIS patients demonstrate:

1. sustained eye-opening
2. quadriplegia or quadriparesis
3. aphonia or hypophonia

as it assesses visual pursuit, one of the first signs that announces emergence from VS/UWS. But it does not test all the behavioral criteria of MCS (Giacino, et al., 2002). It is also more sensitive in detecting LIS patients because it explicitly asks patients to move their eyes on command (Wijdicks, et al., 2005). To differentiate VS/UWS from MCS patients, the most appropriate scale is *the Coma Recovery Scale-Revised* (CRS-R) (Giacino, et al., 2004). The CRS-R has a similar structure to the GCS. It tests audition, arousal and communication abilities next to motor, eye and verbal responsiveness. Despite its longer administration compared to the GCS and the FOUR (i.e. approximately 15 minutes), it is the most sensitive in differentiating VS/UWS from MCS patients (Schnakers, et al., 2006). This is because it assesses every behavior according to the diagnostic criteria of VS/UWS and MCS, such as the presence of visual pursuit.

Apart from the direct evaluation of consciousness levels, the evaluation of pain is another challenge to the clinical assessment of patients with disorders of consciousness. This is because these patients are unable to communicate their feelings and pain in these states needs to be inferred from observing their spontaneous behavior or their motor responses to noxious stimulation. Stereotyped responses (i.e. slow generalized flexion or extension of the upper and lower extremities), flexion withdrawal (i.e. withdrawal of the limb away from the point of the stimulation), and localization responses (i.e. the non-stimulated limb locates and makes contact with the stimulated body part at the point of stimulation) are linked to, respectively, brainstem, subcortical, or cortical activity (e.g., Stevens & Nyquist, 2006). Stereotyped responses are considered as "automatic"' unconscious reflexes, whereas localization of noxious stimulation is usually considered as indicative of conscious perception (Posner, et al., 2007).

Repeated clinical examinations by trained and experienced examiners are paramount for the behavioral assessment of pain. To date, several scales are used for assessing pain in non-communicative individuals such as with end-stage dementia, in newborns, and in sedated intensive care patients. Recently, we developed the Nociception Coma Scale (Schnakers, et al., 2010) a sensitive and specific tool which evaluates motor, verbal, visual, and facial responsiveness to noxious stimulation (Figure 1.3). The scale has high inter-rater agreement and yields significant differences between the total scores as a function of patients' diagnosis (i.e. VS/UWS or MCS).

Conclusions

The study and management of patients with disorders of consciousness offer unique opportunities not only to better understand the neural correlates of healthy consciousness (Laureys, 2005a) but also to gain insight about the brain's plastic abilities (Demertzi et al., 2011b). **Neuroplasticity** in these patients' population can be approached via neurological evidence from neuroimaging technologies in pathological states

5. a primary mode of communication (e.g., via eye blinking or other movements) abilities
6. preserved cognitive abilities

With appropriate medical care, life expectancy is estimated up to several decades (Laureys, et al., 2005).

Neuroplasticity is the ability of the brain and nervous system to change structurally and functionally as a result of environmental influences. Neural plasticity can be studied at many levels, from observable behavioral changes to cerebral maps, synaptic organization, physiological organization, molecular structure, and mitosis (Kolb & Whishaw, 2003b).

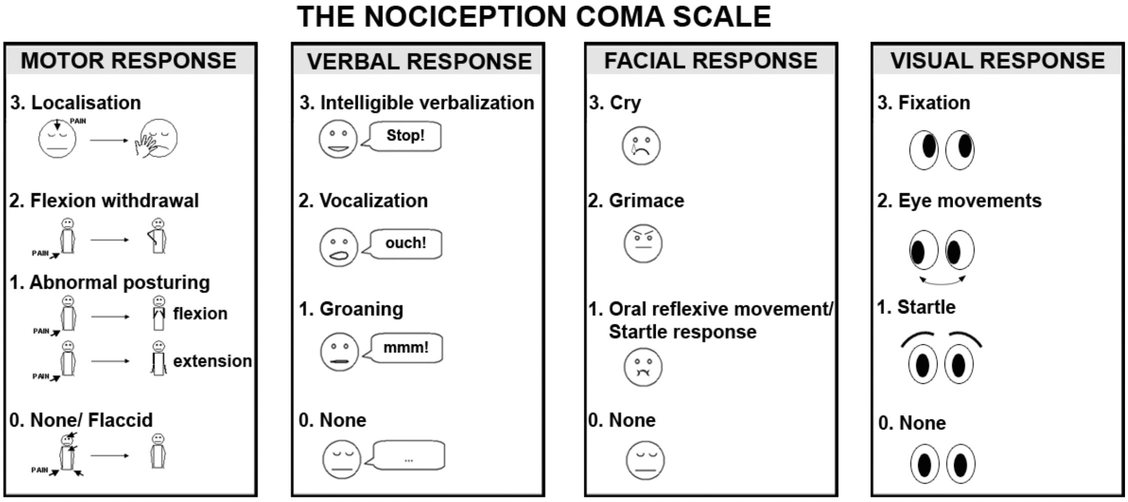

Figure 1.3 *Iconic representation of the Nociception Coma Scale. From Demertzi et al. "I know what you are thinking: brain imaging and mental privacy" (in press); based on Schnakers et al., Pain (2010)*

Functional connectivity is the temporal correlation of a neurophysiological index (hemodynamic or metabolic) measured in different remote brain areas (Friston, 2002)

and after recovery of consciousness. Altered cerebral **functional connectivity**, structural reorganization as well as behavioral amelioration after invasive and non-invasive treatments are some indices for studying plasticity changes in this challenging population.

Most recoveries of consciousness, with or without recovery of social or professional integration, take place within the first 3 months after non-traumatic and after 12 months after traumatic cerebral accidents. Survival beyond 10 years remains unusual (The Multi-Society Task Force on PVS, 1994b)– though it depends on the level of medical and nursing care (Monti et al., 2010a). However, clinical cases of both late spontaneous recoveries (Estraneo et al., 2010; Voss et al., 2006) or after invasive interventional treatments (e.g., with deep brain stimulation; Schiff et al., 2007) challenge the dogma of temporally fixed periods for possible neuronal plasticity. Currently, the beneficial effects of pharmacologic and non-pharmacologic approaches need evidence-based justification (Demertzi et al., 2008). Additionally, no unique hypothesis or theoretical framework can at present combine the temporal dynamics and pathophysiological mechanisms of all the aforementioned interventions and many questions remain as to the precise mechanisms differentiating spontaneous from therapy-induced cerebral plasticity (Tononi & Laureys, 2009). For example, the cellular mechanisms underlying recovery of consciousness after severe brain damage remain speculative. Our understanding of possible neurogenesis (known to occur predominantly in associative frontoparietal cortices in non-human primates; Gould et al., 1999), axonal sprouting and neurite outgrowth, or even apoptosis in this patient population remains very limited.

The residual cerebral function in VS/UWS and MCS patients has been largely overlooked by the medical community and deserves further investigation. In light of continuing societal, political, legal, and ethical debates, it is imperative to better comprehend these challenging states.

Then, the formulation of appropriate frameworks will provide guidance for the medical management and treatment of non-communicating patients. Eventually, this lesion paradigm can/will contribute uniquely in understanding the nature and function of consciousness in healthy conditions.

2

The ethics of treating patients with disorders of consciousness: Attitudes

"Surrendered and absolute
Breathing is like sawing
It cuts the time and spreads
In immaculate silence
Fire and snow"

Thanasis Papakonstantinou

"Like a child", The minimal self (Inner Ear discography, 2011)

Based on:

Demertzi, A., Schnakers, C., Ledoux, D., Chatelle, C., Bruno, M.-A., Vanhaudenhuyse, A., Boly, M., Moonen, G., Laureys, S., **2009**. Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. Prog Brain Res. 177, 329-38.

Demertzi, A., Ledoux, D., Bruno, M.-A., Vanhaudenhuyse, A., Gosseries, O., Soddu, A., Schnakers, C., Moonen, G., Laureys, S., **2011**. Attitudes towards end-of-life issues in disorders of consciousness: a European survey. J Neurol. 258, 1058-65.

Demertzi, A., Laureys, S., Bruno, M.-A., **2011**. The ethics in disorders of consciousness. In: Annual update in intensive care and emergency medicine. Vol., J.L. Vincent (ed.), Springer-Verlag, Berlin, pp. 675-682.

Demertzi, A., Racine, E., Bruno, M.A., Ledoux, D., Gosseries, O., Vanhaudenhuyse, A., Thonnard, M., Soddu, A., Moonen, G., Laureys, S., **2012**. Pain perception in disorders of consciousness: neuroscience, clinical care, and ethics in dialogue. Neuroethics. 1-14.

2.1 The ethical significance of studying attitudes

Thanks to the invention of the positive mechanical ventilator and progress in the intensive care, patients can survive their injuries but can remain in unconscious conditions (see Chapter 1, this thesis). As a result, various ethical and public policy controversies have been raised as to whether it is worth living in such profound states of unconsciousness (e.g., Thompson, 1969). Such medical concerns were reflected in the composition of the first bioethical committees discussing the redefinition of life and the concept of therapeutic obstinacy. As already mentioned in Chapter 1, in 1968 the Ad Hoc Committee of Harvard Medical School published a milestone paper for the redefinition of death as irreversible coma and brain failure (Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, 1968). The committee was comprised of ten physicians, a theologian, a lawyer and a historian of science, betokening the medical, legal, and societal debates that were to follow.

Controversies of these kind mainly stem from how different people regard indefinite survival in disorders of consciousness (Jennett, 2002a). As opinions and attitudes can affect clinical practice, such as non-adherence to medical guidelines (Cabana et al., 1999), we were interested in assessing healthcare workers' views on ethical issues related to the medical management of patients with disorders of consciousness, such as pain perception and end-of-life decision-making.

2.2 Pain perception in disorders of consciousness?

Definition of pain and related notions

The International Association for the Study of Pain defines pain "an unpleasant sensory and emotional experience associated with real or potential tissue damage" (IASP; 1994; Loeser & Treede, 2008). As also stressed by the IASP, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain may also be reported in the absence of tissue damage or any likely pathophysiological cause, such as in patients with thalamic pain (Loeser & Treede, 2008). Pain should be differentiated from activity induced in the **nociceptor** and nociceptive pathways by a **noxious stimulus**. **Nociception** is at the core of many painful states, but pain may occur without (peripheral) nociception and vice versa. Therefore, pain is considered a subjective phenomenon, whereas nociception is the object of sensory physiology (Loeser & Treede, 2008).

Pain and **suffering** are not interchangeable constructs either. A person might experience significant pain-related suffering from a relatively low-level noxious stimulation if she or he believes the implications are ominous, interminable, and beyond their control (Turk & Wilson, 2009). Cassell (1982) also defines suffering as occurring when the physical or psychological integrity of the person is threatened. Although not all suffering is caused by pain, in the medicalized culture suffering is often described in the language of pain (Loeser & Melzack, 1999).

Nociceptor is a sensory receptor that is capable of transduction and encoding noxious stimuli (Loeser & Treede, 2008).

Noxious stimulus is an actually or potentially tissue-damaging event (Loeser & Treede, 2008).

Nociception is the neural processes of encoding and processing noxious stimuli (Loeser & Treede, 2008).

Suffering is the emotional response triggered by nociception or other aversive events associated with it (e.g., fear, anxiety, loss of loved objects, stress and other psychological states) (Gatchel et al., 2007; Loeser & Melzack, 1999).

Pain is in the brain: differential cerebral activity in patients with disorders of consciousness

At the patient’s bedside, we are limited to evaluate pain as the behavioral responsiveness to noxious stimuli. If patients never show any sign of voluntary movement in response to noxious stimulation, it will be concluded they do not experience pain (Schnakers & Zasler, 2007). They may, however, be aroused by noxious stimuli by opening their eyes if they are closed, quickening their breathing, increasing heart rate and blood pressure, and occasionally show grimace-like or crying-like behavior. As all these abilities are also seen in infants with anencephaly

(Payne & Taylor, 1997; The Medical Task Force on Anencephaly, 1990) they are considered to be of subcortical origin and do not necessarily reflect conscious perception of pain. Additionally, patients can show extreme motor impairment or with fluctuating levels of vigilance (e.g., Majerus et al., 2005) and, hence, obtaining a motor response can be limited. Considering that the absence of a behavioral output cannot be taken as an absolute proof of the absence of consciousness (McQuillen, 1991), inferring pain and suffering solely by observing behavioral responses may be misleading. Then, how can we know if these patients experience pain and/or suffering?

Since brain responses are the final common pathway in behavioral responses to pain, we believe that the application of functional neuroimaging will allow us to study pain in an objective manner and to propose evidence-based guidelines on the use of analgesia and symptom management in patients with disorders of consciousness (e.g., Laureys & Boly, 2008; Tracey & Mantyh, 2007). In healthy controls, studies with **positron emission tomography (PET)** and **functional magnetic resonance imaging (fMRI)** have revealed that pain cannot be localized in an isolated "pain centre" but rather encompasses a neural circuitry, the pain **neuromatrix** (Melzack, 1999). More specifically, two distinct cerebral networks have been identified to be involved in pain perception: (i) a lateral pain system or sensory network, encompassing lateral thalamic nuclei, primary and secondary somatosensory, as well as posterior parietal cortices; and (ii) a medial pain system or affective network, which involves the medial thalamus, anterior cingulate, and prefrontal cortices with the insular cortices playing an intermediate role (Hofbauer et al., 2001).

Neuroimaging studies have shown that patients with disorders of consciousness are characterized by distinct cerebral patterns in response to sensory stimulation (Giacino et al., 2006; Laureys et al., 2004; Owen & Coleman, 2008; Schiff, 2007). In 15 studied VS/UWS patients there was no evidence of

Positron emission tomography (PET) measures different aspects of physiological brain function based on the type of radioactive tracer used (e.g., $[^{18}F]$fluorodeoxyglucose –FDG, $H_2{}^{15}O$). Blood flow, glucose metabolism, blood volume, and oxygen consumption are examples of physiological functions studied by PET in the context of hemodynamic changes associated to neuronal activity.

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique which measures brain activity by detecting associated changes in blood flow over time.

The body-self **neuromatrix** comprises a widely distributed neural network that includes parallel somatosensory, limbic and thalamocortical components which subserve the sensory-discriminative, affective-motivational, and evaluative-cognitive dimensions of pain experience (Melzack, 1999).

noxious stimulation-related downstream activation beyond primary somatosensory cortex (Laureys et al., 2002a). More importantly, functional connectivity assessment showed that the observed cortical activation subsided as an island, dissociated from the pain matrix and the higher-order cortices (Figure 2.1). Indeed, higher-order cortico-cortical and thalamo-cortical processing is currently thought to be necessary for conscious awareness, as shown by studies on conscious perception in healthy controls and on loss of consciousness in sleep and anesthesia (e.g., Baars et al., 2003; Dehaene et al., 2003; Laureys, 2005a).

In striking contrast to what we observed in VS/UWS, MCS patients showed pain-related activation in not only midbrain, thalamus, and primary somatosensory cortex but also in secondary somatosensory, insular, posterior parietal and anterior cingulate cortices (Figure 2.1). The spatial extent of the activation in MCS patients was comparable to controls and no brain region showed less activation in MCS compared to healthy individuals. A functional connectivity assessment of insular cortex demonstrated its preserved connections with a large set of associative areas encompassing posterior parietal, motor and supplementary motor, striatum, and dorsolateral prefrontal and temporal associative cortices as observed in controls (Boly et al., 2008).

These neuroimaging studies show large differences in brain activation to pain between VS/UWS and MCS patients, despite a similar bedside clinical evaluation. Also, they strongly indicate preserved capacities of MCS patient to experience pain and potentially suffering, highlighting the need of analgesic treatment in this patients’ population. As healthcare workers are in charge of the patients’ medical management of pain, we were interested in their opinions on how they consider pain perception in patients with disorders of consciousness.

2.3 Attitudes towards pain perception

Between June 2007 and April 2009 we conducted a questionnaire survey of attitudes of healthcare professionals towards pain perception in patients with disorders of consciousness during lectures at medical and scientific conferences and meetings (n=48) within Europe. The study sample included 2059 medical and paramedical professionals coming from 32 European countries (see Methods box for details).

As a whole, the sampled participants replied more often that MCS patients could feel pain compared to VS/UWS patients (p<.001). Participants' opinions were much more consistent for pain perception in MCS (96% of the total sample considered that these patients can feel pain), while responses were much more discordant for VS/UWS (59% considered that unresponsive patients could feel pain). Paramedical

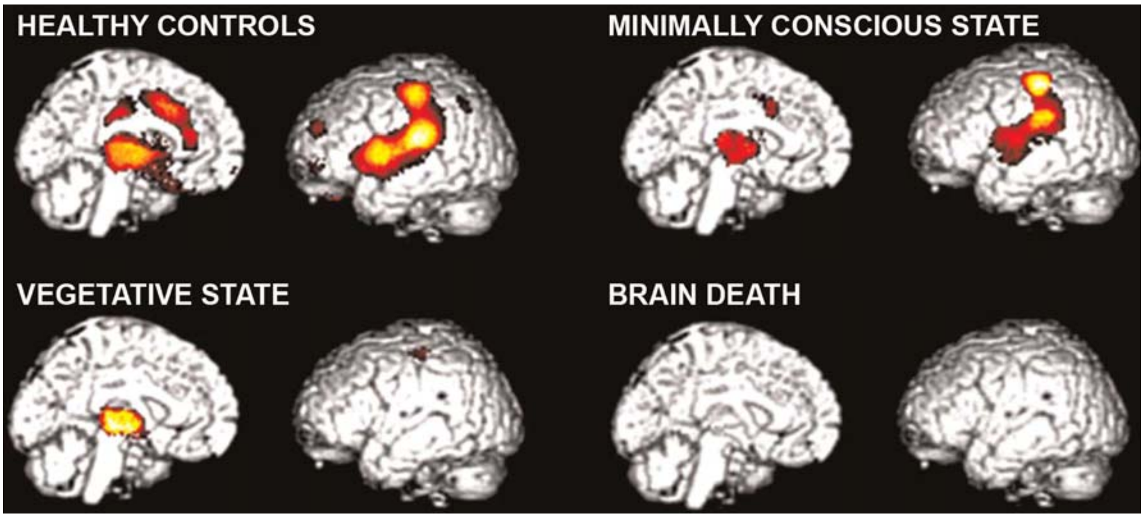

Figure 2.1 *Cerebral activation to noxious stimulation in healthy volunteers, in minimally conscious state patients (from Boly, et al., 2008 with permission), in vegetative state/unresponsive wakefulness syndrome (from Laureys, et al., 2002a with permission) and in brain death (adapted from Laureys, 2005b with permission). Note (i) the absence of activation in brain death; (ii) the preserved but low-level subcortical and primary cortical activation in the vegetative state (the primary cortical activation was disconnected from the rest of the brain), and (iii) the near-normal activation in the minimally conscious state. From Demertzi et al. Prog Brain Res (2009c)*

caregivers (n=538) replied more often that patients in a VS/UWS could feel pain than did medical doctors (n=1166) (68% versus 56%; p<.001; Figure 2.2). Following professional background, religion was the strongest predictor of caregivers' opinion: 64% of religious (n= 1009; 94% Christians) versus 52% of non-religious respondents (n= 830) answered positively. Logistic regression analysis on opinions for pain perception in MCS showed that women and religious respondents reported more often that MCS patients may experience pain compared to men and non-religious respondents. Logistic regression analysis on opinions for pain perception in VS/UWS showed that paramedical professionals, religious, and older respondents reported more often that VS/UWS patients may experience pain compared to medical doctors, non-religious and younger respondents.

Discussion

According to our survey, healthcare workers have different beliefs about possible pain perception in MCS compared to VS/UWS patients. This finding implies that, despite the recent introduction of

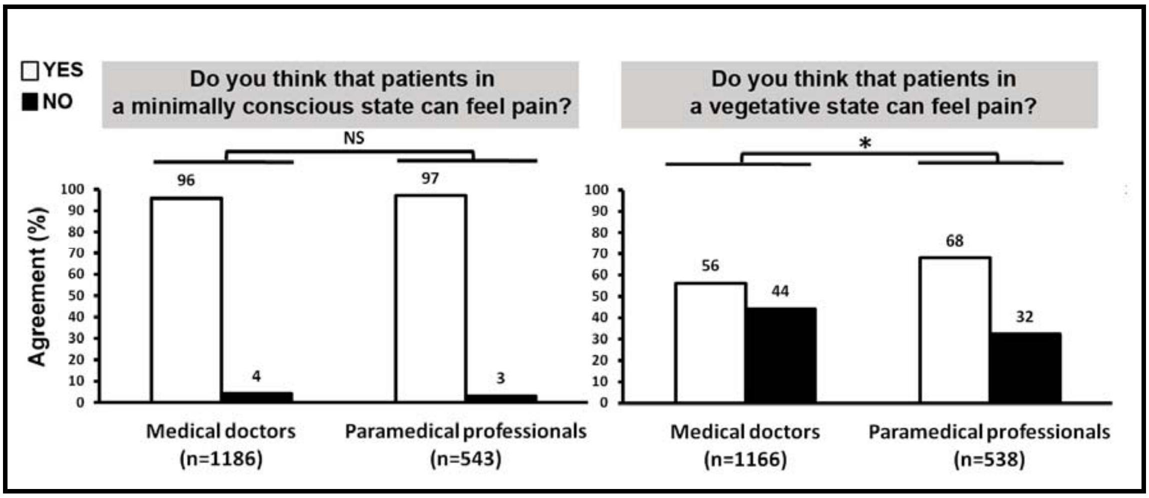

Figure 2.2 *Attitudes toward pain perception in the vegetative and the minimally conscious as expressed by European medical and paramedical professionals. Adapted from Demertzi et al. (2009c)*

MCS (Giacino, et al., 2002), the medical community regards MCS and VS/UWS as two separate clinical entities characterized by different pain perception profiles. The major differences in physicians' beliefs about pain in VS/UWS compared to MCS are supported by results from the functional neuroimaging data discussed above (Boly, et al., 2008; Laureys, et al., 2002a). Nevertheless, our survey indicates that a high proportion of medical doctors (56%) and paramedical professionals (68%) considered that VS/UWS patients can feel pain. The observed differences in viewpoint depending on professional background might be related to many factors including differences in proximity to the patient, time spent at the bedside, and education.

In light of such controversies around pain in VS/UWS and MCS patients, an increase in scientific evidence is essential to enhance our understanding of pain perception in patients with disorders of consciousness. Apart from the clinical and scientific interest around pain perception, ethical issues also raise as to whether it is justifiable to continue treating non-communicating patients for whom pain perception is suspected (e.g., Wilkinson et al., 2009). In order to better comprehend end-of-life issues in terms of possible pain perception, we will first discuss separately how clinicians think about withdrawing life-sustaining treatments in non-communicating patients.

2.4 Attitudes towards end-of-life options

In intensive care settings, medical doctors and assisting staff are confronted daily with clinical situations requiring critical decisions, such as continuing or withdrawing life sustaining treatment. Treatment limitation can be viewed as a refusal of cardiopulmonary resuscitation (CPR) or as a decision to withdraw treatment, such as the artificial respirator or artificial nutrition and hydration (ANH) (Bernat, 2004).

CPR is almost automatically performed as an emergency therapy in order to restore heartbeat and ceased breathing (unless the patient or the legal representative has refused it in advance in a form of a do-not-resuscitate order). ANH limitation is usually discussed after an intervention and when the clinical condition of a patient has been stabilized and denoted as irreversible. In the intensive care, the majority of deaths are the result of a medical decision to withhold or withdraw treatment (Laureys, 2005b).

Despite the controversy as to whether ANH constitutes a medical treatment (Bernat & Beresford, 2006) and thus should never be withdrawn from patients (Rosner, 1993), most of the medical community (especially Anglo-Saxon) would consider it a medical therapy which can be refused by patients and surrogate decision makers (Steinbrook & Lo, 1988). Such decisions in VS/UWS patients are only justified when a case is denoted as irreversible (Royal College of Physicians, 2003).

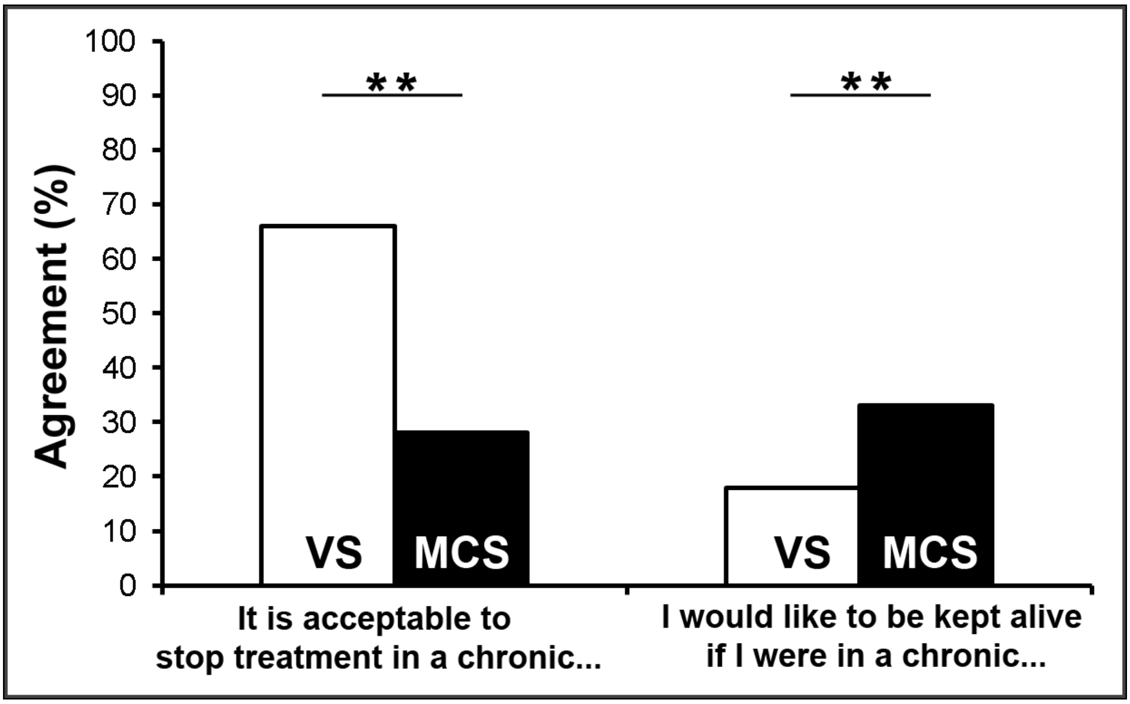

Figure 2.3 *End-of-life attitudes towards vegetative/unresponsive state (VS) and minimally conscious state (MCS) as expressed by 2475 medical and paramedical professionals (**p<.001). From Demertzi et al. (2011a)*

Guidelines with regards to temporal determination of a definitive outcome in VS/UWS currently state that if no recovery is observed within 3 months after a non-traumatic or 12 months after a traumatic accident, the condition of the patient can be denoted as permanent (The Multi-Society Task Force on PVS, 1994a).We here surveyed end-of-life attitudes of European medical and paramedical professionals (n = 2475) towards VS/UWS and determined, for the first time, attitudes towards MCS. In the sample, 66% agreed with treatment withdrawal for VS/UWS and 28% agreed so for MCS patients (p<.001). A dissociation was found between what can be generally applied to patients and what is wished for oneself: the majority (82%) of participants wished not to be kept alive if they imagined themselves in a chronic VS/UWS or chronic MCS (67%); and this dissociation was more important for MCS (interaction analysis; p<.001, Figure 2.3). Chronic MCS was also considered worse than VS/UWS more so from the perspective of the patient (54%) compared to that of the family (42%; p<.001). Inversely, respondents found that chronic VS/UWS was worse than death more so from the perspective of the family (80%) compared to that of the patient (55%; p<.001).

Multiple logistic regression analysis showed that agreement with end-of-life questions was mainly associated with geographic region and respondents' religiosity.

Discussion

Our attempt to open a discussion on treatment withdrawal from patients with chronic disorders of consciousness is not an easy one. Concerning VS/UWS patients, two-thirds of the surveyed participants reported that it was acceptable to withdraw ANH from these patients and most (82%) preferred not to be kept alive if they imagined themselves in this condition. These results are in line with surveys from previous decades, where the majority of physicians, despite different cultural backgrounds, would generally support ANH withdrawal from these patients and would not wish life-sustaining treatments for themselves. Although agreement with withdrawal of treatment was somewhat less compared to historical data, possibly due to different adopted research methodologies, the surveyed sample expressed similar end-of-life attitudes towards permanent VS/UWS despite the recent introduction of the diagnostic criteria for MCS, the recent confirmation of potential diagnostic error in VS/UWS patients (Schnakers, et al., 2009), the apparent evidence for residual cognitive processing coming from functional neuroimaging technologies (Monti et al., 2010b; Owen et al., 2006) and the potential prognostic value of the latter (Di et al., 2007).

Concerning MCS patients, although almost 70% would not wish to be kept alive in this state (considering it worse than VS/UWS), less than one-third of our respondents supported treatment withdrawal from these patients. Such differences in attitudes between the two clinical entities are comparable to a previous survey, where 92% of British physicians considered it appropriate to withdraw ANH from patients for whom the predicted outcome was VS and only 22% would think so for patients who were able to communicate simple needs without the capacity for speech production (thought to reflect similar cognitive processes as in MCS patients) (Grubb et al., 1997) [16].

We here illustrate that most healthcare professionals hold different views on end-of-life issues for VS/UWS compared to MCS. Additionally, the distinction between personal preferences with private consequences (i.e. "I would like to be kept alive if I were…") and more objective statements of societal significance (i.e. "It is acceptable to stop treatment in…") are in accordance with previous findings which show that the majority of surveyed physicians and nurses would refuse treatment for themselves more than for patients (Gillick et al., 1993). The legal ambiguity which exists around MCS may have influenced the audience to draw a virtual line between expressing preferences for self versus others, by implicitly recognizing that the latter could be a step on the slippery slope to legalize euthanasia (Rosner, 1993). We also show that end-of-life decisions are not always governed by clinical circumstances and patients' preferences; rather, physicians' characteristics (i.e. age, religion and geographic region) seem to play a critical role for picking such options. Considering these different attitudes inside and outside of Europe, for example, it has been suggested that an international consensus regarding standards of care needs to be reached (Yaguchi et al., 2005).

In principle, we are unable to account with certainty for the sample's responses, especially in the case of MCS where opinions appeared more dissociated. Such results may be due to the different outcome which characterizes VS/UWS and MCS (Ledoux et al., 2008), or the distinct brain activation patterns of these two clinical entities (Laureys, et al., 2004) or the potential pain perception that the sample ascribes to MCS (Demertzi, et al., 2009c). Importantly for the issue of pain perception, several ethically salient questions arise. For example, it has been argued that patients can be left without administration of opioids or other analgesic drugs during their dying process on the grounds that they are deprived from experiencing suffering due to hunger or thirst (Ahronheim & Gasner, 1990; Laureys, 2005b). Next we illustrate whether and how opinions on pain perception can influence attitudes towards end-of-life in non-communicating patients.

2.5 Attitudes on pain perception mediate end-of-life views

Here, with a further aim to add to the ethical discussion on end-of-life options with regards to pain perception in patients with disorders of consciousness, we reanalyzed the European survey data on healthcare professionals. We assessed whether opinions (n=2259) on end-of-life options associate with beliefs regarding pain perception in these patients and identified variables explaining this association.

For chronic VS/UWS, agreement with treatment withdrawal was negatively correlated with opinions on pain perception in this state. In other words, the more respondents found it appropriate to withdraw treatment from VS/UWS patients, the less they recognized that these patients feel pain. For chronic MCS, end-of-life attitudes were not mediated by opinions on pain perception (Figure 2.4). With respect to professional background, for chronic VS/UWS more paramedical workers than medical doctors supported treatment limitation when they thought that VS/UWS patients feel pain. For chronic MCS, medical doctors and paramedical professionals' opinions did not differ in terms of pain perception in these patients. With respect to religious beliefs, for chronic VS/UWS, less religious than non-religious respondents supported treatment limitation both when they considered pain perception and not in VS/UWS patients. For chronic MCS, less religious than non-religious respondents agreed with treatment withdrawal when they considered that MCS patients feel pain.

Discussion

These data show a connection between beliefs about perception of pain and attitudes toward end-of-life decision-making in VS/UWS. Generally, the more a patient is able to feel pain, the less favorable a clinician is to withdrawal of life support. The high number of participants supporting treatment withdrawal in VS/UWS when considering that pain perception is absent is in line with existing guidelines on pain perception in these patients (The Multi-Society Task Force on PVS, 1994b). However, the overall data suggest conflicting or complex ethical reasoning made by respondents regarding the relationship between pain perception and acceptability of withdrawal of life support.

At first glance, the relationship observed could be justified in as much as a patient with more sentience, and therefore more awareness, could be judged to be apt to be kept alive. Likewise, a patient who does not feel pain could be exhibiting lack of awareness and be allowed to die. With a similar rationale, pain as a subjective conscious experience corresponds to a form of conscious awareness. And such evidence, according to some, may give a strong reason to preserve life (Stumpf, 1986). For the sake of our discussion we can retain this hypothesis as one possible explanation of the relationship observed in the data, also an approach put forth by some commentators (Ropper, 2010) while criticized by others (Kahane & Savulescu, 2009).

The implicit connection between greater pain sentience, greater awareness and therefore greater reticence to withdrawal of life support resonates with a heavy trend in bioethics exploring the

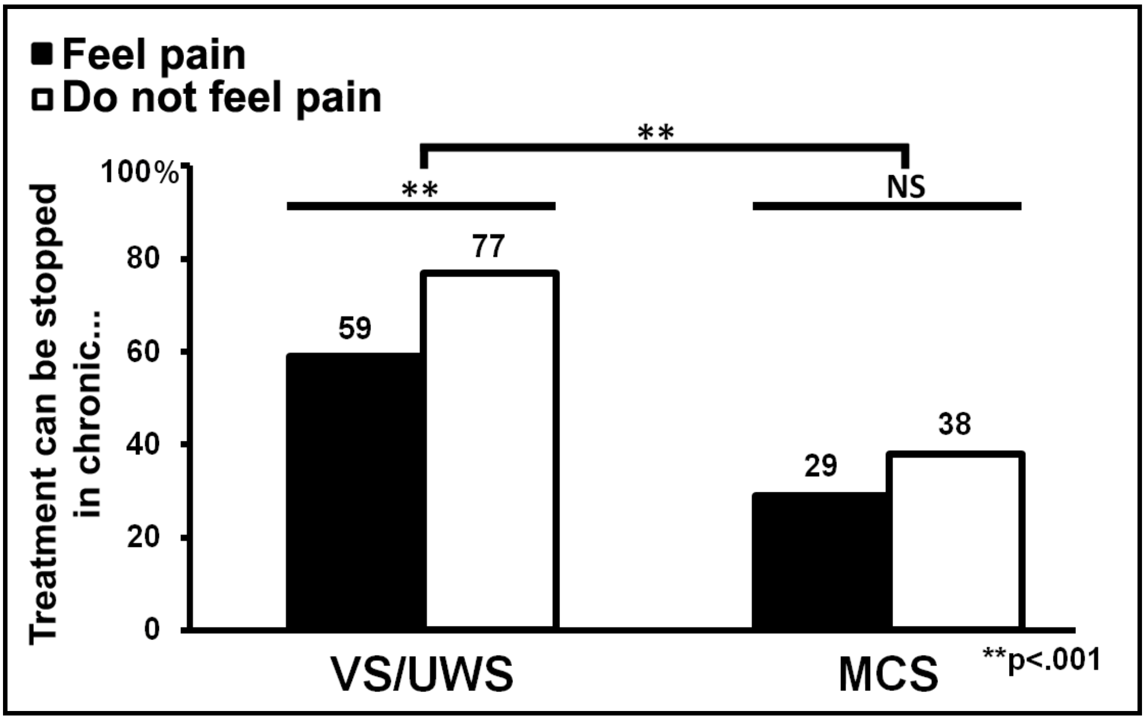

Figure 2.4 *Attitudes towards treatment withdrawal in VS/UWS are mediated by opinions on pain perception in patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS) but not in minimally conscious state (MCS).*

principle of respect for persons in terms of personhood or moral status of the person. This line of argument usually assumes that we respect persons or other moral agents because of their capacity as moral agents or persons. The capacities of persons usually refer to things like sentience and interests (Singer, 2011) or cognitive abilities (Veatch, 2005). An enormous literature has examined and discussed if and what conditions or criteria a person or a moral agent must fulfill (e.g., Fletcher, 1979), hoping thereby to shed light on debates related to the beginning or the end of life (Macklin, 1983). In this scheme, evidence of sentience could very well be understood as a proof of being a moral agent. As suggested, if neuroimaging research shows residual cognitive function or pain perception, it could easily be interpreted by family members as an indication that treatments should be maintained (Ropper, 2010). Underlying this view is the assumption that some ontological status can be correlated to being a person and, once this state established, respect for that person or moral agent is called for.

Generally, equating persons with their brains or neurological status has been described in other areas of neuroethics as neuro-essentialism (Racine et al., 2005) and carries wide-ranging philosophical and practical problems (Glannon, 2009). A closer examination of the ontological understanding of respect for persons reveals specific problems of two different natures. First at a more practical level, greater sentience or pain perception in MCS could mean greater ability to feel pleasurable states or well-being, which would call for specific therapeutic approaches (Kahane & Savulescu, 2009) and an argument in favor of maintaining treatments. But greater sentience could very well mean a greater ability to feel both pain and suffering, i.e. the effects of being in a severely compromised state. In this sense, pain perception does not relate directly or clearly to a specific stance in favor of (or against) maintaining life support. Second and more fundamentally, respect for persons entails other aspects which are not captured in a canonical ontological understanding of respect for persons. On the one hand, the preferences and interests of the person to be maintained in a state of pain sentience could still be argued to depend largely on preferences and interests as defined by the patient herself/himself previously (or as voiced or articulated by a proxy decision-maker). In this sense, the close attention to what the patient would have wanted is crucial and the establishment of pain sentience is not by any standards surrogate for this. On the other hand, still, the ontological view causes problems because it does not capture *stricto sensu* non-ontological aspects of the principle of respect for persons. Respect for persons partly relies on the fact that the respected entities are considered to have a moral status or moral agency but also because they have worth and value for others. Consider the scenario of a loved one (e.g., child, parent, spouse) being in a neurologically severely compromised state and even in a state of disordered consciousness. To treat such a compromised loved one without respect would stir in most (if not all) strong feelings of disapproval, even if one agrees that cognitive capacities have diminished or maybe vanished. This urge for respecting the person is not because the person has certain capacities; on the contrary (s)he may have lost them. It is rather a mixture of obligations towards others, respect for human relationship or respect for what a person was before the injury that support this principle. This is a more *relational (or contextual) understanding* of respect for persons and such an understanding is ill-captured by common arguments, which equate the person to a neurological status as found at the basis of the ontological view.

Consequently, the implicit connection between sentience and attitudes favoring life should be examined critically. This link is debatable because it may rely on a dubious understanding of respect for persons which does not capture the preferences or wishes of the patients as defined by themselves, overly objectifies persons and ontologizies the principle of respect for persons. The ontological view may carry forth a broader reductionist framework which, by strongly linking personhood to some ontological status, does not grasp the relational aspects captured in the principle of respect for persons. By extension, implicit or explicit uses of the ontological understanding in interpretations of recent neuroimaging research should be carefully identified and considered to ensure clarity about the reasons underlying respect for persons. This is reinforced by different studies showing strong appeal of neuroimaging data in the public eye (McCabe & Castel, 2008; O'Connell et al., 2011; Racine et al., 2010; Weisberg et al., 2008), which could easily lead to neuro-essentialism.

Methods

Participants were first introduced to the clinical definitions of consciousness and were then asked to provide "yes" or "no" answers to 16 questions related to consciousness, VS/UWS, MCS, and LIS. We here report the replies obtained in European medical and paramedical professionals to the questions ''Do you think that patients in a vegetative state can feel pain?'' and ''Do you think that patients in a minimally conscious state can feel pain?'(Demertzi et al., 2009c). Additionally, "Being in a chronic VS is worse than death for the patient/for the family", "Being in a chronic MCS is worse than being in a VS for the patient/for the family", "Do you think that it is acceptable to stop treatment (i.e. artificial nutrition and hydration) in patients in chronic VS?", "Do you think that treatment can be stopped in patients in chronic MCS?", "Would you like to be kept alive if you were in a chronic VS?", "Would you like to be kept alive if you were in a chronic MCS?".

Recorded demographic data included age, gender, nationality, profession, and religious beliefs. Nationalities were categorized into three geographical regions based on previous classification criteria (Sprung et al., 2003): *Northern* (Denmark, Estonia, Finland, Lithuania, Netherlands, Norway, Poland, Russia, Sweden, United Kingdom), *Central* (Austria, Belgium, Czech Republic, Germany, Hungary, Luxembourg, Moldavia, Romania, Serbia, Slovakia, Slovenia, Switzerland), and *Southern* Europe (Bulgaria, Croatia, Cyprus, France, FYROM, Greece, Italy, Portugal, Spain, Turkey).

Statistical analyses were performed using SPSS v.16.0 software packages. Multiple logistic regression (stepwise backward; i.e. independent variables are removed from the equation at consecutive steps; entry, p=.05 and removal, p=0.1) was used to assess associations between obtained answers to the two questions and age, gender, profession, region, and religiosity. Chi-square tests assessed differences within categorical variables. Results were considered significant at p<.05 (two-sided). Participation to the survey was voluntary and anonymous.

Conclusions

In healthy controls, pleasure and well-being depends on the positive affect (hedonia) and on the sense of purposefulness or engagement in life (eudemonia) (Berridge & Kringelbach, 2011). Despite the general view that quality of well-being is diminished in disease as a result of limited capacities to functionally engage in everyday living, these attitudes are formulated from a third-person perspective and may underestimate patients' subjective well-being (Demertzi et al., in press). Indeed, we recently showed that a majority of patients in a chronic LIS, despite self-reporting severe restrictions in community reintegration, professed good subjective well-being (Bruno et al., 2011a). In patients with disorders of consciousness, self-ratings are impossible to acquire and only estimates about what it is like to be in this situation can be made (Laureys & Boly, 2007). For example, an analysis of public media reports on Terri Schiavo (a patient in a VS/UWS) showed that in some cases the patient was described as feeling discomfort which was incompatible with her state (Racine et al., 2008). In another study, ratings from family members, who are more acquainted with VS/UWS, showed that 90% of families reported, among others, that the patients perceived pain (Tresch et al., 1991). These figures are incompatible with what has been proposed by formal clinical guidelines concerning pain perception in patients with disorders of consciousness (e.g., The Multi-Society Task Force on PVS, 1994b).

As shown by our surveys, there are inconsistencies among healthcare professionals as to whether unresponsive patients feel pain. Two possible non-mutually exclusive interpretations of this gap between guidelines and clinicians merit our attention. On one hand, perhaps clinicians are blatantly wrong, or are what we could call in *disagreement of knowledge* with guidelines, i.e. they were wrong because they did not know. In support of this interpretation, research on diagnostic accuracy has shown that clinicians have trouble distinguishing the VS/UWS from MCS (Andrews, et al., 1996; Childs, et al., 1993; Schnakers, et al., 2009) and even confuse the VS/UWS with more remote states, like brain death (Youngner et al., 1989). On the other hand, perhaps a *disagreement of apprehension or perspective* could also be at work. This hypothesis entails that clinicians are or were observing pain perception in some patients which was not reflected fully in guidelines offered to them. Following this interpretation, clinicians who may have or have not been in agreement of knowledge with guidelines may have nonetheless been at odds with them, deliberately or not, because of a difference in apprehension of pain perception.

Our analyses further suggest discrepancies between healthcare providers, which merit close attention. For example, respondents' opinions for chronic VS/UWS patients were mediated by professional background as showed above. The observed differences based on professional background might be related to many factors (i.e. differences in proximity to the patient, time spent at the bedside, sensibilities, and education) as mentioned above (Asch et al., 1997; Festic et al., 2011). Nonetheless, this variability is concerning especially if one considers that family members may be exposed to various messages about pain perception based on who they talk to (Racine et al., 2009). Other research, similarly shows that physicians (Racine, et al., 2009) and family members' characteristics (Kuehlmeyer et al., 2012) can shape attitudes toward end-of-life care, judgments about quality of life, and prognosis for post-coma recovery.

Religiosity was also found as an important factor correlating with clinicians' attitudes. We have previously shown that religious beliefs influence personal philosophical convictions towards dualistic views on the relationship between consciousness and the brain (Demertzi, et al., 2009b). Such personal beliefs have also been shown to weigh on physicians' clinical decisions (e.g., Jennett, 2002b). Similarly, other studies on, for example, end-of-life decisions in intensive care patients have shown that older and more experienced doctors and doctors with religious convictions (i.e. Christians) more often refused to opt for treatment limitations (Christakis & Asch, 1995; Sprung, et al., 2003).

Our surveys on pain and end-of-life highlight that the ethical issues accrued from the study and management of patients with disorders of consciousness are variant and multi-faceted. Medical, legal and public controversies are shaped by how different people think about these issues and in many cases are country-dependent. It is, therefore, necessary that a uniform ethical framework is shaped to guide clinicians and caregivers in terms of clinical outcome, prognosis, and medical management. For that reason, bedside research and clinical investigations by means of neuroimaging/electrophysiological technologies are expected to provide valid means to a better comprehension of such severely compromised states.

3

Functional neuroimaging in resting state

> *"The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is…far from restful"*
>
> *Seneca (~ 60 A.D.)*

Based on:

Vanhaudenhuyse*, A., **Demertzi***, A., Schabus, M., Noirhomme, Q., Bredart, S., Boly, M., Phillips, C., Soddu, A., Luxen, A., Moonen, G., Laureys, S., **2011**. Two distinct neuronal networks mediate the awareness of environment and of self. J Cogn Neurosci. 23, 570-8. (*equal contribution)

Demertzi, A., Soddu, A., Faymonville, M.E., Bahri, M., A., Gosseries, O., Vanhaudenhuyse, A., Phillips, C., Maquet, P., Noirhomme, Q., Luxen, A., Laureys, S., **2011**. Hypnotic modulation of resting state fMRI default mode and extrinsic network connectivity. Prog Brain Res. 193, 309-22.

Demertzi, A., Soddu, A., Vanhaudenhuyse, A., Faymonville, M. E., & Laureys, S. (submitted). Functional connectivity changes in hypnotic state measured by fMRI.

Demertzi, A., Soddu, A., Vanhaudenhuyse, A., Gómez, F., Chatelle, C., Tshibanda, L., Boly, M., et al. (submitted). Global breakdown of fMRI resting state network connectivity in patients with disorders of consciousness.

3.1 The resting state paradigm

Growing neuroscientific evidence supports the idea that, in the absence of an external input, the brain is characterized by intrinsic activity. This notion was initially stressed by two meta-analyses of PET activation protocols with healthy subjects. These studies illustrated that a network of mesiofrontal, posterior cingulate/precuneual cortices and lateral parietal areas was more active at rest and showed activation decreases when compared to cognitive tasks (Mazoyer et al., 2001; Shulman et al., 1997). Such task-induced activity decreases led to the assumption that the brain at rest is not silent. On the contrary, the brain's resting state activity is characterized by spontaneous low-frequency fluctuations (in the range of 0.01– 0.1 Hz), which can be detected in the BOLD signal of fMRI measurements and organize the brain in a "default mode network" (Gusnard et al., 2001). Such spontaneous BOLD fluctuations cannot be attributed to peripheral noise, such as cardiac and respiratory fluctuations, motion of the subject etc. Rather, there is synchronized activity with other functionally-related brain regions (Cordes, et al., 2000; Fox & Raichle, 2007). Hence, these "deactivations" were considered to be as deviations from an ongoing metabolic/physiologic baseline which characterizes the function not only of the areas of the default mode network, but also of most areas of the brain (Gusnard & Raichle, 2001; Raichle & Snyder, 2007). Data-driven statistical analyses indeed show that the brain exhibits various large-scale "resting state" networks of functional significance (e.g., Beckmann, et al., 2005; Damoiseaux, et al., 2006; De Luca et al., 2006; Laird, et al., 2011; Smith, et al., 2009). Among the most commonly studied networks are the default mode and its anticorrelated regions, left and right **frontoparietal**, **salience**, **sensorimotor**, **auditory**, and **visual** networks (Figure 3.1).

Importantly for non-communicating patients with disorders of consciousness, resting state acquisitions are a suitable means to study residual cognition.

Frontoparietal network encompasses bilateral inferior frontal gyri and inferior parietal lobes. Independent component analysis classifies this network in two lateralized components (e.g., Beckmann et al., 2005; Damoiseaux et al., 2006). The left corresponds to cognitive and "language" paradigms while the right was shown to correspond to perceptual, somesthetic and nociception paradigms (Laird et al., 2011; Smith et al., 2009).

Salience network mainly encompasses bilateral insular and anterior cingulate cortices (ACC). These areas are commonly observed in conflict monitoring, information integration and response selection (Cole & Schneider, 2007; Roberts & Hall, 2008). The salience network is also involved in interoception and pain-related processes (Ploner et al., 2010; Wiech et al., 2010).

Sensorimotor network encompasses supplementary motor area/ midcingulate cortex, and bilateral primary, premotor and somatosensory cortices (Biswal et al., 1995; Cordes et al., 2000; Greicius et al., 2008; Mannfolk et al., 2011).

This is because resting state protocols do not require sophisticated experimental setup and surpass the need for patients‘ subjective contribution, either verbal or motor or both (Soddu et al., 2011). With the intention to ultimately use the resting state paradigm in patients, we first aimed to validate it in healthy controls.

3.2 Resting state in conscious wakefulness

Since the early studies of resting state it was suggested that the brain’s baseline activity can be organized in two widespread brain networks of anticorrelated activity: an “extrinsic” and an “intrinsic” (Fox et al., 2005; Fransson, 2005; Golland et al., 2007; Tian et al., 2007). The *extrinsic* system encompasses lateral frontoparietal areas, resembling the brain activations during goal-directed behavior, and it has been linked to cognitive processes of external sensory input, such as somatosensory (e.g., Boly et al., 2007), visual (e.g., Dehaene & Changeux, 2005) and auditory (e.g., Brunetti et al., 2008).

The *intrinsic* system (or default mode network) encompasses medial and lateral parietal areas and has been associated with self-related cognitive processes, such as mind-wandering (Mason et al., 2007), task-unrelated thoughts(McKiernan et al., 2006; Stawarczyk et al., 2011), introspection (Goldberg et al., 2006), monitoring of the “mental self” (Lou et al., 2004), and temporal perspective of the “self” (D'Argembeau et al., 2010).With no a priori assumptions, we here aimed to better characterize the subjective cognitive processes inherent to these “external” and “internal” networks by bridging behavioral and neuroimaging data from healthy volunteers.

Behavioral “resting state” experiment

This experiment aimed to determine the relationship between external and internal awareness scores in 31 controls. During an eyes-closed resting condition, subjects were asked to evaluate and score their

Auditory network mainly encompasses bilateral superior temporal gyri/insular cortices, left pars opercularis, left superior temporal gyrus, and midcingulate cortex (e.g., Cordes, et al., 2000). Connectivity in this network has been associated with audition (tone and pitch discrimination), music, speech, phonological and oddball discrimination (Laird, et al., 2011).

Visual networks
Medial: encompasses primary and extrastriate visual cortices (Lowe *et al.*, 1998). It is involved in “low-level” visual processing, such as checkerboard viewing (Laird, et al., 2011).
Lateral: encompasses inferior temporal gyri, including the middle temporal visual association area (MT, MST, V5) at the temporo-occipital junction. It is involved in viewing complex, often emotional, stimuli (e.g., faces, films) (Laird, et al., 2011).
Occipital: is involved higher-level visual processing associated with orthography and covert reading (Laird, et al., 2011).

external and internal awareness levels by button presses after hearing an auditory prompt (randomized interstimulus interval= 11.3-26.8 sec, mean = 19s; see Methods box for details). External awareness was defined as the perception environmental sensory stimuli (e.g., auditory, visual, olfactory, or somesthetic). Internal awareness referred to all environmental stimuli-independent thoughts (e.g., inner speech, autobiographical memories, or wandering thoughts). Upon completion of the experiment, the content of awareness was assessed using a semi-structured interview. External thoughts reported were auditory in 65% of subjects, somesthetic in 58%, olfactory in 13%, and visual in 1%.

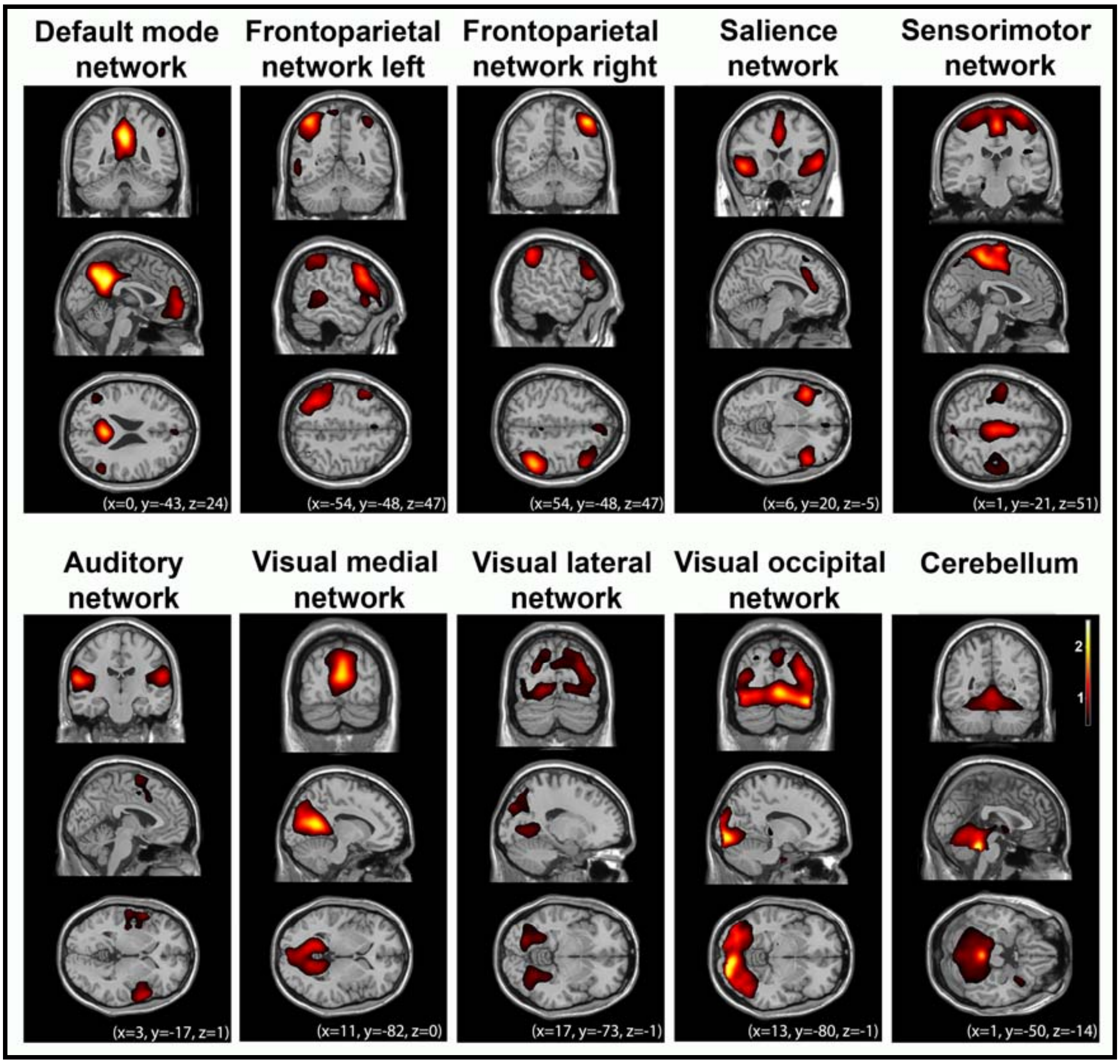

Figure 3.1 *Resting state networks identified in healthy controls. From Heine et al, Front Psychol (submitted)*

Internal thoughts were experiment-related in 52%, autobiographical in 42%, and inner speech in 13% of subjects. The contents of external and internal awareness are summarized in Table 3.1.

At the group level, we observed a significant negative correlation between external and internal awareness behavioral scores (Spearman's r=−.44, p<.02, two-tailed). At the subject level, 24 (80%) participants showed significant negative correlations between internal and external awareness, one showed a positive correlation, and six participants showed non-significant correlations. The switching between external and internal awareness was calculated to occur with a mean frequency of 0.05 ± 0.03Hz (range: .01–.1; Figure 3.2). Interestingly, this frequency is similar to BOLD fMRI slow oscillations suggesting a close link between behavioral and neuronal activity.

Neuroimaging fMRI "resting state" experiment

This experiment aimed to bridge behavioral and neuroimaging "resting state" data. After having established the relationship between external and internal

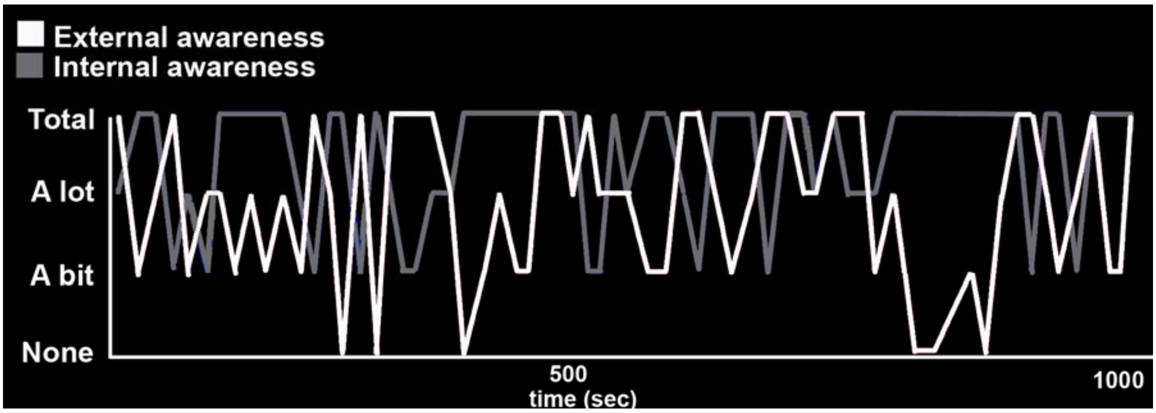

Figure 3.2 *The temporal dynamics of the two components of awareness in a representative subject. The figure illustrates that external and internal awareness scores anticorrelate at the behavioral level. Adapted from Vanhaudenhuyse & Demertzi et al., J Cogn Neurosci (2011)*

Table 3.1. *The contents of the two components of awareness based on semi-structured interview after completion of the behavioral experiment. From Vanhaudenhuyse & Demertzi et al., J Cogn Neurosci (2011)*

	Content	#subjects	Examples
External awareness	Auditory	20	Hearing sounds from outside the room
	Somesthetic	18	Felt itchiness, uncomfortable body posture
	Olfactory	4	Smelling perfume
	Visual	2	Visual perceptions through closed eyelids
Internal awareness	Experiment-related	16	Thoughts related to the length of the study
	Autobiographical (future, past)	13	Vacation, plans for weekend
	Inner speech	4	Instruction to oneself to stay vigilant

awareness with the behavioral experiment (using responses from both hands), the fMRI study was performed in 22 healthy volunteers. Subjects were presented an auditory beep (interstimulus interval= 3–30s, mean=20 sec). After each sound, they were asked to evaluate and score by a button press their state of awareness. In order to reduce the interference with resting state brain function and to reduce motor responses and artifacts to the maximum, behavioral responses were obtained on a single scale reflecting intensity from “more external” to “more internal” (using the left hand for all subjects; see Methods box for more details).

Statistical analyses looked for brain areas where BOLD activity correlated with “internal” and “external” awareness behavioral scores. We found that the intensity of external awareness scores correlated linearly with activity in the bilateral inferior frontal gyrus and inferior parietal lobule (small-volume correction; Figure 3.3 red areas). Additionally, the intensity of internal awareness correlated linearly with activity in posterior cingulate/precuneal, anterior cingulate/mesiofrontal, and bilateral parahippocampal cortices (whole-brain false discovery rate $p<0.05$; Figure 3.3 blue areas). The switching between external and internal awareness was calculated to occur with a mean frequency of 0.03Hz± 0.004 (range = 0.03–0.4 Hz). We here showed a link between extrinsic and intrinsic brain networks and spontaneous subjective mentation. Our data are in line with previous studies showing a competing character of the two systems in the sense that these two systems can disturb or even interrupt one another (Tian, et al., 2007; Weissman et al., 2006). This functional pattern is also illustrated by studies on motor performance (Fox et al., 2007), perceptual discrimination (Sapir et al., 2005),attention lapses (Weissman, et al., 2006) and somatosensory perception of stimuli close to sensory threshold (Boly, et al., 2007) including noxious stimuli (Ploner, et al., 2010). These studies show that high prestimulus baseline activity in the intrinsic system is associated with a tendency to ignore environmental stimuli, whereas perceived external stimuli were associated with an increased activity in the extrinsic system. Similar findings are suggested by psychology literature where engagement to demanding self-oriented tasks makes us less receptive to environmental stimuli

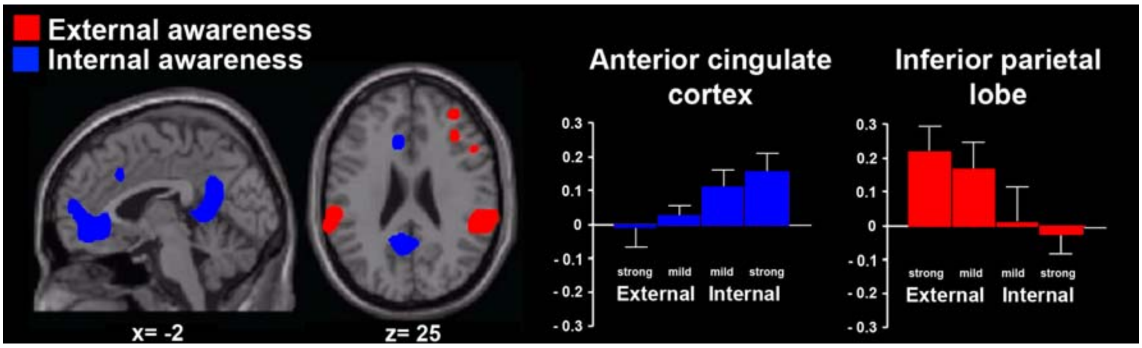

Figure 3.3 *Brain regions showing a correlation between BOLD signal and the intensity of internal and external awareness scores in 22 healthy volunteers. Stronger internal awareness scores correlate with increased activity in anterior cingulate/mesiofrontal, posterior cingulate/precuneal, and parahippocampal cortices (areas in blue). External awareness scores correlate with increased activity in bilateral inferior parietal lobule and dorsolateral prefrontal cortices (in red). Adapted from Vanhaudenhuyse & Demertzi et al., J Cogn Neurosci (2011)*

and this switch in attention can happen without conscious recognition (e.g., Smallwood & Schooler, 2006). In fact, we here showed results concerning the cognitive counterpart of “resting state”. The amount and the precise function of unconscious processes pervading resting state mentation remains to be further elucidated.

Discussion

Our data imply that this anticorrelated pattern between the extrinsic and intrinsic system is of functional significance to conscious awareness. Results from studies in slow-wave sleep (Samann et al., 2011) and under propofol anesthesia (Boveroux, et al., 2010) indeed show a decreased level in connectivity in these two systems. One limitation of such studies, however, is that they do not permit collection of subjective reports, merely because subjects are responsive under these states. With an aim to further characterize the anticorrelated relationship of the extrinsic and intrinsic systems and their contribution to unresponsive states, we opted to measure their behavioral and neuroimaging properties under a minimally responsive condition, such as hypnosis.

Methods

Behavioral Experiment: Subjects placed four fingers of both hands (not the thumb) on the keyboard. For half of the subjects, the left hand corresponded to external awareness (for the other half, the left hand corresponded to internal awareness; randomized order). All subjects were instructed to start responding by using button presses of their left hand on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = maximal). The subjects’ task was to rate both external and internal awareness (prompted by a 60-dB beep presented via headphones). Only when the two scores were given could the next beep be elicited. A familiarization session (11 responses) preceded the main experiment (66 responses). *Statistical analysis:* The relationship between ratings of external and internal awareness was estimated by calculating Spearman’s r correlation coefficients (two-tailed) for every subject and then estimating the mean correlation within the sample. In terms of temporal dynamics, the frequency of switching between internal and external awareness scores was estimated by first subtracting the external from internal ratings in order to get a unique curve for every subject. The frequency spectrum of these obtained scores was estimated using the Lomb periodogram method for unevenly sampled awareness scores (Lomb, 1976; Press et al., 1992).

Methods (continued)

Imaging Experiment: For the fMRI experiment, awareness scores were recorded with the left hand for all subjects (1=strongly external, 2=moderately external, 3=moderately internal, and 4=strongly internal). The fMRI study was terminated when on-line analysis showed 15 responses in each state of awareness. *Statistical analysis*: Functional data were preprocessed and analyzed using SPM5. For each subject, a first-level intra-individual fixed effects analysis aimed at modeling the observed neurophysiological responses into components of interest, confounds, and errors by using GLM. We created a design matrix using a block design (lasting 3–30 sec) for every individual subject incorporating answers of subjects ("strongly external," "moderately external," "moderately internal," and "strongly internal") and time of beeps as regressors of interest; reaction times and movement parameters were included as covariates of no interest. A first analysis identified stimulus-induced brain activation in periods rated as "strongly external", "moderately external", "moderately internal" and "strongly internal." The effects of interest were tested through linear contrasts, generating statistical parametric maps in each subject. Contrasts images were computed, identifying a linear positive correlation with external thoughts (1.5 0.5 −0.5 −1.5) and a linear positive correlation with internal thoughts (−1.5 −0.5 0.5 1.5). The resulting set of voxel values for each contrast constituted a map of t statistic thresholded at $p < 0.001$. These contrast images were entered in a second-level GLM. Correction for multiple comparisons was done at false discovery error rate $p<0.05$ (whole head volume) for areas previously reported to be involved in internal awareness and using a small volume (8 mm radius sphere) at $p <0.05$ for areas previously reported to be involved in external awareness.

3.3 Resting state in hypnosis

Hypnosis was here considered an appropriate means to transiently modulate conscious cognition in controls because it does not lead to general unconsciousness (compared to pharmacological anesthesia or sleep) and does not have long-term effects on neuroplasticity (compared to meditation techniques, e.g., Holzel et al., 2008). Hypnosis is well documented to induce an altered conscious state of distinct cerebral pattern (Oakley & Halligan, 2009). At the phenomenological level, hypnosis is characterized by increased degrees of private processes, such as absorption (i.e. the capacity to remain implicated in a mental state), dissociation (i.e. the mental separation from the environment), disorientation in time, space and person, diminished tendency to judge and censor whereas it reduces spontaneous thoughts and gives the feeling of one's own response as automatic or extravolitional

Hypnosis is a procedure during which a health professional or researcher suggests that a patient or subject experiences changes in sensations, perceptions, thoughts, or behavior (The Executive Committee of the American Psychological Association - Division of Psychological Hypnosis, 1994)

(Rainville & Price, 2003; Terhune & Cardena, 2010). The experimental manipulation of these basic dimensions of experience is thought to provide leverage to investigate not only the contents of consciousness but also the neural correlates of its background states (Chalmers, 2000).

Here, we first aimed to characterize the functional relationship between the extrinsic and intrinsic anticorrelated networks. Then, we sought to explore functional connectivity changes in several “resting state” sensory-sensorimotor and “higher-order” networks.

The experiment

Twelve healthy subjects (4 women; M_{age}=21y±3) with no previous neurological or psychiatric history underwent three resting state scanning runs: during normal wakefulness, under hypnotic state, and during a controlled condition of mental imagery of autobiographical memories (i.e. the same memories used in hypnotic session but here without the hypnotic induction). For subjects to be included in the study, they had to report an absorption and dissociation level >6/10 during a familiarization session with hypnosis which preceded the main experiment. During this session, detailed information about past pleasant life experiences, which the subject wanted to use during hypnotic induction, was obtained through a semi-structured interview.

The hypnotic state was induced in the same way as in patients during surgery (Faymonville et al., 1995; Faymonville et al., 1997; Faymonville et al., 1999) and as in previous functional neuroimaging studies with healthy volunteers (Faymonville et al., 2003; Maquet et al., 1999; Vanhaudenhuyse et al., 2009a). The hypnotic induction encompassed a 3-min instruction procedure involving progressive eye fixation and muscle relaxation. Subjects were then invited to re-experience their pleasant autobiographical memories. As in clinical conditions, permissive and indirect suggestions were used to develop and deepen the hypnotic state. Subjects were continuously given cues for maintaining a hypnotic state. The exact words and details of the

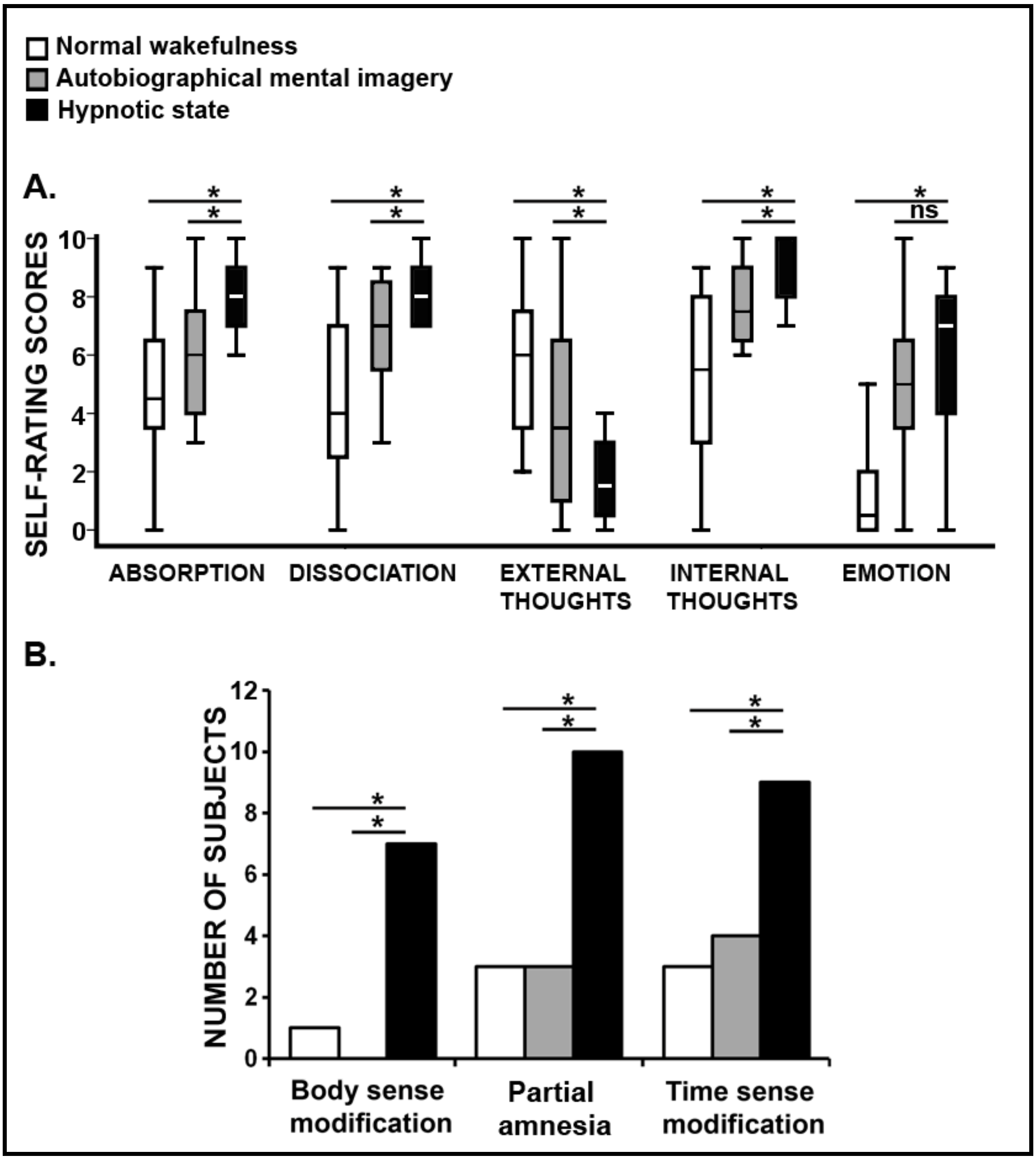

Figure 3.4 *Behavioral self-ratings on various subjective experiences in normal wakefulness, the control condition of autobiographical mental imagery and under hypnotic state. Panel A: For the numeric rating scale, boxplots represent medians with interquartile range (whiskers signify top and bottom quartiles). Panel B: For the dichotomous scale, bars represent the number of subjects consenting on having the putative experience (*p<.05, two-sided). Adapted from Demertzi et al., Prog Brain Res (2011c) and Demertzi et al. (submitted-a)*

induction technique and specific suggestions and details during the course of the induction varied depending upon the experimenter's observation of subject behavior, and on her judgment of subjects' needs. During the experimental session, the experimenter remained silent. After each run, subjective experience was debriefed on a 10-point numericrating scale concerning absorption, dissociation, intensity of external thoughts, and emotion levels; additional subjective reports were acquired using dichotomous (yes-no) scales measuring body sense modification (e.g., one arm felt longer than the other), partial amnesia and time sense modification (i.e. the session felt longer/shorter).

Behavioral changes under hypnotic state

At the behavioral level, participants reported similar arousal scores during normal wakefulness (6.4±2.0; range 2–10), mental imagery 6.1±1.8

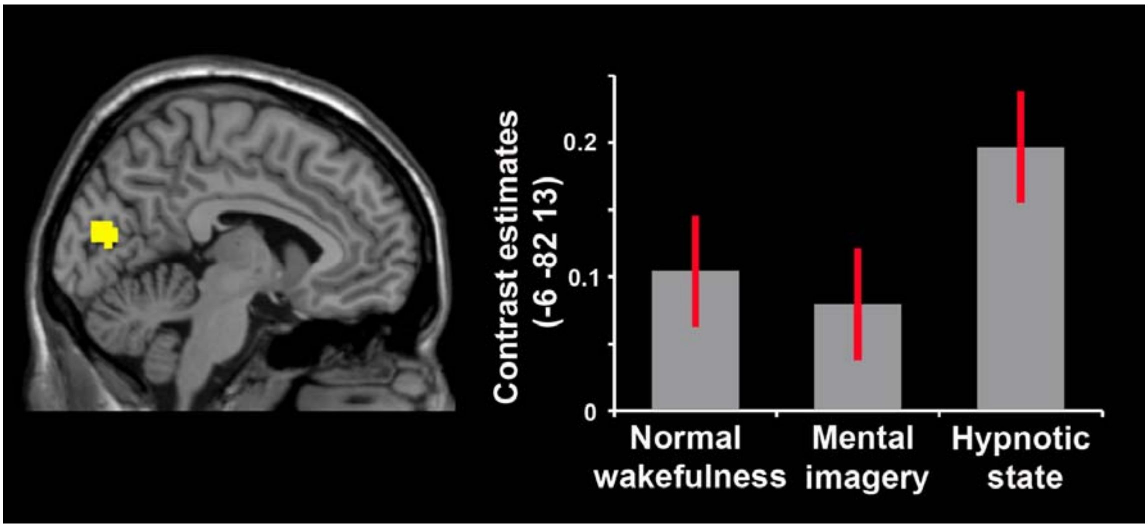

Figure 3.8 *Increased crossmodal interaction between auditory network (seed) and identified visual network (shown in yellow) in hypnotic state (compared to the control condition). For display purposes, data are thresholded at uncorrected p<0.001 superimposed on a structural T1 magnetic resonance template. Effect sizes (expressed as group mean and 90% CI) are shown in the right panel, reflecting for connectivity between auditory and visual cortices during the three conditions. From Demertzi et al. (submitted-a)*

(range 3–8), and hypnotic state (5.3±2.3). Dissociation, absorption and intensity of internal thoughts were higher in hypnosis compared to autobiographical mental imagery and normal wakefulness. Self-reported intensity scores of external thoughts were lower in hypnotic state compared to mental imagery and normal wakefulness. Emotional state ratings were not different under hypnosis compared to the control condition of autobiographical mental imagery (Figure 3.4A). Under hypnosis, more subjects reported body sense modification (n=7), partial amnesia (n=10) and time sense modification (n=9) compared to the control condition (Figure 3.4B).

Resting state extrinsic-intrinsic system anticorrelations diminish under hypnotic state

In normal wakefulness, the identified default mode network encompassed posterior cingulate and adjacent precuneal cortices, anterior cingulate and adjacent medial prefrontal cortices, bilateral angular, middle and inferior temporal, and parahippocampal gyri. The anticorrelated "extrinsic" system encompassed bilateral inferior frontal and supramarginal gyri. In autobiographical mental imagery, the identified default network and the anticorrelated extrinsic networks encompassed similar areas as described above albeit less widespread. In hypnotic state, a further decrease in default mode and "extrinsic" network functional connectivity was observed, as illustrated in Figure 3.5.

The comparison between hypnosis and autobiographical mental imagery showed an increased connectivity in part of the default network encompassing the middle frontal and bilateral angular gyri whereas the restrosplenial/posterior cingulate and bilateral parahippocampal areas showed a decreased connectivity. The "extrinsic" network did not show any increased connectivity but we identified a decreased connectivity in the right supramarginal and left superior temporal areas in hypnosis compared to autobiographical mental imagery (Figure 3.6).

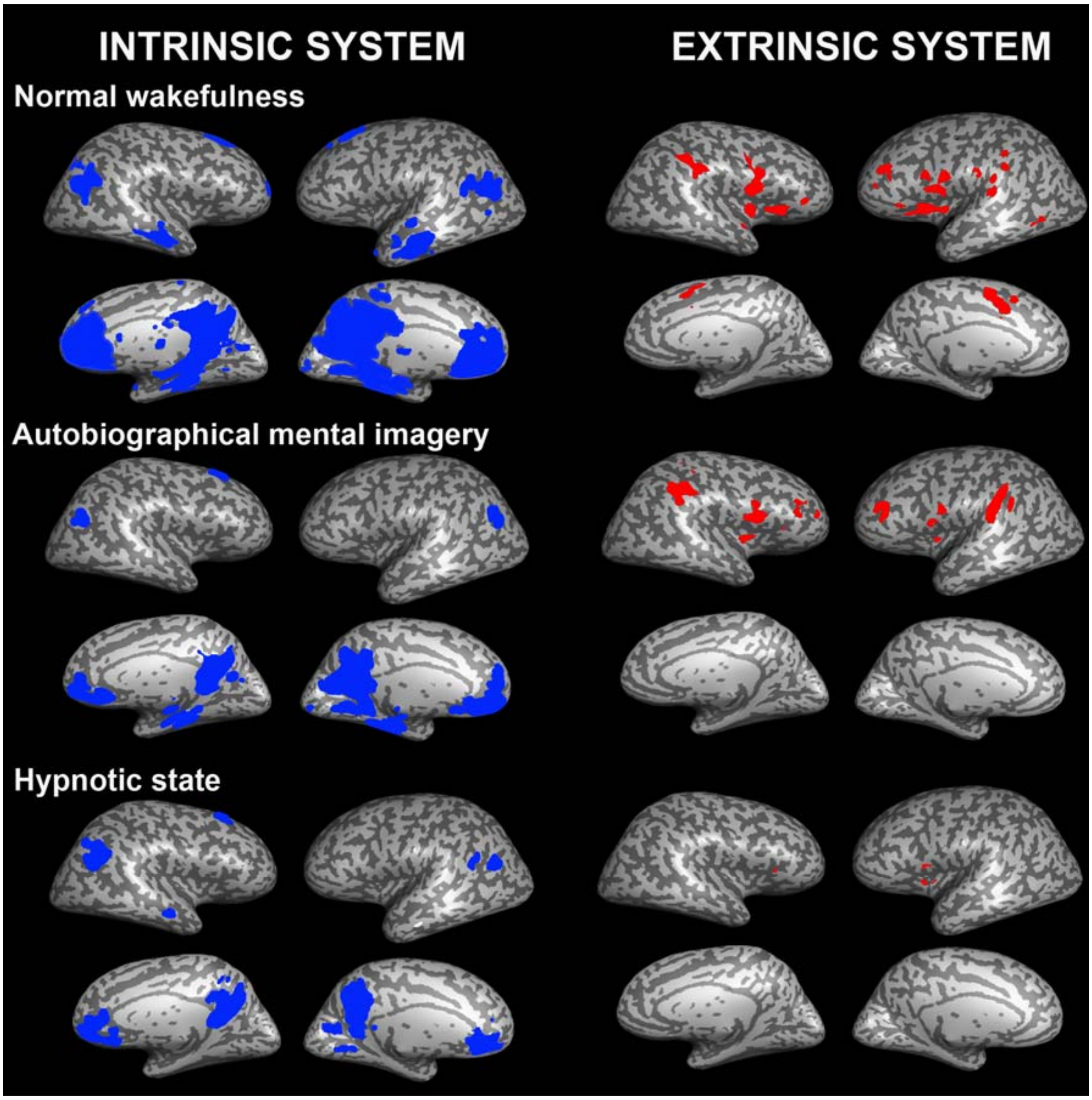

Figure 3.5 *The intrinsic (default mode network, in blue) and its anticorrelated "extrinsic" system (in red) under normal wakefulness, autobiographical mental imagery, and hypnotic state. Note the reduction of the extrinsic system anticorrelations in hypnosis compared to the other two conditions, possibly reflecting altered sensory awareness. Results are thresholded at whole brain false discovery rate p<0.05.Adapted from Demertzi et al., Prog Brain Res (2011c)*

Discussion

The decreased functional connectivity observed in the lateral frontoparietal extrinsic" system, along with the subjective reports of diminished external awareness, might reflect a blockage of the sensory systems to receive external stimuli. Hypnotic suggestions have been previously shown to have such effects on sensory perception by inducing (Derbyshire et al., 2004) or altering somatosensory awareness (Cojan et al., 2009).

The observed reduction in connectivity of the posterior midline parts of the default mode network during hypnosis might reflect a decreased degree of continuous information gathering from the external world with relation to oneself (Gusnard & Raichle, 2001). Additionally, these posterior retrosplenial, cingulate, and precuneal areas of the default mode network were previously shown to support functions concerning both orientation within, and interpretation of the environment (Vogt & Laureys, 2005). Together, the neuroimaging findings on the connectivity of the extrinsic and intrinsic system under hypnosis are respectively in line with the self-scores on an elevated sense of dissociation and diminished intensity of external thoughts on the one hand, and the increased intensity of internal scores, on the other. The functional contribution of the anticorrelated activity between default mode

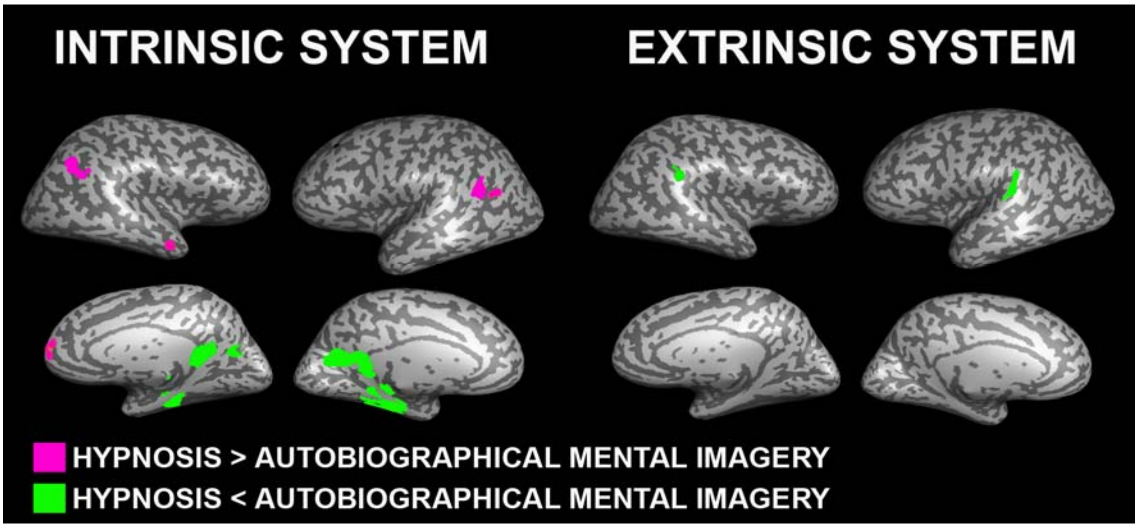

Figure 3.6 *Compared to the control condition of autobiographical mental imagery, for the intrinsic system (default mode network) in hypnotic state there was increased functional connectivity in the medial prefrontal cortex, bilateral angular gyri and decreased connectivity in the parahippocampal gyrus/posterior cingulate cortex. For the anticorrelated extrinsic system, there were only decreases in functional connectivity encompassing temporoparietal cortices (supramarginal gyrus and superior temporal gyrus). Adapted from Demertzi et al., Prog Brain Res (2011c)*

and the extrinsic systems has been modulation of consciousness also supported by studies under physiological (i.e., slow wave sleep; Samann, et al., 2011) and pharmacological (i.e., propofol anesthesia; Boveroux, et al., 2010) modulation of consciousness.

Methods

fMRI data were preprocessed and analyzed with “Brain Voyager” software package (Brain Innovation, Maastricht, The Netherlands). ICA was performed using 30 components (Ylipaavalniemi & Vigario, 2008). Self-organizing ICA (Esposito et al., 2005) permitted a spatial similarity test on single subjects’ independent components and an averaged template obtained in seven independent controls (mean age= 48 years±13, range: 25–65, 3 females). At a first-level, the component of interest was transformed into a statistical parametric map (SPM) for each individual subject: the time courses of all components but that of interest (i.e. which contained the z values of the two systems) were used to regress out the initial BOLD signal; the saved residuals represented the BOLD activity of the default mode and the “extrinsic” system. Then, by using the time course of the component of interest as a predictor of this residual BOLD activity, the t-maps were obtained. At a second-level, the beta values extracted from the previous step were entered in repeated-measures multiple subjects GLM (random effects) with three levels (normal wakefulness, hypnotic state, mental imagery). One-sample ANOVAs (FDR corrected $p<0.05$) were ordered to calculate the mean effects of each level. The contrast between hypnotic state versus mental imagery was ordered. Statistical parametric maps resulting from the voxel wise analysis were considered significant for statistical values that survived a cluster-based correction for multiple comparisons using the “cluster-level statistical threshold estimator” plug-in implemented in Brain Voyager.

Behavioral data were analyzed with SPSS v.16. Wilcoxon’s sign rank tests was used to test differences between conditions for the numerical rating scale. Chi-square tests were used to test differences between conditions for the dichotomous scale. Results were considered significant at $p<0.05$.

Resting state multiple network functional connectivity increases under hypnotic state

Compared to the control condition of pleasant autobiographical memories, we here mainly identified increased within-network functional connectivity for the default mode, left and right frontoparietal, salience, sensorimotor, and auditory networks. The visual network only showed decreases in functional connectivity in both within and between-network areas (i.e. hippocampus) (Figure 3.7). We further observed an increased

crossmodal interaction between the primary auditory and primary visual cortex during hypnosis (Figure 3.8).

Discussion

The decreases in functional connectivity observed in the visual network under hypnosis possibly reflect a free revivification of hypnotic suggestions and not mere memory retrieval. Similar occipital decreases under hypnosis have been observed in hypnosis-induced analgesia with pleasant autobiographical suggestions as studied by PET(Faymonville, et al., 2003). A previous fMRI study with posthypnotic suggestion to forget autobiographical long-term memories (i.e. scenes of a previously watched movie) also showed pronounced diminished activity in the extrastriate occipital lobes in the subjects who underwent the posthypnotic amnesia suggestion compared to those who did not (Mendelsohn et al., 2008). In combination with observed decreases in connectivity in the hippocampus, a structure classically related to the encoding and retrieval of long-term memories (Kolb & Whishaw, 2003a), it can hence be hypothesized that subjects in hypnosis do not merely retrieve stored memories, but rather revive them by following the experimenters instruction. This pattern corroborates the observed significantly higher number of subjects reporting post-hypnotic amnesia that was observed in the hypnotic state.

The increased functional connectivity observed in the other resting state networks potentially reflects lack of inhibitory cortico-cortical mechanisms. This is further supported by an increased crossmodal interaction between the primary auditory and visual cortices, thought to reflect decreased inhibition processes between brain areas (Cohen Kadosh et al., 2009).

The assumption of a less inhibited brain function is also based on similar findings coming from studies

Crossmodal interaction allows the characteristics of one sensory modality to be transformed into stimuli for another sensory modality. In resting state, a visual-auditory crossmodal interaction has been observed (Eckert et al., 2008). Anatomical tracer studies in nonhuman primates confirm this interaction (Falchier et al., 2010) and suggest that audio-visual cortical coupling might be relevant to multisensory integration which subsequently enhances visual awareness (Clavagnier et al., 2004).

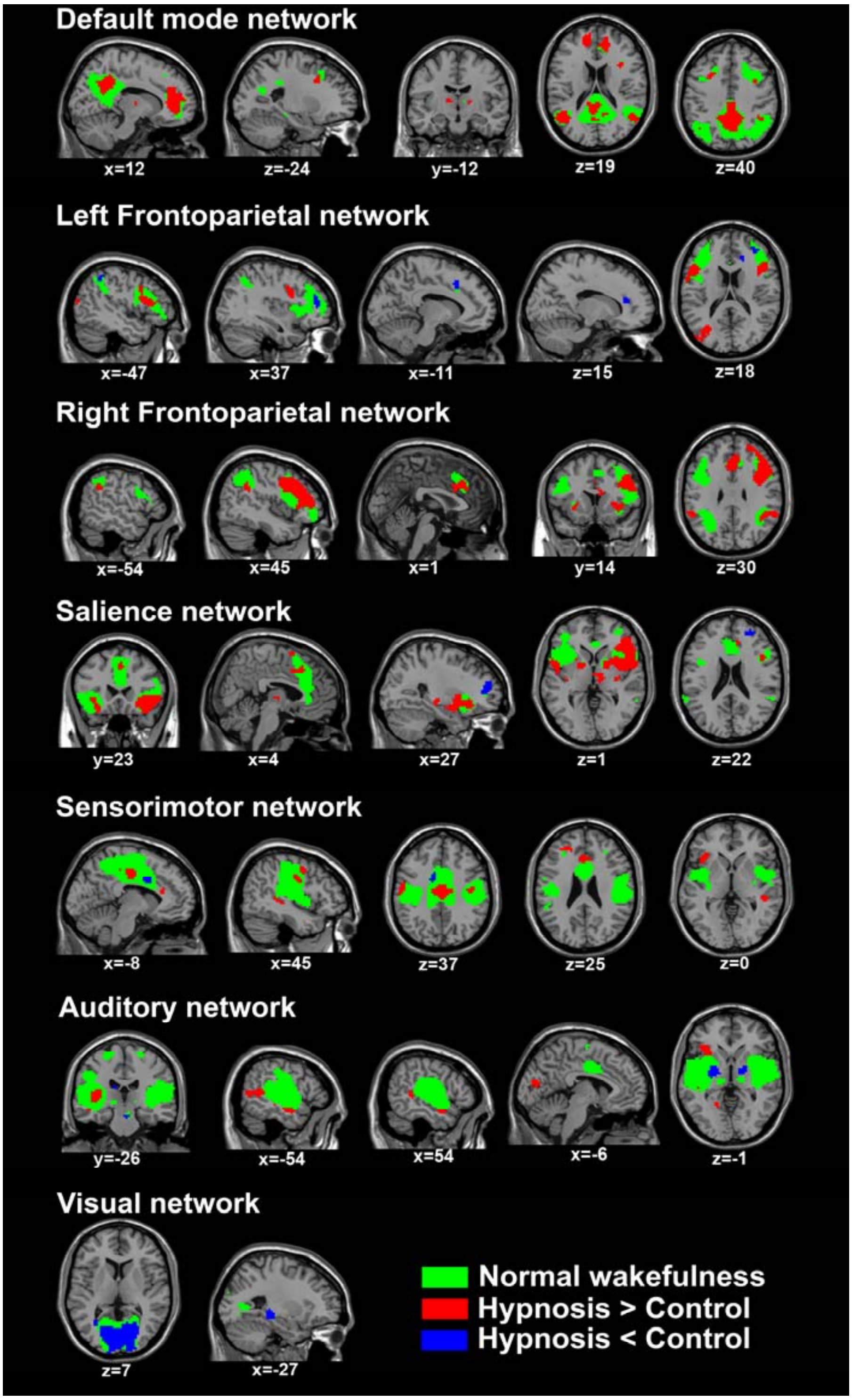

Figure 3.7 *Identified functional connectivity during normal wakefulness (green areas) in large-scale resting state networks. Compared to control condition, resting state networks mainly exhibit hypnosis-related increases in functional connectivity (red areas) with some areas showing decreased functional connectivity (blue areas). Of note is the visual network which exhibits only within-network hypnosis-related functional connectivity decreases. Normal wakefulness results are thresholded at family wise error rate corrected p<0.05 (whole brain) and, for display purposes, functional connectivity increases/decreases in hypnosis are shown at uncorrected p<.001. From Demertzi et al. (submitted-a)*

in light sleep (Larson-Prior et al., 2009), generalized tonic-clonic seizures (Blumenfeld, 2008) and ketamine-induced anesthesia (Seamans, 2008). In these states altered sense of consciousness results from organized aberrant brain activity thought to impede the normal communication necessary to maintain arousal and cognition. Here, increased functional connectivity could be considered to reflect higher temporal coherence between cerebral areas (i.e. time series of a certain seed area correlates with more brain regions in hypnosis). It has been previously suggested (in terms of neuronal firing) that excessively high levels of firing in a system typically result in a dramatic decrease of “integrated information”; in other words, a system is either not informative enough (i.e. cannot discriminate among a large repertoire of alternative experiences) or it does not integrate this information in a way leading to a unified experience (Tononi, 2008). Concerning hypnosis, this could be a potential explanatory mechanism to account for both subjective and neuroimaging data. We need to consider, however, that fMRI is characterized by low temporal resolution. This limits the measurement of integrated information thought to be measurable at the temporal scale of milliseconds, at least for biological systems (Tononi, 2008). Additionally, we here measured fMRI functional connectivity during resting state. Therefore, in order to measure the potential repertoire of a system, one would have to observe for an infinite time. Perturbational approaches, on the other hand, can help to better characterize the informational capacities of a system in hypnotic state. Such approaches (e.g., transcranial magnetic stimulation) induce changes in the system dynamics and, due to neuronal causal interactions, one can record the system reactions to such perturbation (e.g., by EEG). We believe that similar fMRI “resting state” in pathological consciousness states (e.g., coma or related states) will further improve our understanding of the neural correlates of subjective awareness.

Methods

fMRI data were preprocessed and analyzed with SPM8. The identification of resting state networks was done in three steps. First, the six motion parameters were used to regress in the initial signal in order to create a “dummy” BOLD signal, from which the regions of interest (ROIs) would be extracted. A high-pass filter of 128s was used to remove very low frequency fluctuations (.008 Hz). Second, time courses of interest were computed as the first principal component of the BOLD signal in 8-mm spherical ROIs centered on a priori coordinates from published studies: DMN [6 -42 32], left frontoparietal network [-44 36 20], right frontoparietal network [44 36 20], auditory network [-40 -22 8], visual network [-4 -84 8] (Boveroux et al., 2010), salience network [38 26 -10] (Seeley et al., 2007), and sensorimotor network [-2 -12 44] (Greicius, et al., 2008). Similar time course extractions were performed for voxels located in white matter [-22 16 32] and lateral ventricles [-6 20 10]. Third, a design matrix (per subject, per network, per condition (normal waking, control condition of autobiographical mental imagery, hypnotic state) was created with the ROI’s time course and 12 nuisance covariates (time courses in white matter, lateral ventricles, global signal and their derivatives, and the six movement parameters).

The effects of interest were tested by linear contrasts, generating statistical parametric T maps for each subject. A contrast image was computed for each subject, for each network and for each condition, identifying regions correlating with the selected seed-region after removal of sources of spurious variance. For each network, individual summary statistical images were entered in a second-level analysis, corresponding to a random effects model which estimates the error variance across subjects. These second-level analyses consisted of repeated measures analyses of variance (ANOVA) with 3 regressors representing the three experimental conditions (normal wakefulness, control condition, and hypnotic state) and 12 extra regressors modeling the subject-effects for each condition.

The error covariance was not assumed to be independent between regressors, and a correction for nonsphericity was applied. One-sided T contrasts tested for connectivity effects in all analyses. After model estimation, a first T contrast searched for areas correlated with each selected seed region during normal wakefulness.

Increased connectivity in hypnotic state was estimated by a conjunction analysis between normal wakefulness and the mental imagery<hypnotic state contrast. Decreased connectivity in hypnotic state was estimated by a conjunction analysis between normal wakefulness and the mental imagery>hypnotic state contrast. Results were corrected for multiple comparisons at the whole brain level using family wise corrections or cluster level corrections thresholded for significance at $p<0.05$. Small volume corrections for multiple comparisons were only accepted in previously identified networks in the normal waking condition (i.e. identifying within network hypnosis-induced connectivity changes using an 8 mm sphere radius).

3.4 Resting state in disorders of consciousness

The aim of the present study was to assess resting state functional connectivity in distinct fMRI resting state networks (default mode and its anticorrelated regions, left and right frontoparietal, salience, sensorimotor, auditory, and visual networks) networks as a function of the level of consciousness, ranging from controls and LIS, to MCS, VS/UWS and coma patients. Of particular interest for the study of coma and related states is the issue of pain and potential suffering because it raises scientific, clinical and ethical concerns (see Chapter 2 this Thesis). Hence, we further aimed to correlate the functional integrity of the salience network with clinical "pain" scales (i.e., Nociception Coma Scale, Schnakers, et al., 2010) given that previous studies have correlated salience network connectivity with pain-related processes (Ploner, et al., 2010; Seeley et al., 2007; Wiech, et al., 2010).

Twenty-eight patients (11 MCS, 12 VS/UWS, 5 coma) were included in analysis (11 women; mean age 52±17 years (range 20-87); 6 traumatic, 22 non-traumatic of which 7 anoxic). Data from 2 LIS patients (one brainstem stroke, one post-traumatic) were used for visual comparison with controls' values. Data were compared with an age-matched healthy volunteer group (n=22; 8 women; mean age 46±17 years; range 20-75).

We identified that global resting state fMRI connectivity (as reflected by multiple cerebral networks) correlates with the level of consciousness. More specifically, group-level comparisons showed decreased functional connectivity strength in all resting state networks when comparing healthy controls, MCS, VS/UWS and coma patients. Data from the two LIS patients fell in the range of healthy controls. Additional decreases in functional connectivity were observed between visual-auditory networks as a function of the level of consciousness (Figure 3.9). The regression analysis showed that Nociception Coma Scale total scores correlated positively with the functional connectivity of the salience network, in the anterior cingulate cortex (z = 3.26, p=0.001; stereotactic coordinates x=0, y=20, z=37), left insula (z = 3.10, p=.001 SVC; x=-48, y=-7, z=7), and right insula (z = 2.99, p=.001; x=36, y=5, z=-2; Figure 3.10).

Discussion

Although resting state data in patients with disorders of consciousness are technically relatively easier to obtain, compared to auditory (Schiff *et al.*, 2005) or visual activation protocols (Monti *et al.*, 2012) or "active" mental imagery tasks (Bardin et al., 2011; Monti, et al., 2010b), in the present cohort 79% (115 out of 145 initially included in the study) of patients' fMRI data could not be analyzed: 8% showed major structural brain damage making spatial normalization needed for group analyses unreliable (Shen *et al.*, 2007); 45% showed head motion contaminating the fMRI signal and, therefore, had to undergo sedation (Soddu, et al., 2011; Van Dijk et al., 2012) and 23% were excluded because of changing or unclear diagnosis. It is important to stress that when validating a novel assessment tool, the validation should only be based on clear-cut cases in order to avoid circular reasoning. Here, 28 patients with disorders of consciousness (11 MCS, 12 VS/UWS, 5 coma) of unambiguous diagnosis (i.e. same CRS-R diagnosis on repetitive assessments) were compared to 22 healthy controls in terms of functional connectivity. Data from two LIS patients were used for visualization purposes because the small number of patients did not permit their inclusion as a separate group in the design matrix. We here report a consciousness-level dependent breakdown of resting state fMRI (rsfMRI) connectivity in "lower-level" sensory (auditory and visual) and sensorimotor and in "higher-order" associative networks (default mode and its anticorrelations, right and left fronto- parietal and salience) when comparing controls, LIS, MCS, VS/UWS and coma patients. Taken together, our results could account for the patients impaired capacities for conscious awareness. Indeed, it was previously proposed that in order for humans to be conscious of something, incoming information (via sensory networks) needs to be made globally available to multiple brain systems via long-range neurons (associative networks) (Dehaene & Changeux, 2011). Additionally, we show a consciousness-level dependent impairment of crossmodal interaction between visual-auditory networks. Such crossmodal function was previously described in normal conscious conditions (Eckert, et al., 2008) and is considered relevant to multisensory integration which subsequently enhances visual awareness (Clavagnier, et al., 2004). Our findings corroborate data from propofol anesthesia in healthy volunteers also showing decreased crossmodal relationship as a function of pharmacologically-induced unconsciousness (Boveroux, et al., 2010). Finally, the salience network correlated with Nociception Coma Scale scores reflecting nociception-related processes in these patients measured in the absence of an external stimulus. In healthy conditions, activation of the insula and anterior cingulate cortex are commonly observed in conflict monitoring, information integration, response selection (Cole & Schneider, 2007; Roberts & Hall, 2008) and pain (Tracey & Mantyh, 2007). During resting state, the salience network is thought to be involved in emotional, interoception and pain-related processes (Laird, et al., 2011; Seeley, et al., 2007; Smith, et al., 2009). For example, subjective reports of painfulness were shown to be associated with increased fMRI baseline prestimulus activity in the left anterior insula (Ploner, et al., 2010). Additionally, rsfMRI studies have shown that the insula and anterior cingulate connectivity was higher during anticipation of a threatening stimulus, which was subsequent classified as painful

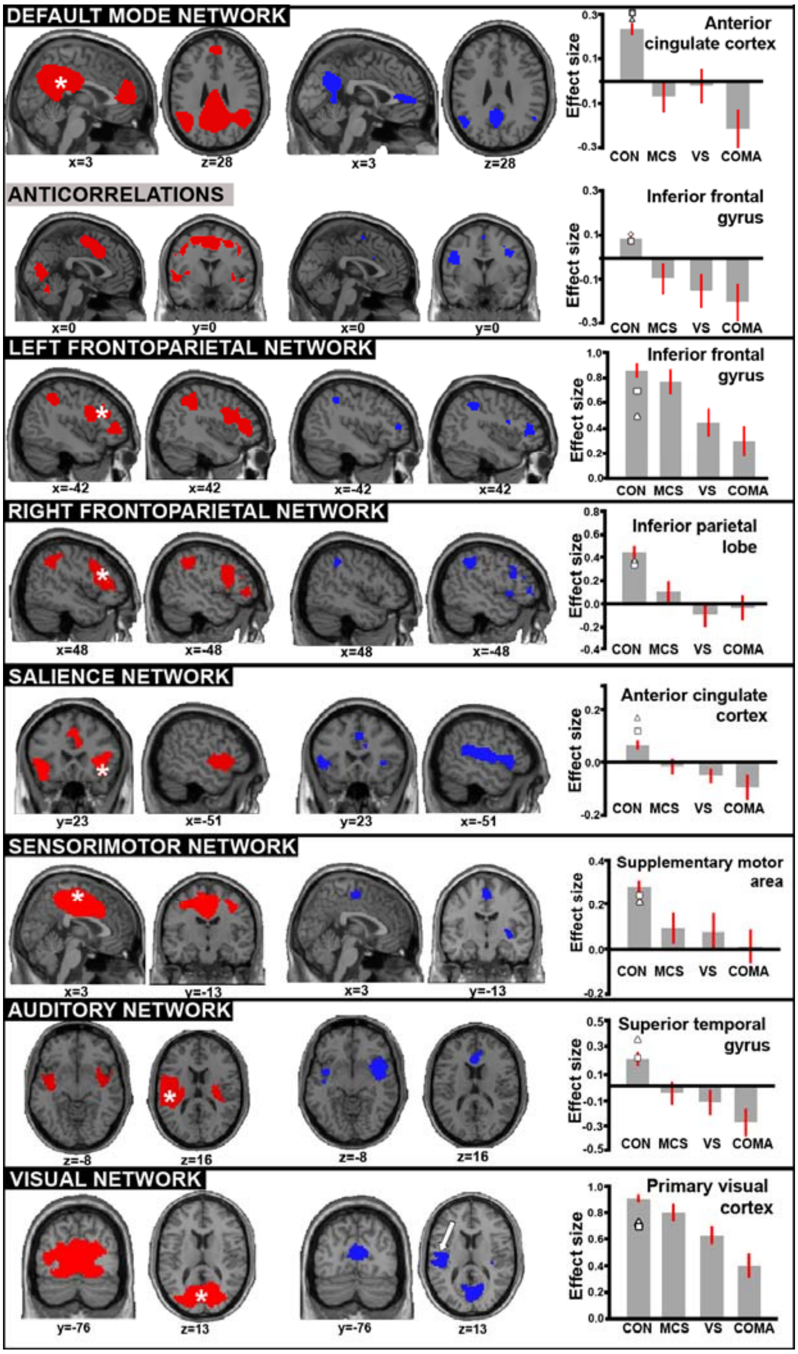

Figure 3.9 *Large-scale resting state functional connectivity is identified in "higher-order" networks and sensory-sensorimotor networks in healthy controls (red areas). Between-group contrasts showed a connectivity breakdown as a function of the level of consciousness (blue areas). Note the decreased crossmodal interaction between visual and auditory cortices (indicated with an arrow) that parallels the decreases in consciousness level. The asterisks indicate the position of seed region. Graphs represent contrast estimates with 90% confidence interval for a representative area of each resting state network in the group of healthy controls (CON), minimally conscious state (MCS), vegetative/unresponsive state (VS) and comatose patients. The effect size for two locked-in syndrome patients is represented by a square and a triangle. From Demertzi et al. (submitted-b)*

(Wiech, et al., 2010). Altogether, our findings might account for a decreased capacity of patients to respond to salient stimuli, including auditory (Boly et al., 2004; Laureys et al., 2000; Schiff, et al., 2005) and noxious. We here propose that salience network rsfMRI can be used as a possible tool to assess residual attentional resources to salient stimuli, including possible pain processing in patients with disorders of consciousness (in the absence of any noxious stimulation) as evidenced by the identified correlation between salience network connectivity and NCS scores.

In summary, in the absence of external stimulation, our aim was to quantify the necessary conditions allowing for conscious cognition; the sufficiency of the identified intra- and inter- network functional connectivity patterns to consciousness remains to be further determined (Churchland, 2007). Next, the observed connectivity impairment in resting state conditions does not permit to make strong claims about the brain's capacity to recruit neural networks in response to (salient) external

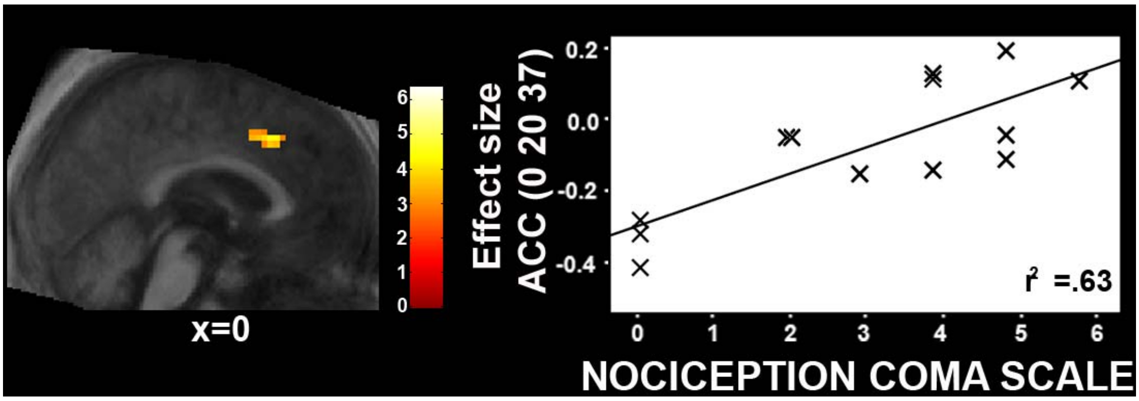

Figure 3.10 *Salience network connectivity reflects nociception processing in patients with disorders of consciousness. The figure illustrates increased functional connectivity between the right anterior insula and anterior cingulate cortex (ACC) (small volume corrected p<.05) as a function of increased total score on the Nociception Coma Scale. The scatterplot summarizes regression results of the Nociception Coma Scale total scores on the ACC connectivity for 13 patients with disorders of consciousness. The statistical map is rendered on a mean structural T1 magnetic resonance of the patients (x indicates the Montreal National Institute coordinate of represented sections). From Demertzi et al.* (submitted-b).

stimulation (Galán, 2008). It is well known from clinical practice that patients with disorders of consciousness show more behavioral responsiveness to emotionally meaningful and salient stimuli in both the auditory domain, (e.g., presentation of the patient's own name; Di, et al., 2007; Qin et al., 2010) and visual domain (e.g., tracking of the own face in a mirror; Vanhaudenhuyse, et al., 2008). Yet, the determination of the qualitative counterpart (the "what it is like" to be in a certain state; Laureys & Boly, 2007) of the observed neural activity merits further investigation. It is important to stress that the discussed results pertain to between-group comparisons and do not permit reliable single-subject interpretation "Brain reading" decoding multivariate applications (e.g., Nishimoto *et al.*, 2011) permit to focus on "mental content" storage and hence are expected to shed light on the subject-specific mental states under various states of consciousness (Haynes, 2011).

In contrast to our findings, brain function under pharmacological coma differs from what we observed in pathological states of consciousness. Under propofol anesthesia, functional connectivity was decreased in "higher-order" networks (default mode network and bilateral frontoparietal) next to relatively preserved functional connectivity in the sensory systems (visual and auditory) (Boveroux, et al., 2010). These differences between anesthesia and pathological coma could be partially explained by the fully preserved structural connectivity shown in healthy subjects undergoing anesthesia. It is indeed well known that part of the measured functional connectivity in resting state EPI paradigms reflects structural (white matter) connectivity as, for example, shown by diffusion tensor imaging studies (Honey *et al.*, 2009). In terms of the underlying mechanisms, it has been proposed that hypnotic agents preferentially act on brainstem, cortex, thalamus and basal ganglia and account for the distinct behavioral responses that subjects show under anesthesia (Brown *et al.*, 2010; Mhuircheartaigh *et al.*, 2010). Nevertheless, the potentially differential mechanisms mediating the loss of consciousness due to pathological causes remain to be better determined (Brown, et al., 2010).

Methods

We prospectively assessed patients with severe brain damage in a university hospital setting, studied at least 5 days after the acute brain insult. Clinical examination was repeatedly performed using the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004). Exclusion criteria were the presence of functional communication, uncertain clinical diagnoses, fMRI scanning under sedation, presence of ferromagnetic material, large focal brain damage (>50% of total brain volume) and the presence of head movements (i.e. >10 mm displacement). Healthy volunteers were free of major psychiatric and neurological history. The study was approved by the Ethics Committee of the Medical School of the University of Liège. Informed consent to participate in the study was obtained from the healthy subjects themselves and from the legal surrogates of the patients.

fMRI data were preprocessed and analyzed with SPM8. The identification of resting state networks was done in three steps as reported in the previous Methods box (Section 3.3). For each network, second-level analysis consisted of one-factor ANOVA with four levels (i.e. controls, MCS, VS/UWS and coma patients). A correction for non-sphericity was applied to account for potentially unequal variance across groups. In controls, one-sided T contrast searched for areas correlating with each selected seed region in each RSN. Assuming that patients with disorders of consciousness show similar brain activity compared to controls, we used a non-linear one-tailed T contrast searching for decreases in functional connectivity as a function of the level of consciousness (controls, MCS, VS/UW, coma) in each RSN (as in Vanhaudenhuyse et al., 2009b). Data of the two LIS patients were not included in the design matrices but their contrast estimates per RSN were displayed for visual comparison. For salience network, a regression analysis was performed with the summed Nociception Coma Scale scores of 13 patients where NCS data could be obtained.

For controls, results were considered significant at $p<0.05$ corrected for multiple comparisons at family wise error (FWE) rate for the whole brain volume. For the between-group contrasts, results were considered significant at FWE $p<.05$ calculated at the whole brain level or after small volume correction (10mm-radius sphere) around *a priori* expected coordinates taken from an independently assessed group of healthy individuals. For the salience network-NCS regression analysis, results were inclusively masked (FWE $p<0.05$) with the salience network connectivity identified in controls and considered significant at uncorrected $p<0.001$.

Conclusions

To date, fMRI resting state studies show that connectivity in cerebral networks is altered under altered states of consciousness, such as sleep, sedation/anesthesia, hypnotic state, and clinical states of disorders of consciousness (MCS, VS/UWS, coma and brain death). Such connectivity alterations can be discussed in two non-mutually exclusive ways. On the one hand, one can refer to functional connectivity reductions as reflecting reduced capacities for (conscious) cognitive processing (e.g., Vanhaudenhuyse, et al., 2009b). On the other hand, we can equally talk about persistent (albeit reduced) connectivity pattern in unconscious states, which transcends the level of consciousness, and which is considered as a physiologic baseline (e.g., Raichle et al., 2001). In any case, it seems that the purposes and questions of each study will eventually determine how such alterations can be further discussed and interpreted. Both the scientific and clinical implications for cognition seem to be the essence of resting state connectivity measurements.

At the scientific level, resting state analyses shed light on the necessary conditions needed for conscious awareness to take place. In other words, in the absence of external stimulation, resting state functional connectivity paradigms quantify the minimal prerequisites under which cognitive processes can become “conscious”. It should be noted here that the spectrum of consciousness is wide and includes various alterations in awareness. For example, much research has been conducted in neuropsychiatric disorders (e.g., dementias and schizophrenia; for a review see Buckner et al., 2008), and drug-related states such as alcohol (Esposito et al., 2010) or amphetamine (Roberts & Garavan, 2010). Here, we focused on changes in functional connectivity as a function of various states of wakefulness, such as normal waking state, hypnotic state and coma-related conditions. Such investigations lay within the ultimate clinical goal to better document, manage and predict residual brain functioning of patients with disorders of consciousness. As these patients are incapable of functional communication, they might be wrongly diagnosed as unconscious when locked-in (Laureys, et al., 2005) or suffering from aphasia (Majerus et al., 2009). The ethical implications of erroneous diagnostics are apparent, especially when pain (Demertzi et al., 2012; Demertzi, et al., 2009c) and end-of-life issues (Demertzi, et al., 2011a) are discussed. Despite the intrinsic limitations of resting state analyses in these patients, the resting state paradigm to study this population is promising (Soddu, et al., 2011). The challenge now is twofold: first, to unravel the relationship (i.e. correlations, anticorrelations) between and among different resting state networks under various conscious conditions. And second, to move from static functional connectivity measurements to the assessment of the temporal dynamics of associations. At the clinical level, such advancements are expected to improve the clinical translation of this approach as a routine para-clinical marker. We think that such evolution will eventually bring relevant ancillary information on patients' residual brain function adding to their medical management, including end-of-life decisions.

4

Perspectives

Our increasing understanding of brain function under resting conditions in health and disease suggests that such intrinsic activity is essential to the support of conscious awareness. Importantly, clinical reality requires reliable individual assessments with diagnostic and prognostic value. Hence, the challenge now is to move from group-level to single-subject analyses and indentify the appropriate thresholds of various biomarkers capable of distinguishing between the different clinical states of consciousness.

Especially for the issue of pain, our surveys show that socio-cultural factors (profession, religion, region of residence) influence clinicians' attitudes towards pain perception (Demertzi, et al., 2009c) and end-of-life attitudes in terms of pain perception (Demertzi, et al., 2012) for patients with disorders of consciousness. To date, no data exist on how healthcare providers and family members think about pain diagnosis and treatment in these patients. Knowing their views is of crucial importance because they inform on the ethical-societal dimensions of pain management in these patients, especially when end-of-life options are discussed. For example, the death of Terri Schiavo (a patient diagnosed as in VS for fifteen years) was the result of artificial nutrition and hydration withdrawal without the administration of opiods or other analgesic drugs (Fins, 2006), leading to long-lasting judicial battles (Quill, 2005) and wide media coverage (Racine, et al., 2008).

So far, behavioral and neuroimaging studies have focused on the investigation of pain from a psychological, biological, and socio-ethical perspective in isolation. Here, it is suggested that the subjective counterpart of pain in non-communicating patients can be better understood by adopting an interdisciplinary approach, such as that offered by the *biopsychosocial model* (Engel, 1977). The biopsychosocial paradigm recognizes the multi-dimensionality of pain by differentiating between nociception, pain, suffering, and pain behaviors (Gatchel, et al., 2007): nociception involves the stimulation of nerves which convey information about potential tissue damage to the brain; pain is the subjective conscious perception resulting from the transduction, transmission, and modulation of sensory information; suffering is the emotional response triggered by nociception or other aversive events associated with it (e.g., fear or depression); pain behaviors encompass those things that people say or do when they are in pain or when they suffer (e.g. avoidance of activities for fear of re-injury).

Here, a biopsychosocial investigation of pain could be approached by obtaining from the same patient population simultaneously neuroimaging, clinical and social data.

We believe that by bridging empirical interdisciplinary evidence we will eventually determine a pain-specific model for non-communicating coma emergent patients. Eventually for clinical practice, the adoption of a biopsychosocial approach to illness will generally provide a helpful antidote to the separation of the care of “diseases of the mind” from those “of the body”.

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APPENDIX I: Scientific publications

Review

EXPERT REVIEWS

Is there anybody in there? Detecting awareness in disorders of consciousness

Expert Rev. Neurother. 8(11), 1719–1730 (2008)

Athena Demertzi, Audrey Vanhaudenhuyse, Marie-Aurélie Bruno, Caroline Schnakers, Mélanie Boly, Pierre Boveroux, Pierre Maquet, Gustave Moonen and Steven Laureys†

†Author for correspondence
Coma Science Group, Neurology Department and Cyclotron Research Centren, Sart Tilman-B30, 4000 Liège, Belgium
Tel.: +32 4366 2316
Fax: +32 4366 2946
steven.laureys@ulg.ac.be

The bedside detection of awareness in disorders of consciousness (DOC) caused by acquired brain injury is not an easy task. For this reason, differential diagnosis using neuroimaging and electrophysiological tools in search for objective markers of consciousness is being employed. However, such tools cannot be considered as diagnostic *per se*, but as assistants to the clinical evaluation, which, at present, remains the gold standard. Regarding therapeutic management in DOC, no evidence-based recommendations can be made in favor of a specific treatment. The present review summarizes clinical and paraclinical studies that have been conducted with neuroimaging and electrophysiological techniques in search of residual awareness in DOC. We discuss the medical, scientific and ethical implications that derive from these studies and we argue that, in the future, the role of neuroimaging and electrophysiology will be important not only for the diagnosis and prognosis of DOC but also in establishing communication with these challenging patients.

KEYWORDS: assessment • brain–computer interface • brain death • coma • communication • deep brain stimulation • default mode network • disorder of consciousness • electrophysiology • functional neuroimaging • minimally conscious state • neurorehabilitation • vegetative state

Defining consciousness & picturing its clinical states

Consciousness is here defined as a first-person experience that consists of two major components: arousal and awareness (FIGURE 1) [1]. Arousal refers to the level of alertness and is supported by the function of the subcortical arousal systems in the brainstem, midbrain and thalamus [2]. Clinically, it is indicated by opening of the eyes. Awareness refers to the content of consciousness, and it is thought to be supported by the functional integrity of the cerebral cortex and its subcortical connections. Awareness can be further reduced to awareness of environment and of self [3]. Clinically, awareness of environment is assessed by evaluating command following and observing nonreflex motor behavior, such as eye tracking and localized responses to pain. Awareness of self, clinically a more ill-defined concept, can be assessed by the patients' response to autoreferential stimuli, such as the patients' own face in the mirror. An illustrative example of the relationship between the two components of consciousness is the transition from full wakefulness to deep sleep: the less aroused we get, the less aware we become of our surroundings.

This review focuses on clinical methods and research techniques that are currently employed for assessing residual consciousness in coma survivors. The disorders of consciousness (DOC) are described below.

Brain death

The concept of brain death, as death based on neurological criteria, has been widely accepted worldwide [4]. Irreversible coma and absence of brain stem reflexes are the major clinical criteria that are followed by most US hospitals, but these criteria are apparently not practised in the same way by all institutions [5]. This implies that brain death may be determined in various ways, a fact that may have consequences in after death practices, such as organ transplantation [6]. In 1995, the American Academy of Neurology published the diagnostic guidelines for brain death [7], which are:

- Demonstration of coma;
- Evidence for the cause of coma;
- Absence of confounding factors, including hypothermia, drugs, electrolyte and endocrine disturbances;

10.1586/14737175.8.11.1719 ISSN 1473-7175

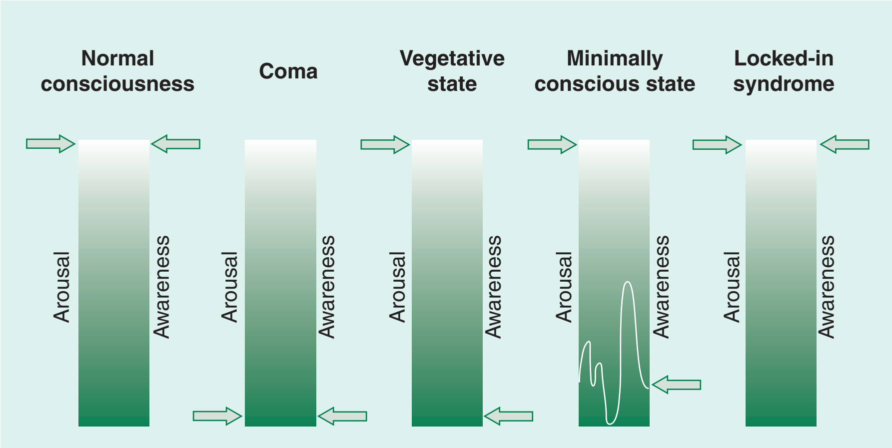

Figure 1. Spectrum of disorders of consciousness as defined by the relationship between arousal and awareness. Comatose patients cannot be aroused and, hence, are not aware of the environment or of themselves [3]. In the vegetative state, there is a dissociation between arousal, which recovers, and awareness, which remains absent [12]. The minimally conscious state characterizes patients who demonstrate inconsistent but reproducible behavioral evidence of awareness of self or environment, but are unable to communicate their thoughts and feelings [15]. The locked-in syndrome describes patients who are awake and conscious, but can only communicate by using small eye movements [18]. The locked-in syndrome is not a disorder of consciousness but it is included here as it can be misdiagnosed as one.
Adapted from [58].

- Absence of brainstem reflexes;
- Absent motor responses;
- Positive apnea testing;
- A repeat evaluation in 6 h is advised, but the time period is considered arbitrary;
- Confirmatory laboratory tests are only required when specific components of the clinical testing cannot be reliably evaluated.

Classically, brain death is caused by a massive brain lesion, such as trauma, intracranial hemorrhage or anoxia. No recovery from brain death has ever been reported over the last 50 years in a patient fulfilling the above mentioned clinical criteria [8].

Coma

After severe brain damage, patients may spend a couple of days or weeks in coma. Coma is a time-limited condition leading either to death, to recovery of consciousness or to transition to vegetative state (VS) [9]. It can result from bihemispheric diffuse cortical or white matter damage or brainstem lesions bilaterally, affecting the subcortical reticular arousing systems. Many factors, such as etiology, the patient's general medical condition, age, clinical signs and complimentary examinations influence the management and prognosis of coma. In terms of clinical signs, after 3 days of observation, bad outcome is heralded by the absence of pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, bilateral absent cortical responses of somatosensory evoked potentials (SEPs) and, for anoxic coma, biochemical markers (i.e., high levels of serum neuron-specific enolase) [10].

Vegetative state

The VS is a 'state of arousal without awareness' (Figure 1). These patients regain sleep–wake cycles. However, their motor, auditory and visual functions are restricted to mere reflexes and they show no adapted emotional responses [11]. According to the 1994 Multi-Society Task Force, the criteria for the diagnosis of VS are the following [12]:

- No evidence of awareness of self or environment and an inability to interact with others;
- No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile or noxious stimuli;
- No evidence of language comprehension or expression;
- Intermittent wakefulness manifested by the presence of sleep–wake cycles;
- Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care;
- Bowel and bladder incontinence;
- Variably preserved cranial nerve and spinal reflexes.

The VS is usually caused by diffuse lesions on gray and white matter. It can be a transition to further recovery, or it may be permanent. 'Permanent' VS refers to patients whose chances for recovery are close to zero. This is the case for VS that lasts more than 1 year after traumatic injury or 3 months after nontraumatic injury. The VS is characterized as 'persistent' when the patient is in this state for more than 1 month [12]. As both terms are abbreviated as 'PVS' (persistent vegetative state), it has been suggested to avoid this abbreviation and, instead, mention the etiology and the time spent in VS [201]. At present, there are no validated paraclinical prognostic markers for individual patients except that the chances of recovery depend on the patient's age, etiology and length of time spent in the VS [13].

Minimally conscious state

The minimally conscious state (MCS) was defined as a DOC in 2002 by the Aspen Workgroup. Patients in MCS manifest at least one of the following:

- Purposeful behavior, including movements or affective behavior contingent to relevant environment stimuli which are not due to reflexive activity, such as: visual pursuit or sustained fixation occurring in direct response to moving or salient stimuli, smiling or crying in response to verbal or visual emotional but not neutral stimuli, reaching for objects demonstrating a relationship between object location and direction of reach, touching or holding objects in a manner that accommodates the size and shape of the object, and vocalizations or gestures occurring in direct response to the linguistic content of questions;

- Following simple commands:
  - Gestural or verbal yes/no response, regardless of accuracy;
  - Intelligible verbalization [14].

Like the VS, MCS may be chronic and sometimes permanent. Emergence from MCS is defined by the ability to exhibit functional interactive communication or functional use of objects. It should be kept in mind that the boundary between MCS and higher states of consciousness is arbitrary and merely set for convention (i.e., allowing clear communication and enrollment in research studies) as opposed to the boundary between VS and MCS which is, at least in principle, absolute (i.e., any evidence of awareness suffices to define MCS). Similarly to the VS, traumatic etiology has a better prognosis than nontraumatic anoxic brain injuries [15]. Additional data from the Belgian Federal Project on PVS suggest that overall outcome in MCS is better than for VS [16].

Locked-in syndrome

In the locked-in syndrome (LIS) there is no dissociation between arousal and awareness. According to the 1995 American Congress of Rehabilitation Medicine criteria, LIS patients demonstrate [17]:

- Sustained eye opening (bilateral ptosis should be ruled out as a complicating factor);
- Quadriplegia or quadriparesis;
- Aphonia or hypophonia;
- A primary mode of communication via vertical or lateral eye movements, or blinking of the upper eyelid to signal yes/no responses;
- Preserved cognitive abilities.

Based on motor capacities, LIS can be divided into three categories:

- Classic LIS, which is characterized by quadriplegia and anarthria with eye-coded communication;
- Incomplete LIS, which is characterized by remnants of voluntary responsiveness other than eye movements;
- Total LIS, which is characterized by complete immobility including all eye movements, combined with preserved consciousness [18].

The LIS can result from a bilateral ventral pontine lesion [3] but mesencephalic lesions have also been reported [19]. Once a LIS patient becomes medically stable and is given appropriate medical care, life expectancy is estimated up to several decades [19]. Even if the chances of good motor recovery are very limited, existing eye-controlled computer-based communication technology currently allows these patients to control their environment [20]. Neuropsychological testing batteries adapted and validated for eye-response communication have shown preserved intellectual capacities, at least in LIS patients whose lesions are restricted to brainstem pathology [21]. Recent surveys seem to show that chronic LIS patients self-report meaningful quality of life and the demand for euthanasia, albeit existing, is infrequent [19,22].

Clinical assessment

The objective assessment of consciousness is difficult due to its first-person nature. For that reason, clinicians need to infer awareness via the evaluation of motor activity and command following. This is extremely challenging for DOC and LIS, as these patients are usually deprived of the capacity to make normal physical movements and they often show limited attentional capacities. Aphasia, apraxia and cortical deafness or blindness are other possible confounders in the assessment of DOC. We will next discuss the clinical consciousness scales that are mostly used in clinical settings [23].

Consciousness scales

The most common and most widely used tool, mainly thanks to its short and simple administration, is the Glasgow Coma Scale (GCS) [24]. The GCS measures eye, verbal and motor responsiveness. However, there may be some concern as to what extent eye opening is sufficient evidence for assessing brainstem function [25]. Additionally, the verbal responses are impossible to measure in cases of intubation and tracheostomy. The scale requires the clinician to arrive at a certain judgment (e.g., 'the patient follows commands') without any formal guidance on how to arrive at that judgment (i.e., what and how many commands to use and how to assess confounds such as motor or sensory or spontaneous movements). Finally, the GCS is not sensitive to detect transition from VS to MCS [26].

A recently proposed alternative to the GCS is the Full Outline of Unresponsiveness (FOUR) [27]. The scale is named after the number of subscales it contains (eye, motor, brainstem and respiratory functioning) as well as after the maximum score that each subscale can take (four). The advantage of the FOUR is that it does not need a verbal response and, hence, can be employed in intubated patients. The FOUR can discriminate between VS and MCS patients as it assesses visual pursuit, one of the first signs that announces emergence from VS, but it does not test all the behavioral criteria of MCS [14]. It is also more sensitive in detecting LIS patients because, in contrast to the GCS, it explicitly asks patients to move their eyes to command [27].

To differentiate VS from MCS patients, the most appropriate scale is the Coma Recovery Scale-Revised (CRS-R) [28]. The CRS-R has a similar structure to the GCS, testing, in addition to motor, eye and verbal responsiveness, audition, arousal and communication abilities. Despite its longer administration compared with the GCS and the FOUR (i.e., approximately 15 min), it is the most sensitive at differentiating VS from MCS patients [26]. This is because it assesses every behavior according to the diagnostic criteria of VS and MCS, such as the presence of visual pursuit and visual fixation [14]. Importantly, the way we assess these behavioral signs needs to be standardized and uniform, permitting between-center comparisons. For example, for the assessment of visual pursuit, the CRS-R [28] and the Western Neuro-Sensory Stimulation Profile (WNSSP) [29] employ a moving mirror; the Coma/Near Coma Scale [30], the Wessex Head Injury Matrix (WHIM) [31] and the Sensory Modalities Assessment and Rehabilitation Technique (SMART) [32] use a moving person; and the WNSSP, the SMART, the WHIM and the FOUR [27] use a moving object or finger. We recently demonstrated that the use of a mirror is the most sensitive in detecting eye tracking. These findings stress that self-referential stimuli have attention grabbing properties and are preferred in the assessment of DOC [33].

The clinical assessment via behavioral scales can be biased by several limitations: first, by intrinsic limitations in the measures' precision and validity, which can be overcome by selecting the 'best' measure each time; and second, by intrinsic behavioral fluctuations of the patients which can be corrected by repeated sessions of evaluation. Despite their pros and cons, each scale contributes differently in establishing the diagnosis and prognosis of DOC. The administration and interpretation of the results should be decided and discussed in terms of the person who uses the scale, the place where it is administered (e.g., intensive care vs chronic rehabilitation settings) and the reasons for their administration (e.g., clinical routine vs research purposes) [34].

Misdiagnosis

Incorrect diagnosis of DOC is not a rare phenomenon and it has been estimated that approximately 40% of VS patients are misdiagnosed [35,36]. It was recently found that of 29 patients that were initially diagnosed as VS using the GCS, four of them were in a MCS according to the FOUR scale and seven more patients were identified as MCS using the CRS-R scale [26]. These results imply that even though the diagnostic criteria for VS and MCS have been clearly established, the rate of misdiagnosis has not changed since the 1990s [35,36]. This may be attributed partially to the fact that, although the criteria may have been defined, they still remain not operationalized in the sense that there is not an exact procedure as to how to identify evidence of conscious behavior [37,38].

In LIS, diagnostic error is also frequent. Unless the physicians are familiar with the syndrome, it may be up to a couple of years before LIS it is diagnosed and, in many cases, it is a family member who realizes that the patient is conscious [39].

The high diagnostic error rate can be explained by the fact that physical function in these patients, which is the main way to exhibit their awareness, is limited. Additionally, it is difficult to differentiate between voluntary and reflexive behavior, as there is inconsistency in responses and lack of sensitivity of the personnel to accurately observe signs of consciousness [23]. An objective way that has been proposed to overcome such obstacles is to follow single-case experimental designs, adapting the assessment procedure on the patient's particular case, in the form of an individualized quantitative behavioral assessment [40]. This method identifies a particular behavior that is tested for consistency in response to command and it further checks whether this behavior changes over time, either in response to treatment or spontaneously. It has been proposed that the rate for the incorrect diagnostic evaluation of the VS will be minimized by combining behavioral, electrophysiological and functional neuroimaging procedures [41,42].

Paraclinical assessment

Electrophysiological and functional neuroimaging methods permit the identification of objective markers of consciousness and quantify residual brain function in DOC. The EEG is informative of the general vigilance level of patients and can detect functional abnormalities, such as seizures. However, evoked responses to environmental stimuli, such as evoked potentials (EPs), may be more informative about the cognitive state of a patient. EPs derive statistically from the EEG and they are comprised of different components which can be classified into two main categories: short latency or exogenous, and cognitive or endogenous [43]. Exogenous components are elicited within a time range between 0 and 100 ms after the presentation of a stimulus; they correspond to the activation of the ascending pathways to the primary cortex and are thought to reflect the physical properties of the stimulus. Examples of exogenous components are the SEPs, the brainstem auditory EPs (BAEPs) and middle-latency auditory EPs (MLAEPs). Endogenous components are obtained after 100 ms of the presentation of a stimulus, reflecting the activity of both cortical and subcortical structures including associative areas, and are thought to depend on the psychological significance of the stimulus. Examples of endogenous components are the mismatch negativity (MMN; a response to an oddball situation in an inattentive subject) and the P300 (a response to an unpredictable target stimulus) [44]. Evoked electrophysiological responses, as is mentioned later, are signatures of neural activity that may differentiate conscious from unconscious processing and are easy to employ at the patient's bedside.

Functional neuroimaging permits objective measurement of the brain's activity at rest and during various states of external stimulation [45]. The main principle behind this methodology is that performance on a sensorimotor or a cognitive task increases the brain's need for extra energy. One form of energy is glucose, the metabolic levels of which are measured by the fluoro-deoxy-D-glucose PET (FDG-PET) technique. Another form of energy is oxygen, the excessive levels of which in certain brain areas are measured by the functional MRI (fMRI) technique.

Diagnostic value

The EEG is the most employed test to confirm the diagnosis of brain death. This is done by showing absence of electrocortical activity (i.e., isoelectric EEG), which diagnoses brain death with a sensitivity and specificity of approximately 90% [46]. In the VS, the EEG most often shows continuous diffuse slowed electrical activity in the theta (4–7.5 Hz) and/or delta (1–3.5 Hz) frequency ranges. In the MCS, bilateral, but predominantly ipsilesional polymorphic theta activity may be the most prominent abnormality [47]. In LIS, the EEG pattern differs across patients and, thus, cannot be used as a reliable measure for detecting consciousness and to discriminate LIS from DOC [48]. However, when a close-to-normal EEG pattern is observed, the possibility of LIS should be taken into consideration [19]. The patients' underlying background EEG was also shown to influence the evoked electrophysiological responses to stimuli of different complexity [49].

Certain types of P300, such as the P3a and P3b, are a function of attention and memory, respectively [50]. It was shown that VS and MCS patients elicit a P300 response more frequently when ecological stimuli were used as compared with meaningless tones [51]. The patient's own name, a salient attention-grabbing stimulus, was found to elicit a P300 response in VS and MCS [52]. However, as P300 can also be elicited during subliminal perception [53] and during sleep [54], it can be considered as a purely conditioned response to one's own name, and therefore may not imply consciousness [55]. Recently, the P300 as a response to a patient's own name and to other target names was employed to document command following in DOC. Schnakers and colleagues studied 22 severely brain damaged patients employing an 'active' auditory paradigm [56]. Subjects were instructed to count the number of times they heard either their own name or an unfamiliar target name. In controls, this increase of attention to a target leads to an increase of the P300 response. Similar results were obtained in low-level MCS patients (i.e., those only showing visual fixation tracking but no behavioral command following). None of the studied VS patients demonstrated such responses.

In terms of neuroimaging methodology, PET scans in brain death show absence of neuronal metabolism in the whole brain, that is, an 'empty-skull sign' [8]. Cortical metabolism in coma and in VS is reduced by up to 40–50% of normal values. Recovery from the VS, however, is not always associated with a return to near normal global cerebral metabolic levels; rather, metabolic changes are observed regionally [57]. PET studies on pain perception in the VS have demonstrated restricted brain activation to primary somatosensory cortices, isolated and disconnected from the rest of the brain [58]. However, in absence of a full understanding of the neural correlates of conscious perception, it remains difficult to interpret functional imaging data in brain damaged patients as proof or disproof of their conscious experience [59]. LIS patients demonstrate higher global brain metabolic levels compared with the VS [60]. The absence of metabolic signs of reduced function in any area of the gray matter highlights the fact that these patients suffer from a pure motor de-efferentation and recover an entirely intact intellectual capacity [19].

Functional MRI data collected by Owen and colleagues from Cambridge University in collaboration with our group suggested that a patient, behaviorally diagnosed as vegetative, showed indistinguishable brain activity from that observed in healthy people when asked to imagine playing tennis and mentally visit rooms of her house [61]. This implies that this patient, despite the clinical diagnosis of VS, understood the tasks and, hence, must have been conscious. Of note is the fact that, a few months later, the patient evolved into a MCS. The most likely explanation of these results is that the patient was no longer in a VS at the time of the experiment.

Prognostic value

Some clinical studies have suggested that ventricular dilatation, the motor score on the GCS, spontaneous eye movements [62] and blinking to threat herald favorable outcome in the VS [63]. Recent evidence, however, have suggested that presence of blinking to threat does not reliably predict recovery in the VS as its positive predictive value (i.e., patients showing preserved blinking to treat response who subsequently recovered) was estimated at 30% [64].

Electrophysiological data in coma support the suggestion that a burst suppression EEG heralds bad outcome [3]. The presence or absence of exogenous and endogenous EPs plays an important role in the prognosis of DOC. Although the absence of cortical SEPs herald poor outcome, their presence does not necessarily imply recovery [65]. Given the low positive predictive values of exogenous EPs, it has been suggested that clinical routine tests should also include the assessment of higher order cortical activity via endogenous EPs. The presence of MMN, for example, has been found to be of high positive prognostic value notably in anoxic coma [66]. In summary, it can be concluded that absent exogenous EPs are well established prognosticators of poor outcome, whereas the presence of endogenous components, notably the MMN and P300, appear to predict favorable outcome [67].

In the postacute phase, structural MRI findings have demonstrated that lesions of the corpus callosum, corona radiata and dorsolateral brainstem are predictors of bad outcome in VS patients [68]. A recent review of fMRI activation studies has shown that activation of higher-level brain regions also seem to predict recovery [69]. Compared with seven VS patients who exhibited a more frequently encountered low-level primary cortical activation when the patient's own name paradigm was employed, Di and colleagues identified two VS patients who demonstrated a more widespread activation, beyond the primary auditory cortices. Only these two VS patients showing close-to-normal brain activation functionally improved to MCS at 3 months follow-up. In that sense, the fMRI precedes the results of the clinical recovery.

Treatment

To date, there are no 'standards of care' for therapeutic management in DOC. Studies were conducted under suboptimal or uncontrolled settings and, for that reason, no evidence-based recommendations can be made. However, pilot data demonstrate that DOC patients and, more particularly, MCS patients, can benefit from some rehabilitative interventions [70]. These interventions can be separated between pharmacologic and nonpharmacologic.

Pharmacologic treatment

Generally speaking, the response of DOC patients to pharmacologic treatment remains unsatisfactory [71]. However, pharmacologic studies have shown that amantadine, mainly a dopaminergic agent, was linked to better outcome in traumatic DOC [72,73]. In addition to behavioral amelioration, a recent PET study with a chronic anoxic MCS patient showed a drug-related increase in frontoparietal metabolism after the administration of amantadine (Figure 2) [74]. Nevertheless, cohort placebo-controlled randomized trials or blinded within-subject crossover designs are needed before making any assertive conclusions for the effectiveness of the drug.

Other pharmacologic agents that have been reported to lead to favorable functional outcome are levodopa and bromocriptine (also dopaminergic agents) [75], baclofen [76] (GABA agonist administered mainly against spasticity) and zolpidem (nonbenzodiazepine sedative drug that is used against insomnia in healthy people). Table 1 summarizes recent pharmacologic studies in DOC (after the year 2000), estimating their quality of evidence based on the criteria proposed by the Oxford Centre of Evidence-Based Medicine [202]. As can be shown from Table 1, no level-1a studies have been conducted yet.

Nonpharmacologic treatment

Despite some sparse evidence that deep brain stimulation (DBS) may have some ameliorating effects on arousal in VS [77], generally speaking, its effectiveness to this population is limited. This can be attributed to the uncontrolled settings of these studies in combination with the underlying neuropathology of VS patients. More particularly, VS patients exhibit widespread thalamic and cortical neuronal damage [78], whose stimulation is difficult to lead to functional reintegration [79]. Schiff and colleagues recently proposed a protocol for the application of DBS, which mainly focuses on patients' selection based on the neuropathological and behavioral profile. According to this protocol, patients eligible for DBS application will be those who manifest preserved states of arousal, fluctuating behavioral performance and for whom there is specific information about the connections between the central thalamus (coming from functional neuroimaging evidence), cerebral cortex, basal ganglia and other subcortical structures [79]. The first application of their protocol took place in a recent study of a 38-year-old, severe traumatic brain-injured patient, who was in a MCS for 6 years [80]. The patient's condition did not ameliorate despite a 2-year rehabilitation program and 4 years in a nursing home. However, after applying DBS in the central thalamus, the patient exhibited improved levels of arousal, motor control and interactive behavior. It should be noted that the fMRI of this patient demonstrated a preserved large-scale bihemispheric language network, which implied that there was at least a preserved substrate for a neural recovery to take place [81].

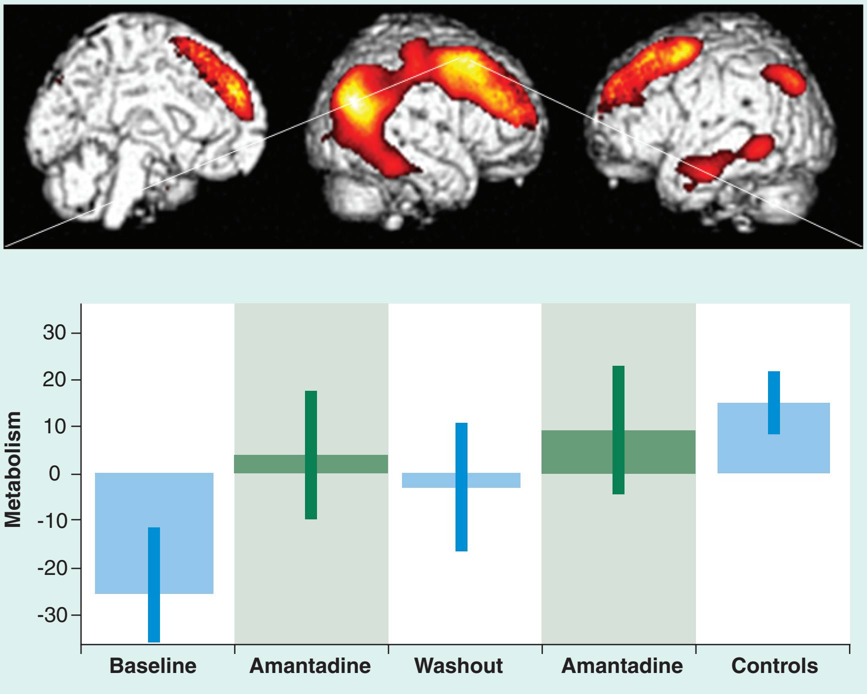

Figure 2. Amantadine-related changes in cerebral metabolism in an anoxic minimally conscious patient. The metabolic activity of bilateral fronto–temporo–parietal associative and right sensory–motor cortices is decreased at baseline, increases after 5 weeks of amantadine treatment, decreases during washout and returns to near-normal levels after re-administration.
Adapted from [75].

Other nonpharmacologic interventions for DOC are sensory stimulation techniques, physical and occupational therapy. These techniques are mainly conducted for two purposes: to prevent complications and/or to enhance recovery. It should be noted that, in terms of efficacy, preventing complications in a patient (e.g., contracture or pressure sore prevention) does not necessarily imply effects on recovery. Sensory stimulation refers to two types of approaches: the multisensory stimulation approach and the sensory regulation approach [82]. The former embraces the principles of behaviorism and states that enhanced environmental stimulation of the sensory systems is hoped to enhance synaptic reinnervations and eventually improve outcome. Sensory regulation is based on the principles of information processing and focuses on the enhancement of selective attention by regulating the environment. At present, the beneficial effects of all approaches described above remain debated and not evidence-based [83].

Physical therapy aims to improve motor and physical disturbances via techniques that include protocols of postural changes, management and prevention of joint contractures as well as hygienic management. There is evidence that early [84] and increased intervention [85] leads to better outcomes. VS patients, however, are often denied the opportunity of early intervention either because, due to their slow progress, physicians estimate that they have already achieved the final level of responsiveness or because they need to be on the waiting list for a specialized rehabilitation center [86].

Occupational therapy supports the view that being engaged in a creative and productive activity will enhance the physical and emotional rehabilitation of patients [87]. Occupations differ between patients based on their needs, roles and interests, and concern three different areas of function: self-maintenance (e.g., personal care), productivity (e.g., work) and leisure [88]. Nevertheless, occupational therapy interventions in DOC are not frequent and, when employed, the aim is to enhance motor function, sensory/cognitive skills and interpersonal/intrapersonal performance components [88]. The effectiveness of this treatment is also limited [89].

Expert commentary

The diagnosis of DOC is difficult due to its subjective character. Clinicians need to infer the presence of awareness in these patients based on motor responses to external stimulation. Distinguishing between voluntary and reflexive behavior will eventually disentangle VS from MCS patients. To date, however, there is no consensus as to what 'reflexive' and 'voluntary' means [90], similar to the debate about what consciousness means. Additionally, DOC patients can manifest muscular spasticity or paralysis. In that perspective, high diagnostic error in DOC is common. Therefore, the need for standardized, validated behavioral scales is emphasized.

From the previous discussion it is clear that there is a need for an alternative nonmotor-dependent means for the assessment of DOC. Such opportunity is offered by functional neuroimaging and electrophysiological tools. The fMRI study of mental imagery to command by Owen and colleagues [61] challenge the present status of clinical bedside diagnosis and encourage the application of sophisticated neuroimaging techniques in clinical practice. Similarly, subclinical electromyography (EMG) was shown to detect preserved awareness (i.e., command following) in one of ten VS and in both tested MCS patients [91]. In that perspective, the gray zone that lies between these two distinct clinical entities of consciousness is expected to be more clearly defined. However, the evidence of such studies should be interpreted carefully as it concerns case reports or small cohort groups, and it is characterized by physiological and behavioral variability. This means that the employed paraclinical methods to study DOC do not solve the problem of confounding impairments in sensory processing. Additionally, if the paraclinical examination of the patient measures a 'trait' (i.e., an enduring

Table 1. The efficacy of pharmacologic treatment in disorders of consciousness.

Drugs	Study (first author, year)	Number of patients and etiology	Diagnosis	Placebo control	Reported functional outcome	Level of evidence	Ref.
Dopaminergic agents							
Amantadine	Schnakers (2008)	1 anoxic	MCS	No	Positive	3b	[74]
	Patrick (2006)	10 TBI	Low responsive level	No	No effect	1b	[99]
	Hughes (2005)	123 TBI	Coma	NA	No effect	2b	[100]
	Saniova (2004)	41 TBI	'Persistent unconsciousness'	NA	Positive	2b	[101]
	Meythaler (2002)	35 TBI	MCS	Yes	Positive	1b	[102]
Bromocriptine	Brahmi (2004)	4 intoxication	Coma	No	Positive	4	[103]
Levodopa	Matsuda (2003)	3 TBI	VS	No	Positive	4	[104]
Nonbenzodiazepine sedative							
Zolpidem	Cohen (2008)	1 anoxic	Lethargic	No	Positive	4	[105]
	Shames (2008)	1 anoxic	MCS	No	Positive	4	[106]
	Singh (2008)	1 TBI	MCS	No	No effect	4	[107]
	Brefel-Courbon (2007)	1 hypoxic	Akinetic mutism	Yes	Positive	3b	[94]
	Clauss (2006)	2 TBI, 1 anoxic	VS	No	Positive	4	[108]
	Clauss (2000)	1 TBI	Semi-comatose	No	Positive	4	[109]
GABA agonist							
Baclofen	Sarà (2007)	1 non-TBI	VS	No	Positive	4	[110]

Medline search included studies conducted between January 2000 and June 2008.
MCS: Minimally conscious state; NA: Not applicable; TBI: Traumatic brain injury; VS: Vegetative state.
Level of evidence data from [202].

pattern characteristic of the patient), a single examination may prove useful, but if it targets at a patient's 'state' (i.e., a psychological or physiological pattern that may fluctuate), then multiple measures are needed.

Another critical point to the study of awareness in DOC is the subsequent ethical considerations. According to some authors, it is ethically controversial whether noncommunicative patients can be included in clinical trials since they are unable to provide informed consent and, thus, cannot protect themselves from potential dangers. However, excluding such patients from research studies under the argument of nonmaleficence, they are also excluded from the opportunity to potentially benefit from these studies. For that reason, an ethical framework that balances between clear protections for patients with DOC and access to research and medical progress is preferred [92,93]. Based on this framework, better end-of-life decisions can be made by allowing severely brain-injured patients, who have been misdiagnosed based on bedside evaluation but who have relatively preserved cognitive capacity, decide on the course of their own lives.

Five-year view

The clinical and subclinical detection of awareness in DOC, with the aid of functional neuroimaging and electrophysiological tools, is expected to flourish in the next 5 years. Clinical diagnosis will be facilitated by moving from isolated case reports toward large-scale multicenter cohort studies. The derivates of such studies are expected to become more widely applicable in clinical routine. In this way, prognosis and outcome prediction will be further validated. In terms of treatment, nowadays no evidence-based recommendations can be made in favor of this or the other therapeutic option. Preliminary evidence of the efficacy of some pharmacologic (e.g., amantadine [74] and zolpidem [94]) and nonpharmacologic interventions (e.g., DBS [80]) in DOC patients will be further supported by functional neuroimaging studies, which are expected to reveal the physiological modifications of these interventions. Advances in communication technology are also expected in the coming years [42]. To date, facilitation in communication is beginning to be achieved for LIS patients. Salivary pH changes, for example, have been reported as an alternative paradigm to communicate with a LIS patient who was providing 'yes' answers by imagining lemon and 'no' answers by imagining milk [95,96]. A recent impressive breakthrough, however, is the use of brain–computer interfaces (BCIs) [20], a technique which allows electrical brain signals to control external devices that do not require muscular activity. In the future, BCI devices are expected to be applicable also in DOC, by providing these patients with a 'voice' of their own [97,98]. It would be thrilling to view the use of these powerful technologies in the assessment and possible treatment of DOC.

Financial & conflicts of interest disclosure

This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission, the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC), the Fondation Médicale Reine Elisabeth and the University of Liège.

Athena Demertzi is funded by the DISCOS Marie-Curie Research Training Network, Audrey Vanhaudenhuyse and Pierre Boveroux are funded by ARC 06/11-340, Melanie Boly and Marie-Aurelie Bruno are research fellows at the FNRS, Pierre Maquet is research director and Steven Laureys senior research associate at the FNRS. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Information resources

- Coma Science Website
  www.comascience.org
- American Academy of Neurology (AAN) clinical practice guidelines
  www.aan.com/go/practice/guidelines

Key issues

- Incorrect diagnosis of disorders of consciousness (DOC) is still very common in clinical practice, despite the introduction of clear-cut diagnostic criteria.
- Standardized validated behavioral tools should be employed in the assessment of DOC.
- The Glasgow Coma Scale remains the gold standard in the behavioral assessment of comatose patients, but the Coma Recovery Scale–Revised is probably the most validated scale to disentangle vegetative from minimally conscious state patients.
- The bedside diagnosis of the vegetative state is difficult, and requires repeated examination by trained experts. The interest of paraclinical markers is currently being studied.
- The vegetative state is not brain death.
- The therapeutic management of DOC currently lacks large-scale randomized controlled trials permitting conclusive answers to propose or reject specific pharmacologic or nonpharmacologic interventions.
- Pharmacologic treatment with amantadine and zolpidem show behavioral amelioration in some DOC patients but still no conclusive recommendations for the efficacy of these drugs can be made.
- Functional neuroimaging is expected to show the putative therapeutic efficacy in smaller cohort studies and be quicker and cheaper.
- Functional neuroimaging and electrophysiological tools offer an objective way to measure the brain's activity in DOC. Despite their great promise, at present no evidence-based recommendations for their diagnostic and prognostic use in clinical routine can be proposed.

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Affiliations

- Athena Demertzi
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 62
  Fax: +32 436 629 46
- Audrey Vanhaudenhuyse
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 62
  Fax: +32 436 629 46
- Marie-Aurélie Bruno
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 62
  Fax: +32 436 629 46
- Caroline Schnakers
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 62
  Fax: +32 436 629 46
- Mélanie Boly
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 62
  Fax: +32 436 629 46
- Pierre Boveroux
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 62
  Fax: +32 436 629 46
- Pierre Maquet
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 27
  Fax: +32 436 629 46
- Gustave Moonen
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 685 55
- Steven Laureys
  Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium
  Tel.: +32 436 623 16
  Fax: +32 436 629 46
  steven.laureys@ulg.ac.be

Dualism Persists in the Science of Mind

Athena Demertzi,[a] Charlene Liew,[b] Didier Ledoux,[a]
Marie-Aurélie Bruno,[a] Michael Sharpe,[c] Steven Laureys,[a]
and Adam Zeman[d]

[a] *Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium*
[b] *Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK*
[c] *Department of Psychological Medicine, Royal Edinburgh Hospital, Edinburgh, UK*
[d] *Peninsula Medical School, Exeter, UK*

The relationship between mind and brain has philosophical, scientific, and practical implications. Two separate but related surveys from the University of Edinburgh (University students, $n = 250$) and the University of Liège (health-care workers, lay public, $n = 1858$) were performed to probe attitudes toward the mind–brain relationship and the variables that account for differences in views. Four statements were included, each relating to an aspect of the mind–brain relationship. The Edinburgh survey revealed a predominance of dualistic attitudes emphasizing the separateness of mind and brain. In the Liège survey, younger participants, women, and those with religious beliefs were more likely to agree that the mind and brain are separate, that some spiritual part of us survives death, that each of us has a soul that is separate from the body, and to deny the physicality of mind. Religious belief was found to be the best predictor for dualistic attitudes. Although the majority of health-care workers denied the distinction between consciousness and the soma, more than one-third of medical and paramedical professionals regarded mind and brain as separate entities. The findings of the study are in line with previous studies in developmental psychology and with surveys of scientists' attitudes toward the relationship between mind and brain. We suggest that the results are relevant to clinical practice, to the formulation of scientific questions about the nature of consciousness, and to the reception of scientific theories of consciousness by the general public.

Key words: **consciousness; survey; dualism; materialism; religiosity; health-care professionals; neuroscience**

Introduction

The scientific study of consciousness indicates that there is an intimate relationship between mind and brain.[1] However, surveys of highly educated samples have suggested that "dualistic" attitudes toward the mind–brain relationship remain very common.[2] These are revealed, for example, by religious beliefs that the mind or soul is separable from the body, or by the conviction that some spiritual part of us can survive after death. Although some might expect that nowadays the existence of the supernatural would be denied by scientists, it has been reported that about 40% of this population believe in a personal God or in life after death, a similar figure to that obtained almost a hundred years ago.[3] The clinical and theoretical implications of such figures have been stressed in a recent questionnaire survey: students from various disciplines reported that different perspectives on the mind–brain problem were likely to influence doctors' and psychologists' choice of research methods, treatment options, and their behavior toward patients.[4]

Address for correspondence: Steven Laureys, Coma Science Group, Cyclotron Research Centre and Neurology Department, Sart Tilman B30, University of Liège, Liège, Belgium. steven.laureys@ulg.ac.be

Disorders of Consciousness: Ann. N.Y. Acad. Sci. 1157: 1–9 (2009).
doi: 10.1111/j.1749-6632.2008.04117.x

Given the relevance of philosophical positions on the mind–brain relationship to practice and theory, we shall briefly review the most representative philosophies of mind. In the present chapter we use the terms mind and consciousness interchangeably to refer to the first-person perspective that we enjoy in our everyday experience.[5]

The *"–isms"* of Consciousness

Dualism

Rene Descartes developed the view that mind and matter involve different kinds of "substance," a view now known as "substance" or "Cartesian" dualism. In this view, the brain belongs to the physical world, the mind to the nonphysical, yet they are closely related to each other.[6] Physical events can cause mental events and vice versa. Dualism, however, notoriously fails to explain how physical and mental entities can interact.

Functionalism

This view, one of the varieties of physicalism, denies the "separateness" of mental and physical phenomena. Instead, mental phenomena are considered as states of the brain (beliefs, desires, feelings of pain, etc.) with a functional role. In this view, mind is analogous to the operation of a software package in the hardware in the brain. The key feature of mind, according to functionalism, is the algorithmic transformation of inputs into outputs.[7] If so, computers and robots may one day be conscious.

Reductive Materialism (or "Identity Theory")

This position holds that there are no "hard questions" to be answered and no "gaps" to be explained. The mind cannot be separated from the brain. It is the brain. Experience can be explained simply by revealing what happens within the brain, just as heat is explained by the motion of atoms. The difficulty for this perspective is that it seems to give no account of the subjective qualities of experience,[5] why it should be "like something" to undergo experience. This view, albeit convenient for neuroscience, has been accused of "leaving out the mind."[8]

In the present chapter, we survey attitudes toward the mind–brain relationship sampled from two related surveys, the first conducted by the University of Edinburgh, UK, the second by the University of Liège, Belgium. The aim was to identify attitudes toward the mind–brain relationship and the variables that account for differences of views. The two surveys shared four key statements on which participants were asked to state their views.

Methods

Material and Procedure

The statements presented to participants were: (1) the mind and brain are two separate things; (2) the mind is fundamentally physical; (3) some spiritual part of us survives after death; and (4) each of us has a soul that is separate from the body.

In the Edinburgh survey, $n = 250$ participants were included. The sample was comprised of students from the University of Edinburgh, who came from eight academic disciplines: anthropology (33), astrophysics (19), civil engineering (32), computer science (30), divinity (36), medicine (30), mechanical engineering (34), and physics (36). The students were addressed as a class after their lectures and then asked to complete and return the questionnaire within the next 15 minutes. Participants' views were expressed on a four-point Likert scale (Agree- Somewhat agree- Somewhat disagree- Disagree), which was collapsed into two categories ("agree" vs. "disagree") for further analysis. The participants were also asked to provide information about possible belief in the existence of a God or Gods.

The Liège survey included $n = 1858$ participants, who were attending public or scientific meetings on consciousness. The majority were European ($n = 1293$) and U.S. ($n = 125$)

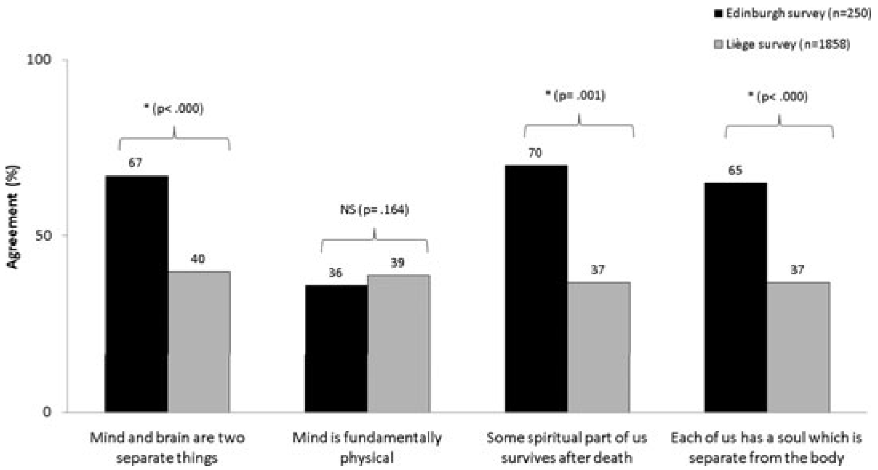

Figure 1. The attitudes toward mind and brain of the Edinburgh ($n = 250$) and the Liège survey sample ($n = 1858$).

citizens, as well as citizens from other countries around the world ($n = 86$) ($n = 354$, missing data on nationality). The sample was comprised of medical professionals (782/1858); paramedical health-care workers, such as nurses, psychologists, physiotherapists (290/1858); and other professional backgrounds (455/1858; 331 missing data on profession). The administration was oral and it took approximately 15 minutes for the completion of the questionnaire. The answers were expressed dichotomously ("agree–disagree"). Information about belief in a personal God was also collected.

The data were analyzed using SPSS 14.0 for Windows (SPSS, Inc., Chicago, IL, USA). Internal consistency was assessed by calculating interitem correlations. Chi-square tests for categorical data were used to test the differences in responses between groups. Logistic Regression analyses (method: backward stepwise) were ordered to describe the relationship between agreement on the four statements and a set of explanatory variables (i.e., age, gender, profession, and religiosity, tests thresholded at $P = .05$).

Results

The histogram of Figure 1 summarizes the initial results of the two surveys. The undergraduate students were generally more inclined to dualistic views about the mind–brain relationship than the second sample (i.e., health-care workers, lay public). Internal consistency was satisfactory for both surveys (see Table 1).

Edinburgh Survey

Two hundred fifty participants, 144 (56%) men and 106 (44%) women, completed their questionnaires. The average age of the students was 20 years (SD: 5; range: 17–57), and 98% of them were doing their first degree. The results were: 168/250 (67%) of responders agreed that "mind and brain are two separate things," while 158/248 (64%) disputed the statement that "the mind is fundamentally physical"; 161/246 (65%) agreed that "each of us has a soul that is separate from the body," and 174/248 (70%) agreed that some spiritual part of us survives after death; and 150/239 (63%) believed in the existence of God or Gods.

Women were more likely than men to subscribe to the existence of the soul ($\chi^2(1, 246) = 8.277$, $P = .004$) and to deny that the mind is physical ($\chi^2(1, 248) = 8.810$, $P = .003$). Belief in God was strongly associated with belief in the soul and spiritual survival ($\chi^2(1, 237) = 101.310$, $P < .001$), and with

TABLE 1. Correlations between Responses to the Four Statements

	Statements	Mind and brain are two separate things	Mind is fundamentally physical	Some spiritual part of us survives after death	Each of us has a soul that is separate from the body
Edinburgh survey	Mind and brain are two separate things	1			
	Mind is fundamentally physical	−.345[a]	1		
	Some spiritual part of us survives after death	.186[a]	−.248[a]	1	
	Each of us has a soul that is separate from the body	.292[a]	−.252[a]	.773[a]	1
Liège survey	Mind and brain are two separate things	1			
	Mind is fundamentally physical	−.162[a]	1		
	Some spiritual part of us survives after death	.235[a]	−.196[a]	1	
	Each of us has a soul that is separate from the body	.326[a]	−.173[a]	.518[a]	1

NOTE: Statements 1, 3 and, 4 showed high positive correlation with one other, whereas all three were significantly anticorrelated with statement 2.

[a] Correlations are significant at the $P = .01$ level (two-tailed).

disagreement with the view that the mind is fundamentally physical ($\chi^2(1, 246) = 14.124$, $P < .001$). The differences between students of different disciplines were less striking on the whole, although students in the humanities were more likely than those in the sciences to believe that the mind is nonphysical ($\chi^2(1, 148) = 8.195$, $P = .0042$).

Liège Survey

In the Liège Survey, 1858 participants, 908 (49%) women and 840 (45%) men ($n = 110$, 6% missing data on gender), were included in the analysis. The average age of the participants was 41 years (SD: 15, range: 16–85). The results were: 737/1773 (42%) respondents agreed that “the mind and the brain are separate”, while 725/1766 (41%) disputed the statement that “the mind is fundamentally physical”; 686/1735 (40%) agreed that some spiritual part of us survives after death and 688/1741 (40%) that “each of us has a soul which is separate from the body”. The number of religious believers (789/1858) was approximately the same as the number of nonbelievers (783/1858) (286 missing data on religiosity).

Table 2 summarizes the results of the Logistic Regression models for each philosophical statement. The statement “The mind and brain are two separate things” was supported more often by religious than nonreligious responders and less often by middle-aged (31–49 years) and older (>50 years) responders as compared to younger ones (<30 years). The statement that “The mind is purely physical” was endorsed less often by religious participants, and more often by men as compared to women. Religious responders agreed significantly more often with the statement “Some spiritual part of us survives after death” more than nonreligious ones. The statement that “each of us has a soul that is separate from the body” received more support from religious responders and paramedical professionals than it did from from nonreligious participants and medical professionals. The interactions age/religiosity, age/gender, and gender/religiosity were also tested, but no significant effects were found in the Logistic Regression models.

Figures 2 and 3 summarize the effects of age, gender, religiosity, and professional background on agreement with the four statements.

A majority of medical (55%) and paramedical professionals (51%) stated that they were

TABLE 2. The Most Significant Predictors of the Logistic Regression Models (method: backward stepwise) on the Four Statements

Statement predictors	Odds ratio	95% CI	*P*-value[a]
The mind and brain are two separate things			
Religious	1.778	1.347–2.347	<.001
Middle age (31–49 yr)	.490	.336–.716	<.001
Older (>40 yr)	.535	.361–.795	.002
The mind is fundamentally physical			
Religious	.519	.395–.681	<.001
Men	2.186	1.664–2.871	<.001
Some spiritual part of us survives after death			
Religious	7.892	5.694–10.938	<.001
Each of us has a soul that is separate from the body			
Religious	5.456	3.987–7.465	<.001
Paramedical professionals	1.633	1.161–2.297	<.001

NOTE: An odds ratio greater than one implies that agreement is more likely in the predictor. An odds ratio less than one implies that agreement is less likely in the predictor.

[a] *P* significant at $\alpha = 0.05$.

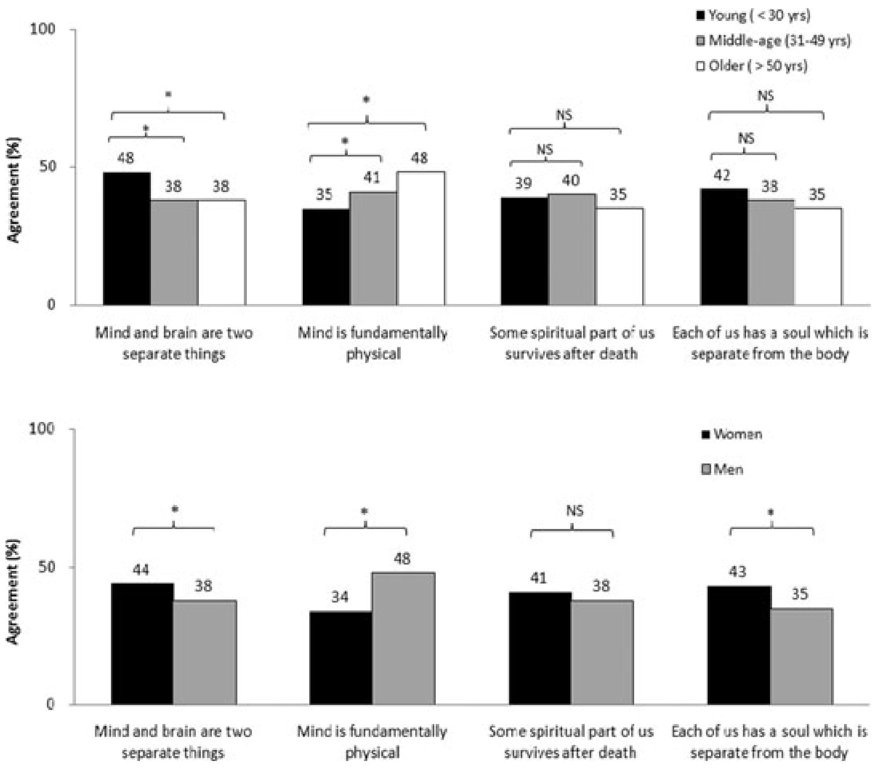

Figure 2. The effect of age and gender on attitudes toward mind–brain relationship (Liège survey, $n = 1858$).

religious. A substantial number of medical professionals (39.5%) ($n = 304$) endorsed the statement distinguishing mind and brain as separate entities as compared to 38.2% ($n = 92$) of the paramedical professionals. The physicality of mind was denied by 55.4% ($n = 425$) medical and 63.5% ($n = 153$) of paramedical professionals. The continuation of the

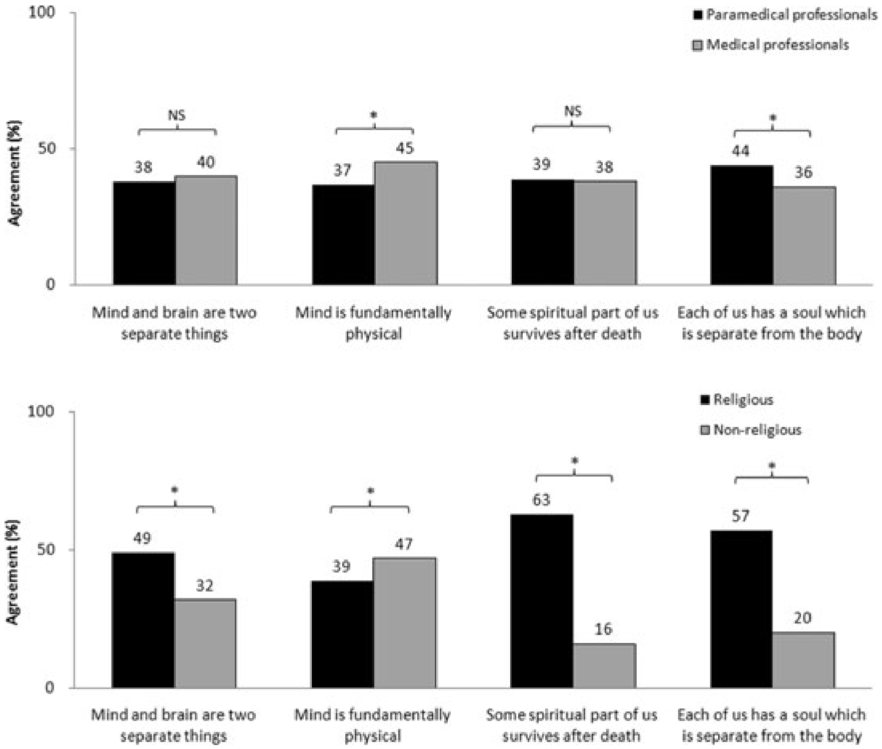

Figure 3. The effect of professional background and religiosity on attitudes toward mind–brain relationship (Liège survey, $n = 1858$).

spirit after death found support from 37.9% ($n = 285$) of medical and 38.5% ($n = 92$) of paramedical professionals. Finally, the view that that we have a soul that is separate from the body was supported by 36% ($n = 272$) of the group of medical workers and by 44.1% ($n = 105$) of paramedical professionals.

Discussion

The present article provides data from two separate but related surveys on attitudes on mind and brain, based in Scotland and Belgium. A majority of undergraduates, sampled in the Edinburgh survey, held a dualistic view of the relationship between mind and brain (i.e., mind and brain are separate). The majority disagreed that the mind is a purely physical entity and endorsed the existence of a soul that is separate from the body and survives death. The views of a wider group (health-care professionals, lay public, students), sampled in the Liège survey, were less dualistic (Fig. 1), but nevertheless, over a third of health-care workers expressed dualistic opinions and half reported religious belief. Younger participants, women, and those with religious beliefs were more likely to endorse dualism (Figs. 2 and 3). However, the tendency for women to endorse dualism more often than men was not explained by an association between female sex and religious belief.

Our findings must be considered in the context of the groups we have surveyed and the approach we have taken. A larger survey, including participants from a broader range of educational and cultural backgrounds, would shed more light on such attitudes. Additionally, the closed "agree-disagree" statements used in the survey forced participants to endorse attitudes that they might have wished to qualify had they been given an opportunity to do so. For example, a majority of the Liège survey supported the view that mind is not fundamentally physical. Yet the group's perspective was not consistently dualistic, as a majority also endorsed the statement that the mind is not separable from the brain. This may reflect the complexities of the concept of mind, or understandable confusion about its nature, which remains controversial among philosophers.

Dualism in Development

Dualism expresses itself in religious beliefs in two prominent ways: in the idea of the soul existing independently of the body, and in the idea of an afterlife.[9] Research in developmental psychology suggests that although the precise formulation of such beliefs is culturally determined, the idea that consciousness is different from the body is universal. For example, when young (4 years) and older (12 years) children were asked whether psychological functioning (i.e., consciousness) persisted after the death of a mouse, four-year-olds held that both biological functioning and consciousness survived in the dead animal. Older children believed that only consciousness survived death.[10]

Besides their tendency to regard consciousness as being separable from the body, children are inclined to "promiscuous teleology": they tend to attribute human-like purpose both to living and nonliving entities. This was shown experimentally in infants who inferred purpose in abstract geometrical figures moving systematically on a monitor.[11] Children are "intuitive theists"[12] in the sense that they tend to view nature as an artefact of design by a deity. What is the advantage of such teleological thinking? Daniel Dennett has explained its evolutionary significance in his theory of "intentional stance."[13] We adopt the intentional stance when we explain events or behavior in terms of the mental lives of agents. This is appropriate and advantageous in our dealings with one another, but our innate tendency to adopt this stance can lead to misattribution of mentality to processes that, arguably, do not involve purpose of this kind.

Dualism in Science

Although one might have expected that dualistic attitudes would grow less common with scientific progress, especially among scientists, this may not be the case. At the beginning of the twentieth century, Leuba's survey of religious beliefs among scientists found that 40 percent believed in a personal God and in afterlife.[14] Eighty years later, Larson and Witham replicated the survey and found little change,[3] in accordance with our finding that almost one-third of health-care professionals support dualistic views on mind–brain relationship. In their survey, beliefs in a personal God and in afterlife were found to be considerably lower, at 7% and 7.9% respectively, when the sampled group was "leading scientists" (i.e., members of the National Academy of Science), in contrast to what was found in 1914.[15]

Being a Dualist: Clinical and Scientific Implications

The persistence of dualistic attitudes toward mind and brain has direct implications for clinical practice. In neurological practice, around one-third of outpatients have medically unexplained symptoms, which are associated with high levels of psychiatric comorbidity (i.e., somatoform disorders). These patients are especially reluctant to accept psychological explanations for their condition,[16] because psychological symptoms are often considered shameful and associated with the social stigma of "mental" disease. Physical symptoms, on the other hand, are perceived as being free from such stigma or implication of blame. The difficulty patients with somatoform disorders experience in accepting psychological explanations for their symptoms partly flows from, and reinforces, dualistic attitudes toward the relationship between mind and body. Similarly, a recent survey found that mental-health workers utilized the mind–brain dichotomy to reason about the patients' responsibility for their condition: when a problem was considered of a psychological etiology, the patients were more often thought to be responsible for their condition, whereas when the problem was thought to have a neurobiological cause, the patients were considered less blameworthy.[17]

We suggest that dualism is also at work in neuroscientific thinking about consciousness. Thus, talk of consciousness being "generated by" or "conjured from" the brain is reminiscent of the Cartesian view that our mental lives interact with our physical being, but are radically separate from it. Some contemporary philosophers of mind[18] regard dualism of this kind as being theoretically appropriate. Here, we simply draw attention to the fact that the widespread dualism revealed by our survey continues to exert an influence on scientific thought. Whether or not dualistic views are correct, their continuing influence should be acknowledged.

Dualistic preconceptions about mind and brain may also influence the reception of scientific theories of consciousness by the general public. If such views remain alive among scientists who formulate and try to answer questions within the science of consciousness, they are likely to be all the more influential among the wider public.

Conclusions

Efforts in clinical medicine, cognitive neuroscience, and in the wider public arena are gradually reshaping our attitudes toward mind and brain. In clinical practice, the adoption of a bio–psycho–social approach to illness generally provides a helpful antidote to the separation of the care of "diseases of the mind" from those "of the body."[19] Cognitive neuroscience reflects a sustained attempt by scientists to reinstate mind within nature, from which it was exiled by Descartes at the inception of modern science. Efforts to enhance the public understanding of science are creating lively dialog between scientists and a wider public. Nevertheless, the conceptual clarification of the relationship between mind and brain remains a challenge for scientists and philosophers, as we have inherited concepts and assumptions that may not do justice to their intimate connection.

Acknowlegments

AD is funded by the DISCOS Marie Curie Research Training Network. SL and MAB are respectively Senior Research Associate and Research Fellow at the Fonds de la Recherche Scientifique (FRS). AZ is funded by The Health Foundation through a Mid-career Award. This research was also supported by the Mindbridge, the McDonnell Foundation, the Mind Science Foundation, the Reine Elisabeth Medical Foundation, and University of Liège.

Conflicts of Interest

The authors declare no conflicts of interest.

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Coma, Persistent Vegetative States, and Diminished Consciousness

A Demertzi, S Laureys and M Boly, University of Liège, Liège, Belgium

Glossary

Apnea testing – A test needed to confirm brain death by checking whether the patient has a breathing reflex when disconnected from the positive pressure ventilator.

Brain–computer interfaces (BCIs) – Real-time muscular-independent systems that permit the translation of the electrical activity of the brain into commands, to control devices.

Deep brain stimulation (DBS) – An invasive surgical treatment involving the implantation of a medical device (brain pacemaker), which sends electrical impulses to specific parts of the brain.

Default mode network – A set of brain areas, encompassing the posterior cingulate cortex/precuneus, the medial prefrontal cortex, and bilateral temporoparietal junctions, which seem to be activated in the absence of any external stimulation, and show decreased activity during cognitive processing.

Event-related potentials (ERPs) – Averaged EEG signals that detect time-locked responses to sensory, motor, or cognitive activities. Short-latency or exogenous ERPs, ranging from 0 to 100 ms after the presentation of a stimulus, correspond to the activation of the ascending pathways to the primary cortex. Cognitive or endogenous ERPs are obtained after 100 ms of the presentation of a stimulus, and reflect both subcortical and cortical structures, including associative areas.

Functional connectivity – The temporal correlation of a neurophysiological index (i.e., cerebral metabolic rates of glucose, regional cerebral blood flow) measured in different remote brain areas.

Neuron-specific enolase – The neuronal form of the glycolytic enzyme enolase, which is found almost exclusively in neurons and cells of neuroendocrine origin and is used as a marker of ischemic brain damage.

Introduction

The management of coma and related disorders of consciousness (DOC) is a major clinical challenge. Patients in a vegetative state and minimally conscious state continue to pose problems in terms of their diagnosis, prognosis, and treatment. Bedside assessment remains the gold standard. Neuroimaging and electrophysiological measures can now identify signs of awareness inaccessible to clinical examination, which permit a better understanding of the mechanisms of human consciousness and improve our care of DOC patients.

Defining Consciousness

Consciousness is a first-person experience, which consists of two major components, wakefulness and awareness. Wakefulness refers to the level of consciousness and it is supported by the function of the subcortical arousal systems in the brainstem, the midbrain, and the thalamus. Clinically, it is indicated by opening of the eyes. Awareness refers to the contents of consciousness and it is thought to be supported by the functional integrity of the cerebral cortex and its subcortical connections. Awareness can be further reduced to awareness of the environment and of self. Clinically, awareness of the environment is assessed by evaluating command following and observing nonreflex motor behavior, such as eye tracking and oriented

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responses to pain. Awareness of self, clinically a more ill-defined concept, can be assessed by the patients' response to autoreferential stimuli, such as the patients' own face in the mirror. An illustrative example of the relationship between the two components of consciousness is the transition from full wakefulness to deep sleep: the less aroused we get, the less aware we become of our surroundings and ourselves (see Figure 1).

A Short History of Disorders of Consciousness

About 50 years ago, before the era of neurocritical care, things were relatively simple. After a severe brain damage, comatose patients either died or, more rarely, recovered with more or less cognitive deficits. The invention of the positive pressure mechanical ventilator by Bjorn Ibsen in the 1950s, and the widespread use of intensive care in the 1960s, in the industrialized world, changed the picture. They stated that severely brain damaged patients could now have their heartbeat and systemic circulation sustained by artificial respiratory support. Such profound unconscious states had never been encountered before as, until that time, all these patients had died instantly from apnea. As a consequence, medicine was forced to redefine death, using a neurological definition, that of brain death.

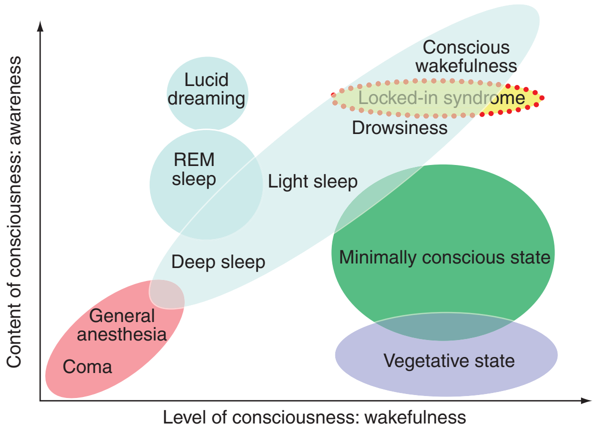

Figure 1 Simplified illustration of the two major components of consciousness and the way they correlate within the different physiological, pharmacological and pathological modulations of consciousness. Reproduced from Laureys S (2005) The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences* 9: 556–559.

In the 1960s, Fred Plum and Jerome Posner described for the first time the locked-in syndrome (LIS), to refer to fully conscious coma survivors who are unable to communicate due to physical paralysis. In 1972, Bryan Jennet and Fred Plum published the clinical criteria of another artifact of modern intensive care, the vegetative state (VS), a state of 'wakefulness without awareness.' In 2002, the Aspen Neurobehavioral Conference Workgroup realized that clinical reality was yet more complicated. Some patients showed signs of voluntary behavior, and therefore they were no longer vegetative, but still remained unable to functionally communicate. Based on these observations, they published the diagnostic criteria of a new clinical entity, the minimally conscious state (MCS).

Defining the Clinical Entities of Consciousness

Brain Death

Brain death means human death determined by neurological criteria. The current definition of death is the permanent cessation of the critical functions of the organism as a whole, such as, neuroendocrine and homeostatic regulation, circulation, respiration, and consciousness. Most countries, including the United States, require death of the whole brain including the brainstem. Some other countries, like the United Kingdom and India, rely on the death of the brainstem only, arguing that the brainstem is at once the through-station for nearly all hemispheric input and output, the center generating wakefulness (an essential condition for conscious awareness), and the center of respiration. Classically, brain death is caused by a massive brain lesion, such as trauma, intracranial hemorrhage, or anoxia. Using the brainstem formulation of death, however, unusual but existing cases of catastrophic brainstem lesions, usually of hemorrhagic origin, sparing the thalami and cerebral cortex, can be declared brain dead in the absence of clinical brainstem function, despite intact intracranial circulation. Hence, a patient with a primary brainstem lesion who did not develop raised intracranial pressure might theoretically be declared dead by the UK doctrine, but not by the US doctrine.

In 1995, the American Academy of Neurology published the criteria for brain death, which have been used to model many institutional policies. The criteria are (1) demonstration of coma; (2) evidence for the cause of coma; (3) absence of confounding factors, including hypothermia, drugs, electrolyte, and endorcrine disturbances; (4) absence of brainstem reflexes; (5) absent motor responses; (6) positive apnea testing (see 'Glossary'); (7) a repeat evaluation in 6 h is advised, but the time period is considered arbitrary; and (8) confirmatory laboratory tests are only required when specific components of the clinical testing cannot be reliably evaluated. At present, no recovery from brain death has been reported.

Coma

Patients that sustain severe brain damage may spend some time in coma, which lasts for a couple of days or weeks. Patients in coma cannot be awakened even when intensively stimulated and, hence, are not aware of the environment and of themselves (see Figure 1). Coma is distinguished from syncope or concussion in terms of its duration, which is at least 1 h. Coma can result from bihemispheric diffuse cortical or white matter damage or brainstem lesions bilaterally, affecting the subcortical reticular arousing systems. Many factors such as etiology, the patient's general medical condition, age, clinical signs, and complementary examinations influence the management and prognosis of coma. Traumatic etiology is known to have a better outcome than nontraumatic anoxic cases. In terms of clinical signs, after 3 days of observation, a bad outcome is heralded by the absence of pupillary or corneal reflexes, stereotyped or absent motor response to noxious stimulation, bilateral absent cortical responses of somatosensory-evoked potentials (SEPs) (see 'Glossary'), and (for anoxic coma) biochemical markers, such as high levels of serum neuron-specific enolase (see 'Glossary').

Vegetative State

In the VS there is dissociation between wakefulness, which is preserved, and awareness, which is absent (see Figure 1). These patients regain sleep–wake cycles. However, their motor, auditory, and visual functions are restricted to mere reflexes and show no adapted emotional responses. The VS is usually caused by diffuse lesions on the gray and white matter. According to the 1994 Multi-Society Task Force on persistent vegetative state (PVS), the criteria for the diagnosis of VS are the following: (1) no evidence of awareness of self or environment and an inability to interact with others; (2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness manifested by the presence of sleep–wake cycles; (5) sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care; (6) bowel and bladder incontinence; and (7) variably preserved cranial nerve and spinal reflexes.

The VS may be a transition to further recovery, or may be permanent. 'Permanent' VS refers to patients whose chances for recovery are close to zero. This is the case for VS that lasts more than 1 year after traumatic, or 3 months after nontraumatic (anoxic) injury. The VS is characterized as 'persistent,' when a patient is in this state for more than 1 month. As both terms are abbreviated as 'PVS,' it has been suggested to avoid these terms and, instead, mention the etiology and the time spent in VS. At present, there are no validated prognostic markers for individual patients except that the chances for recovery depend on patient's age, etiology, and time spent in the VS.

Minimally Conscious State

The MCS has been defined in 2002 by the Aspen Workgroup as a DOC in order to describe noncommunicating patients that show inconsistent, but discernible signs of behavioral activity that is more than reflexive in at least one of the following behavioral signs: (1) purposeful behavior, including movements or affective behavior that occurs in contingent relation to relevant environment stimuli and is not due to reflexive activity, such as: pursuit eye movement or sustained fixation occurring in direct response to moving or salient stimuli, smiling or crying in response to verbal or visual emotional but not neutral stimuli, reaching for objects, demonstrating a relationship between object location and direction of reach, touching or holding objects in a manner that accommodates the size and shape of the object, and vocalizations or gestures occurring in direct response to the linguistic content of questions, (2) following simple commands; (3) gestural or verbal yes/no response, regardless of accuracy; and (4) intelligible verbalization.

Like the VS, the MCS may be chronic and sometimes permanent. Emergence from the MCS is defined by the ability to exhibit functional interactive communication or functional use of objects. Given that the criteria for the MCS have only recently been introduced, there are few clinical studies of patients in this condition. Similar to the VS, traumatic etiology has a better prognosis than nontraumatic anoxic brain injuries. Preliminary data show that the overall outcome in the MCS is more favorable than in the VS.

The Locked-In Syndrome

The LIS describes patients who are awake and conscious, but have no means of producing speech, limb, or facial movements, resembling patients in a VS. LIS most commonly results from lesions to the brainstem. According to the 1995 American Congress of Rehabilitation Medicine criteria, LIS patients demonstrate: (1) sustained eye-opening (bilateral ptosis should be ruled out as a complicating factor), (2) quadriplegia or quadriparesis, (3) aphonia or hypophonia, (4) a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses, and (5) preserved cognitive abilities. Since there is only motor output problem, LIS is not a DOC, but it is included here as it can be misdiagnosed as one. Based on motor capacities, LIS can be divided into three categories: (1) classic LIS, which is characterized by quadriplegia and anarthria with eye-coded communication; (2) incomplete LIS, which is characterized by remnants of voluntary responsiveness other than eye movement; and (3) total LIS, which is characterized by complete immobility including all eye movements, combined with preserved consciousness.

Once an LIS patient becomes medically stable, and given appropriate medical care, life expectancy now is for several decades. Even if the chances of good motor recovery are very limited, existing eye-controlled, computer-based communication technology (i.e., BCI, see 'Glossary') currently allows these patient to control their environment. Neuropsychological testing batteries adapted and validated for eye-response communication, have shown preserved intellectual capacities in LIS patients, whose lesions are restricted to brainstem pathology. Recent surveys show that chronic LIS patients self-report a meaningful quality of life and the demand for euthanasia, albeit existing, is infrequent.

Evaluation of the Disorders of Consciousness

Good medical management starts with good diagnosis. However, as awareness is a first-person perspective, its objective assessment is difficult. For that reason, at the bedside, clinicians need to infer it via the evaluation of motor activity and command following. Diagnosing DOC correctly is extremely challenging. This is mainly because these patients are usually deprived of the capacity to make normal physical movements and may show limited attentional capacities. Aphasia, apraxia, and cortical deafness or blindness are other possible confounders in the assessment of DOC. This, in combination with the difficulty to define uncertain behavioral signs as voluntary or reflexive, can partially explain the high rate of incorrect diagnosis of DOC, which has been estimated to be around 40% of the cases. Besides these difficulties, one should also consider that some of the diagnostic criteria for VS and MCS do not share international consensus, such as, visual fixation, eye tracking, blinking to visual threat, and oriented motor responses to noxious stimuli.

Behavioral Evaluation

In 1974, Teasdale and Jennett's Glasgow coma scale (GCS) was published in '*The Lancet*.' This standardized bedside tool to quantify consciousness became a medical classic, thanks mainly to its short and simple administration. The GCS measures eye, verbal, and motor responsiveness. There may be some concern as to what extent eye-opening is sufficient evidence for assessing brainstem function. Additionally, the verbal responses are impossible to be measured in cases of intubation and tracheotomy. Most importantly, the GCS is not sensitive enough to detect transition from the VS toward the MCS.

To differentiate VS patients from MCS patients, the most appropriate scale is the coma recovery scale-revised (CRS-R). The CRS-R has a similar structure to the GCS, containing, in addition to motor, eye, and verbal subscales, also auditory, arousal, and communication subscales. Despite its longer administration (i.e., *c.* 20 min) as compared to the GCS and the full outline of unresponsiveness (FOUR), it is the most sensitive in differentiating VS patients from MCS patients. This is because it assesses every behavior according to the diagnostic criteria of the VS and the MCS, such as, the presence of visual pursuit and visual fixation. Importantly, the way we assess these behavioral signs need to be standardized and uniform, permitting between-centers comparisons. For example, for the assessment of visual pursuit, some scales use an object or finger (FOUR), some use a mirror, a person, an object, and a picture (Western Neuro-Sensory Stimulation Profile), some use an object and a person (Wessex Head Injury Matrix; Sensory Modalities Assessment and Rehabilitation Technique), and some a moving person (Coma/Near Coma Scale). We have shown that the use of a mirror is more sensitive in detecting eye tracking and, hence, identify MCS patients. These findings stress that self-referential stimuli have attention-grabbing properties and are important in the assessment of DOC.

Despite their pros and cons, each scale contributes differently in establishing the diagnosis and prognosis of DOC. The administration and interpretation of findings should be decided and discussed in terms of the person who uses the scale, the place where it is administered (e.g., intensive care vs. chronic rehabilitation settings), and the reasons for administration (e.g., clinical routine vs. research purposes).

In Search for Objective Markers of Consciousness

Electrophysiology

The EEG allows recording of the spontaneous electrical brain activity, permitting the identification of the level of vigilance and the detection of functional cerebral anomalies, such as seizures or encephalopathy. In brain death, the EEG shows absent electrocortical activity with a sensitivity and specificity of around 90%. In coma, a burst suppression in the EEG heralds a bad outcome. In the VS, the EEG often shows a diffuse slowing and it is only sporadically isoelectric. Similarly, in MCS there is a general slowing on the EEG. In LIS, the EEG does not reliably distinguish these patients from VS patients. However, a close-to-normal EEG should have the physician consider the possibility of LIS.

The use of ERPs (see 'Glossary') is useful to predict the outcome in DOC. Bilateral absence of cortical potentials (i.e., N20) or SEPs heralds a bad outcome in coma. The presence of 'mismatch negativity' (MMN), a late cognitive ERP component that is elicited in auditory 'oddball' paradigms, is predictive of recovery of consciousness. In VS, SEPs may show preserved primary somatosensory cortical potentials (SEPs), and brainstem auditory-evoked potentials (BAEPs) often show preserved brainstem potentials. Endogenous-evoked potentials, measuring the brain's response to complex auditory stimuli, such as the patient's own name (as compared to other names) permits to record a P300 response, which delayed in DOC patients when compared to controls. However, a P300 is not a reliable marker of consciousness as it can also be detected during deep sleep and anesthesia.

Resting cerebral metabolism

Cortical metabolism in coma survivors is reduced on an average to 50%–70% of the normal values. A global depression of cerebral metabolism is not unique to coma. When anesthetic drugs are titrated to the point of unresponsiveness, the resulting reduction in brain metabolism is similar to that observed in pathological coma. Another example of transient metabolic depression can be observed during slow-wave sleep. In this daily physiological condition, the cortical cerebral metabolism can drop to nearly 40% of the normal values – while in REM-sleep, the metabolism returns to normal waking values (see Figure 2).

In brain death the so-called 'empty-skull sign' is observed, denoting functional decapitation. VS patients show substantially reduced, but not absent, overall cortical metabolism, up to 40%–50% of the normal values. In some VS patients who subsequently recovered, global metabolic rates for glucose metabolism did not show substantial changes. Hence, the relationship between the global levels of brain function and the presence or absence of awareness is not absolute. It rather seems that some areas in the brain are more important than others for its emergence. Statistical analyses of metabolic positron emission tomography (PET) data have identified a dysfunction in a wide frontoparietal network encompassing the polymodal associative cortices: bilateral lateral frontal regions, parieto-temporal and posterior parietal areas, mesiofrontal, posterior cingulate, and precuneal cortices (see Figure 3). However, awareness seems not to be exclusively related to the activity in this 'global workspace' cortical network, but, as importantly, to the functional connectivity within this system and with the thalami. Long-range, frontoparietal, and thalamocortical 'functional disconnections,' with nonspecific intralaminar thalamic nuclei, have been identified in the VS. Moreover, recovery is paralleled by a functional restoration of this frontoparietal network and part of its thalamocortical connections.

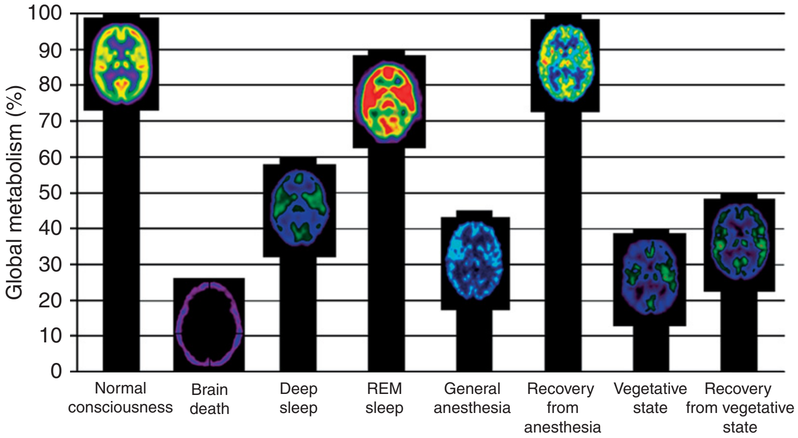

Figure 2 Global cerebral metabolism in healthy, pharmacological and disorders of consciousness. Adapted from Laureys S, Owen AM, and Schiff ND (2004) Brain function in coma, vegetative state, and related disorders. *Lancet Neurology* 3: 537–546.

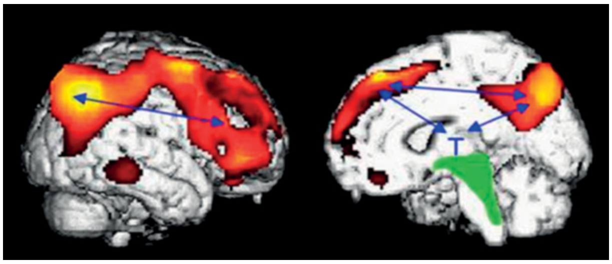

Figure 3 The frontoparietal ''awareness network'' (orange) is systematically the most impaired region in the vegetative state. The blue arrows represent the functional disconnections within this ''awareness network'' and with the thalami. The green area represents the relatively spared activity in the brainstem and hypothalamus. Adapted from Laureys, *et al*. (1999), *NeuroImage*.

Cortical activation to passive external stimulation

In brain death, external stimulation does not lead to any neural activation. In coma and VS patients, noxious stimulation was shown to activate only low-level primary cortices. Hierarchically higher-order areas of the pain matrix, encompassing the anterior cingulate cortex, failed to activate. Importantly, the activated cortex was shown to be isolated and functionally disconnected from the frontoparietal network, considered critical for conscious perception.

Similarly, auditory stimulation in VS was found to activate primary auditory cortices, but not higher-order, multimodal areas, from which they were disconnected (see Figure 4). In MCS, the activation was more widespread and there was an integrate functional connectivity between primary auditory cortices and the posterior temporal/temporoparietal and prefrontal associative areas.

Emotionally complex auditory stimuli, such as stories told by a familiar voice, lead to more widespread brain activation as compared to meaningless noise. Such context-dependent, higher-order auditory processing in MCS, often not assessable at the patient's bedside, indicate that content does matter when talking to these patients.

However, given the absence of a thorough understanding of the neural correlates of consciousness, functional neuroimaging results must be used with caution as proof or disproof of awareness in severely brain-damaged patients. Recently, Adrian Owen from Cambridge University in collaboration with our laboratory proposed a more powerful approach to identify 'volition without action' in noncommunicative brain-damaged patients. Rather than using passive external stimulation paradigms, patients were being scanned while asked to perform a mental imagery task. In one exceptional VS patient, task-specific activation was observed, unequivocally demonstrating consciousness in the absence of behavioral signs of consciousness. Interestingly, the patient subsequently recovered. Other studies also showed that VS patients with atypical brain activation patterns, after functional neuroimaging, showed clinical signs of recovery of consciousness – albeit sometimes many months later.

Treatment

To date, there are no 'standards of care' for therapeutic management in DOC. Many studies have been conducted under suboptimal or uncontrolled settings, and for that reason, no evidence-based recommendations can be made. MCS patients, however, were shown to benefit more than VS

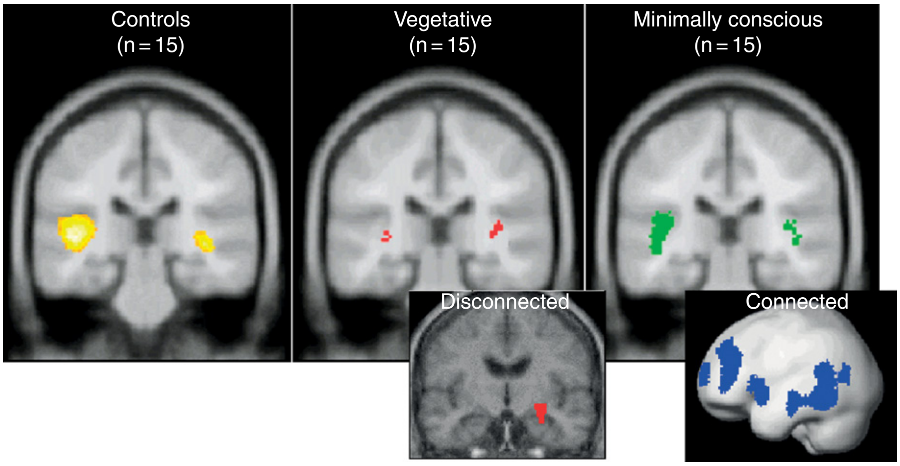

Figure 4 External stimuli still induce robust activation in primary sensory areas in vegetative patients. In the minimally conscious state, the activation is more widespread extending to multimodal associative areas. Functional connectivity studies (see 'Glossary') show that the activity of the primary cortex is isolated and disconnected from the rest of the brain, like the parahippocampal gyrus (red areas in the left inset). In the minimally conscious state, we observe a more integrated processing with preserved functional connectivity between low-level sensory areas and frontalparietal regions, which are thought to be involved in the emergence of conscious perception (blue areas in the right inset). Adapted from Boly, *et al*. (2004), *Archives of Neurology*.

after invasive treatment with DBS (see 'Glossary'). More particularly, bilateral thalamic stimulation, implanted over 6 years after acute trauma, has just been shown to cognitively improve an MCS patient, resulting in stimulation-related recovery of functional object use and intelligible verbalization. In the VS, despite some sparse evidence that DBS may benefit these patients, its effectiveness to this population is limited, mainly due to uncontrolled experimental settings. In any case, the technique awaits confirmation from studies on larger cohorts of patients, but illustrates that DBS in well-chosen patients, selected on the basis of functional neuroimaging results, can offer a real therapeutic option, at least in chronic MCS patients.

Pharmaceutical interventions with amantadine, mainly a dopaminergic agent, was shown to increase metabolic activity in a chronic MCS patient. Similarly, zolpidem, a nonbenzodiazepine sedative drug, may improve arousal and cognition in some brain-injured patients. However, placebo controlled randomized trials are needed before we making assertive conclusions about the effectiveness of the drug in DOC patients.

Conclusion

Currently, it is an exciting time for the study of DOC. The gray zone transitions between them, in the clinical spectrum following coma, are beginning to be better defined by adding powerful imaging methodology to bedside behavioral assessment. However, it should be stressed that these exciting developments are not yet a reality. The first obstacle to be overcome relates to the engendered ethical problems. An ethical framework that emphasizes balancing clear protections for patients with DOC along with access to research and medical progress is preferred. Moreover, most of the discussed areas of advances in coma science regard single case studies. Only large scale multicentric clinical trials will enable these research tools to find their way to a better evidence-based care for coma survivors.

Acknowledgments

Athena Demertzi is funded by the DISCOS Marie Curie research Training Network. Steven Laureys is senior research associate at the Belgian Fonds National de la Recherche Scientifique (FNRS). Melanie Boly is research fellow at FNRS. This research was funded by the European Commission, Mind Science Foundation, James McDonnell Foundation, French Speaking Community Concerted Research Action, and Fondation Médicale Reine Elisabeth.

See also: Ethical Implications: Pain, Coma, and Related Disorders; General Anesthesia.

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Biographical Sketch

Athena Demertzi, MSc, PhD student, graduated from the Faculty of Psychology at the Aristotle University of Thessaloniki, Greece in 2005. Soon after, she pursued her research master's in cognitive neuroscience, neuropsychology, and psychopathology, at Maastricht University, The Netherlands, where she specialized in the field of neuropsychology. During her master's, she conducted her research internship at the Blixembosch Rehabilitation Centre, Eindhoven, The Netherlands, where she studied self-awareness deficits in everyday life following brain injury. She graduated in August 2007, and next joined the Coma Science Group as an early stage researcher appointed by the Marie Curie Research Training Network 'DISCOS' – Disorders and Coherence of the Embodied Self. Under the supervision of Steven Laureys, she investigates the neural basis of the elementary personal identity in patients with altered states of consciousness, such as vegetative and minimally conscious patients.

Encyclopedia of Consciousness (2009), vol. 1, pp. 147-156

Steven Laureys, MD, PhD, is a senior research associate at the Belgian National Fund of Scientific Research (FNRS) and Clinical Professor at the Department of Neurology, Sart Tilman Liège University Hospital. He graduated as a medical doctor from the Vrije Universiteit Brussel, Belgium. While specializing in neurology he entered his research career and obtained his MSc in pharmaceutical medicine working on pain and stroke, using *in vivo* microdialysis and diffusion magnetic resonance imaging (MRI) in the rat (1997). Drawn by functional neuroimaging, he moved to the Cyclotron Research Center at the University of Liège, Belgium, where he obtained his PhD (2000) and his 'thèse d'agrégation de l'enseignement supérieur' (2007), studying residual brain function in coma, vegetative, minimally conscious, and locked-in states. He is board-certified in neurology (1998), and in palliative and end-of-life medicine (2004). A recipient of the William James Prize (2004) from the Association for the Scientific Study of Consciousness (ASSC) and the Cognitive Neuroscience Society (CNS) young investigator award (2007), he recently published *The Boundaries of Consciousness* (Elsevier 2005) and The Neurology of Consciousness (Academic Press 2009). He nowadays leads the Coma Science Group at the Cyclotron Research Centre at the University of Liège, Belgium.

Melanie Boly, MD, PhD student, is currently a research fellow at the Belgian National Funds for Scientific Research (FNRS) and Neurologist in training at the University Hospital CHU Sart Tilman. Under Steven Laureys' supervision, she performed several studies comparing auditory and noxious stimuli cerebral processing in minimally conscious and vegetative state patients. In collaboration with the team of Adrian Owen in Cambridge, she also elaborated a method to assess the presence of voluntary brain activity, and thus of consciousness, in noncommunicative, brain-injured patients. This method has already proven to be of potential interest in the early detection of signs of awareness in patients previously diagnosed as being in a vegetative state. Her interests include the study of recovery of neurological disability and of neuronal plasticity by means of multimodal functional neuroimaging (EEG-fMRI, PET, and MEG), and behavioral assessment in severely brain-damaged patients with altered states of consciousness.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 22

Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals[☆]

A. Demertzi[1], C. Schnakers[2], D. Ledoux[3], C. Chatelle[1], M.-A. Bruno[1], A. Vanhaudenhuyse[1], M. Boly[1], G. Moonen[4] and S. Laureys[1,*]

[1]*Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, Liège, Belgium*
[2]*Coma Science Group, Cyclotron Research Center and Neuropsychology Department, University of Liège, Liège, Belgium*
[3]*Coma Science Group, Cyclotron Research Center and Intensive Care Department, University of Liège, Liège, Belgium*
[4]*Department of Neurology, CHU University Hospital, Liège, Belgium*

Abstract: Pain management in severely brain-damaged patients constitutes a clinical and ethical stake. At the bedside, assessing the presence of pain and suffering is challenging due to both patients' physical condition and inherent limitations of clinical assessment. Neuroimaging studies support the existence of distinct cerebral responses to noxious stimulation in brain death, vegetative state, and minimally conscious state. We here provide results from a European survey on 2059 medical and paramedical professionals' beliefs on possible pain perception in patients with disorders of consciousness. To the question "Do you think that patients in a vegetative state can feel pain?," 68% of the interviewed paramedical caregivers ($n = 538$) and 56% of medical doctors ($n = 1166$) answered "yes" (no data on exact profession in 17% of total sample). Logistic regression analysis showed that paramedical professionals, religious caregivers, and older caregivers reported more often that vegetative patients may experience pain. Following professional background, religion was the highest predictor of caregivers' opinion: 64% of religious ($n = 1009$; 850 Christians) versus 52% of nonreligious respondents ($n = 830$) answered positively (missing data on religion in 11% of total sample). To the question "Do you think that patients in a minimally conscious state can feel pain?" nearly all interviewed caregivers answered "yes" (96% of the medical doctors and 97% of the paramedical caregivers). Women and religious caregivers reported more often that minimally conscious patients may experience pain. These results are discussed in terms of existing definitions of pain and suffering, the remaining uncertainty on the clinical assessment of pain as a subjective first-person experience and recent functional neuroimaging findings on nociceptive processing in disorders of

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[☆] Both A. Demertzi and C. Schnakers have contributed equally to this study.

*Corresponding author.
Tel.: +32 4 366 23 16; Fax: +32 4 366 29 46.;
E-mail: steven.laureys@ulg.ac.be

DOI: 10.1016/S0079-6123(09)17722-1

consciousness. In our view, more research is needed to increase our understanding of residual sensation in vegetative and minimally conscious patients and to propose evidence-based medical guidelines for the management of possible pain perception and suffering in these vulnerable patient populations.

Keywords: pain; brain injury; disorders of consciousness; survey; neuroimaging; ethics; end-of-life; vegetative state

Introduction

The International Association for the Study of Pain (IASP, 1994) defines pain as ‘‘an unpleasant sensory and emotional experience associated with real or potential tissue damage.’’ As stressed by the IASP, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain may also be reported in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though pain most often has a proximate physical cause. Pain is a subjective first-person experience with both physical and affective aspects (Kupers et al., 2005). It is a sensation in a part or parts of the body, which is, always unpleasant and, therefore, an emotional experience. Pain and suffering are not interchangeable constructs. However, the concept of suffering is surprisingly ill defined and given relatively little attention in medicine. A person might experience significant pain-related suffering from a relatively low-level noxious stimulation if she or he believes the implications are ominous, interminable, and beyond their control (Turk and Wilson, 2009). Cassell (1991) defined suffering as ‘‘the state of severe distress associated with events that threaten the intactness of the person.’’ Pain by itself does not seem to be sufficient to cause suffering; rather it seems that the person’s interpretation of the symptoms is crucial. We will here consider (as expressed by the Multi-Society Task Force on PVS, 1994) that pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that they may emanate endogenously from the depths of human self-perception.

The management of pain and suffering in disorders of consciousness (DOCs) is challenging because, by definition, patients in a vegetative state (VS) or minimally conscious state (MCS) cannot verbally or nonverbally communicate their feelings or experiences (e.g., McQuillen, 1991; Bernat, 2006; Laureys and Boly, 2007). The VS is a condition of preserved wakefulness contrasted with absent voluntary interaction with the environment (Jennett and Plum, 1972). The MCS was only recently defined (Giacino et al., 2002) and is characterized by discernible but fluctuating signs of awareness without consistent communication with the environment. How can we know if patients in VS or in MCS feel pain or suffering? The perceptions of pain and suffering are conscious experiences: the wakeful unconsciousness of vegetative patients, by definition, precludes these experiences. Of course, there is a theoretical problem to evaluate the subjective experience of pain (and any other conscious perception or thought) in another person. At the patient’s bedside, we are limited to evaluate the behavioral responsiveness to pain. If patients never show any sign of voluntary movement in response to noxious stimuli it will be concluded they do not experience pain. They may, however, be aroused by noxious stimuli by opening their eyes if they are closed, quickening their breathing, increasing heart rate and blood pressure, and occasionally show grimace-like or crying-like behavior. As all these abilities are also seen in infants with anencephaly (The Medical Task Force on Anencephaly, 1990; Payne and Taylor, 1997) they are considered to be of subcortical origin and not necessarily reflecting conscious perception of pain. We also know from studies in general anesthesia that motor or autonomic responses are no reliable indicators of consciousness (e.g., Halliburton, 1998).

DOC patients classically are bed- or chair-bound and may suffer from spasticity, contractures, fractures, pressure sores, soft tissue ischemia, peripheral nerve injuries, complex regional pain syndrome, central pain syndromes, and post-surgical incisional pain (Schnakers and Zasler, 2007). Since they cannot communicate their potential painful state, the existence of pain is clinically inferred from observing their spontaneous behavior or their motor responses to noxious stimulation. Stereotyped responses (i.e., slow generalized flexion or extension of the upper and lower extremities), flexion withdrawal (i.e., withdrawal of the limb away from the point of the stimulation), and localization responses (i.e., the nonstimulated limb locates and makes contact with the stimulated body part at the point of stimulation) are linked to, respectively, brainstem, subcortical, or cortical activity (e.g., Stevens and Nyquist, 2006). No response after intense noxious stimulation reveals a deep stage of coma; stereotyped responses are considered as "automatic" unconscious reflexes, whereas localization of noxious stimulation is usually considered as indicative of conscious perception (Posner et al., 2007).

Repeated clinical examinations by trained and experienced examiners are paramount for the behavioral assessment of pain. To date, several scales are used for assessing pain in noncommunicative individuals with end-stage dementia, in newborns and in sedated intensive care patients, but no scale was developed to assess pain in DOCs (Schnakers et al., 2009b). We therefore recently proposed the Nociception Coma Scale as a standardized and validated tool measuring motor, verbal, and visual responses and facial expression in response to pain (Schnakers et al., 2009a). However, the absence of a behavioral response cannot be taken as an absolute proof of the absence of consciousness (McQuillen, 1991; Bernat, 1992) and inferring pain and suffering solely by observing behavioral responses may be misleading, especially in patients with extreme motor impairment or with fluctuating levels of vigilance (e.g., Majerus et al., 2005). Given these limitations of our bedside clinical assessment of pain in noncommunicative brain injured patients, inherent to the first-person subjective dimension of pain, we will next review the usefulness of functional neuroimaging methods in the study of pain and suffering in VS and MCS.

Neuroimaging of pain

Since brain responses are the final common pathway in behavioral responses to pain (unconscious and conscious), we believe that the application of functional imaging will allow us to study pain in an objective manner and to propose evidence-based guidelines on the use of analgesia and symptom management in DOCs (e.g., Borsook and Becerra, 2006; Laureys et al., 2006; Laureys and Boly, 2008). In healthy controls, studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed that pain cannot be localized in an isolated "pain centre" but rather encompasses a neural circuitry, the pain "neuromatrix" (Jones et al., 1991; Peyron et al., 2000). More specifically, two distinct cerebral networks have been identified to be involved in pain perception: (i) a lateral pain system or sensory network, encompassing lateral thalamic nuclei, primary and secondary somatosensory, as well as posterior parietal cortices; and (ii) a medial pain system or affective network, which involves the medial thalamus, anterior cingulate, and prefrontal cortices; the insular cortices playing an intermediate role (Hofbauer et al., 2001). For example, increased activity in the insular and anterior cingulate cortices prior to painful stimulation has been linearly associated with increased painfulness (Boly et al., 2007). Inversely, a hypnotic-induced absence of activation in these areas was associated with reduced subjective pain reports (Vanhaudenhuyse et al., 2009). These and other studies are increasing our understanding of the neural correlates of the sensory and affective components of pain (e.g., see review in Kupers et al., 2005), but it should be noted that at present our understanding of suffering (i.e., distress associated with events that threaten the intactness of the person; Cassell, 1991) is very limited and barely studied.

Recent neuroimaging studies have shown that DOCs are characterized by distinct cerebral patterns in response to sensory stimulation (e.g., Laureys et al., 2004; Laureys, 2005a; Giacino et al., 2006; Schiff, 2007; Owen, 2008). In 15 VS patients, our group found no evidence of noxious stimulation-related downstream activation beyond primary somatosensory cortex (Laureys et al., 2002). More importantly, functional connectivity assessment showed that the observed cortical activation subsisted as an island, dissociated from the pain matrix and the higher-order cortices that are currently thought to be necessary for conscious awareness (as shown by studies on conscious perception in healthy controls and on loss of consciousness in sleep and anesthesia; e.g., Baars et al., 2003; Boveroux et al., 2008; Laureys, 2005b). However, another study reported additional activation of secondary somatosensory and insula cortices in VS patients (Kassubek et al., 2003), implying the possibility of affective experiences of pain.

In striking contrast to what we observed in VS, MCS patients showed activation in not only midbrain, thalamus, and primary somatosensory cortex but also in secondary somatosensory, insular, posterior parietal, and anterior cingulate cortices (Fig. 1). The spatial extent of the activation in MCS patients was comparable to controls and no brain region showed less activation in MCS as compared to healthy individuals. A functional connectivity assessment of insular cortex demonstrated its preserved connections with a large set of associative areas encompassing posterior parietal, motor and supplementary motor, striatum, and dorsolateral prefrontal and temporal associative cortices as observed in controls (Boly et al., 2005). These neuroimaging data show large differences in brain activation between VS and MCS patients, despite a similar bedside behavioral evaluation. In the next section, we report differences in healthcare workers' beliefs toward possible pain in DOCs.

Attitudes toward pain perception

To our knowledge, no data exist on the thoughts of physicians and paramedical personnel toward pain perception in patients in VS as compared to MCS. We here present results from a questionnaire survey on attitudes on DOCs, which was distributed during lectures at medical and scientific conferences and meetings ($n = 48$) within

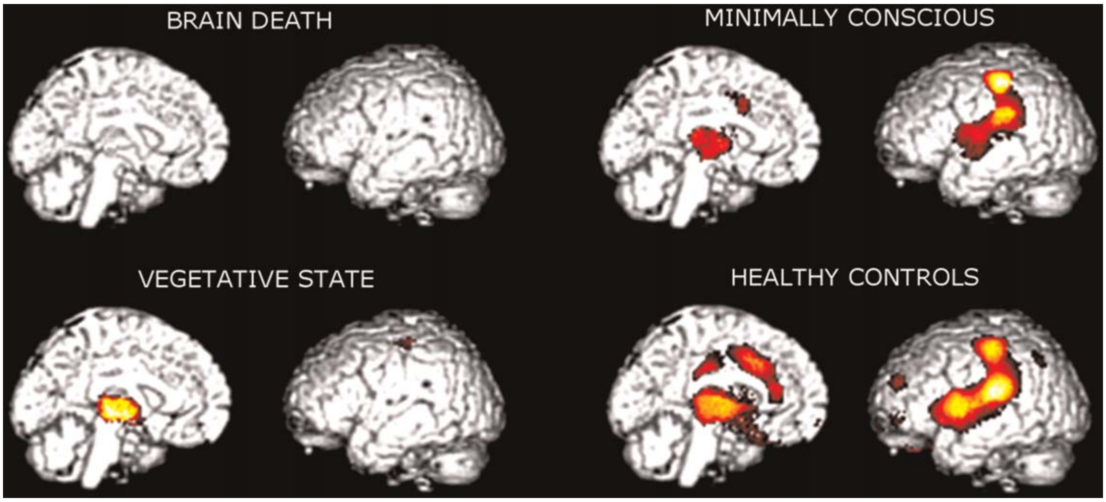

Fig. 1. Cerebral activation to noxious stimulation in brain death (adapted from Laureys, 2005a with permission), the VS (Laureys et al., 2002 with permission), and the MCS (Boly et al., 2008 with permission) as compared to healthy volunteers. Note: (i) the absence of activation in brain death; (ii) the preserved but low-level subcortical and primary cortical activation in the VS (the primary cortical activation was disconnected from the rest of the brain), and (iii) the near-normal activation in the minimally conscious state.

Europe (data were collected by SL, AD, MAB, AV, MAB, and DL between June 2007 and April 2009). Participation to the survey was voluntary and anonymous. Participants were first introduced to the clinical definitions of DOCs and were then asked to provide 'yes' or 'no' answers to 16 questions related to consciousness, VS, MCS, and locked-in syndrome. We here report the replies obtained in European medical and paramedical professionals to the questions "Do you think that patients in a vegetative state can feel pain?" and "Do you think that patients in a minimally conscious state can feel pain?" — the questions related to consciousness and the brain have been reported elsewhere (Demertzi et al., 2009). Recorded demographic data included age, gender, nationality, profession, and religious beliefs. Nationalities were categorized into three geographical regions based on previous classification criteria (Sprung et al., 2003): Northern (Denmark, Estonia, Finland, Lithuania, Netherlands, Norway, Poland, Russia, Sweden, United Kingdom), Central (Austria, Belgium, Czech Republic, Germany, Hungary, Luxembourg, Moldavia, Romania, Serbia, Slovakia, Slovenia, Switzerland), and Southern Europe (Bulgaria, Croatia, Cyprus, France, FYROM, Greece, Italy, Portugal, Spain, Turkey). Statistical analyses were performed using SPSS v.16.0 software packages. Multiple logistic regression (stepwise backward; i.e., independent variables are removed from the equation at consecutive steps; entry, $p = 0.05$ and removal, $p = 0.1$) was used to assess associations between obtained answers to the two questions and age, gender, profession, region, and religiosity. Chi-square tests assessed differences within categorical variables. Results were considered significant at $p < 0.05$ (two-sided).

Table 1. Demographic characteristics of the study sample ($n = 2059$)

Age, mean ± SD (range), years	43 ± 12 (18–83)
Gender, no. (%)	
Women	993 (47%)
Men	962 (48%)
Missing	104 (5%)
Respondents by geographical region, no. (%)	
Northern Europe	283 (13%)
Central Europe	1011 (49%)
Southern Europe	470 (24%)
Missing	295 (14%)
Profession, no. (%)	
Medical professionals	1196 (58%)
Paramedical professionals	548 (27%)
Missing	315 (15%)
Religiosity, no. (%)	
Religious respondents	1033 (50%)
Non-religious respondents	849 (41%)
Missing	177 (9%)

The study sample included 2059 medical and paramedical professionals coming from 32 European countries (see Table 1 for demographic data). As a whole, the sampled participants replied more often that MCS patients could feel pain than that VS patients could feel pain ($\chi^2(1) = 7.9$, $p < 0.001$). Participants' opinions were much more consistent for pain perception in MCS (96% of the total sample considered MCS patients can feel pain), while responses were much more discordant for VS (59% considered vegetative patients could feel pain). Paramedical caregivers ($n = 538$) replied more often that patients in a VS could feel pain than did medical doctors ($n = 1166$) (68% versus 56%; $\chi^2(1) = 23.07$, $p < 0.001$; Fig. 2a). Following professional background, religion was the highest predictor of caregivers' opinion: 64% of religious ($n = 1009$; 94% Christians) versus 52% of nonreligious respondents ($n = 830$) answered positively (see Fig. 3a). There was no effect of religion practice (317 were practicing and 664 were not practicing their religion) on attitudes toward pain perception in the VS ($\chi^2(1) = 0.261$, $p = 0.609$). Logistic regression analysis showed that paramedical professionals, religious caregivers, and older caregivers reported more often that vegetative patients may experience pain (Table 2). To the question "Do you think that patients in a minimally conscious state can feel pain?" nearly all interviewed caregivers answered "yes" (96% of the medical doctors and 97% of the paramedical caregivers; Fig. 2b). Logistic regression analysis showed that women and religious caregivers reported more often that minimally conscious patients may experience pain. For attitudes on pain in MCS, the difference between medical

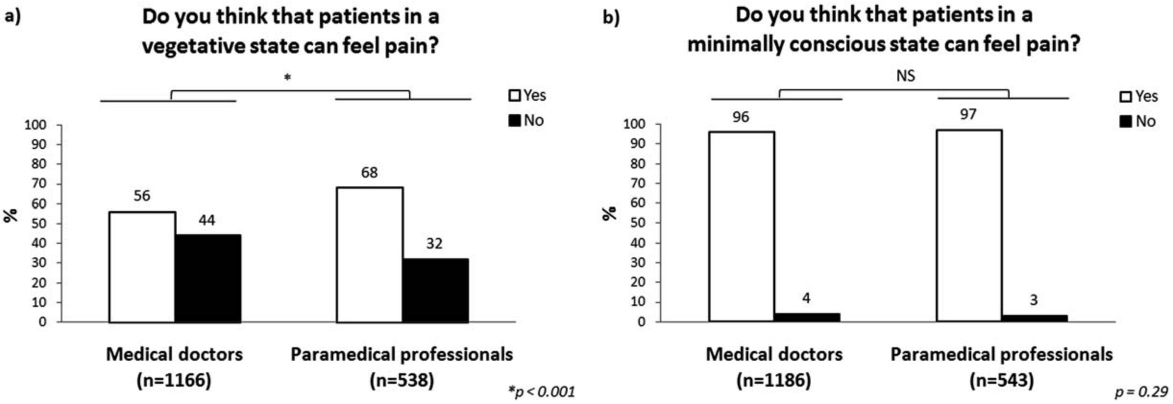

Fig. 2. Attitudes toward pain perception in the vegetative and the minimally conscious as expressed by European medical and paramedical professionals.

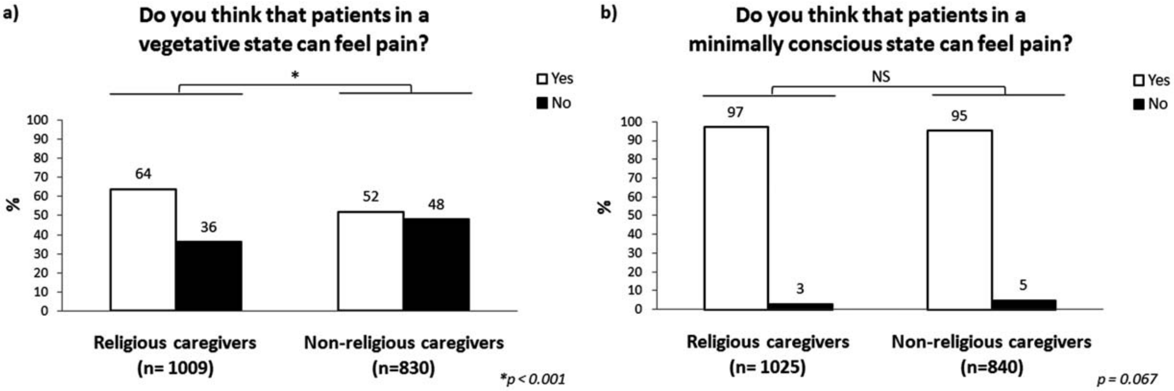

Fig. 3. The effect of religion on attitudes toward pain perception in patients with DOCs.

and paramedical professionals was not significant ($\chi^2(1) = 1.07$, $p = 0.295$).

According to our survey, healthcare workers have different beliefs about possible pain perception in MCS as compared to VS patients. This finding implies that, despite the recent introduction of MCS (Giacino et al., 2002), the medical community regards MCS and VS as two separate clinical entities characterized by different pain perception profiles. The major differences in physicians' beliefs about pain in VS as compared to MCS are supported by results from the functional neuroimaging data discussed above (Laureys et al., 2002; Boly et al., 2008). However, our survey showed that a high proportion of medical doctors (56%) and paramedical professionals (68%) considered that VS patients feel pain. The observed differences in viewpoint depending on professional background might be related to many factors including differences in proximity to the patient, time spent at the bedside, sensibilities, and education. Previous American studies reported a smaller minority of physicians holding these views. Payne et al. (1996) surveyed 170 physicians from the American Academy of Neurology and 150 from the American Medical Directors Association and reported that only 30% believed VS patients experience pain (they found no differences between academic and non-academic physicians). Similarly, an unpublished survey by the American Neurological Association reported that 31% of its members

Table 2. Logistic regression results on participants' characteristics (age, gender, region, professional background, religiosity) and "Yes" versus "No" answers to the questions on pain perception in VS and MCS

Question predictors	Odds ratio[a]	95% Confidence interval		*p*-value
Do VS patients feel pain?[b]				
Age	1.01	1.00	1.02	0.05
Women	1.25	0.99	1.58	0.06
Northern Europe	1			
Central Europe	0.81	0.58	1.14	0.24
Southern Europe	1.1	0.76	1.6	0.6
Paramedical professionals	1.56	1.2	2	<0.001
Religious respondents	1.37	1.1	1.7	0.004
Do MCS patients feel pain?[c]				
Women	2.38	1.33	4.26	0.003
Religious respondents	1.83	1.05	3.18	0.031

[a] For the continuous variables, the odds ratio equals the relative change in the odds ratio when the variable is increased by one unit.

[b] Stepwise backward (Step 1).

[c] Stepwise backward (Step 4).

were "uncertain" about whether VS patients could experience pain (31%) and suffering (26%) (Daroff, 1990). Tresch et al. (1991) found that only 22% of the relatives of patients in VS believed that their relative could experience pain and suffering. We can only speculate about possible explanations for the seemingly increased proportion of physicians considering that VS patients feel pain. It maybe that the recent publication of the diagnostic criteria for the MCS (Giacino et al., 2002) or the highly mediatized report of a VS patient "playing tennis in her head" (Owen et al., 2006) may have changed physicians opinions. In addition, cultural and religious differences could underlie the observed discrepancies between our European study and the older American surveys.

Physician and caregivers' opinions on patients' pain perception was significantly influenced by religious beliefs. We have previously shown that personal philosophical convictions are of major influence on our views on the relationship between consciousness and the brain (Demertzi et al., 2009). Such personal beliefs have also been shown to weight on physicians' clinical decisions (e.g., see Jennett, 2002). In line with our findings on the influence of religion and age on beliefs on pain perception in VS, other studies on, for example, end-of-life decisions in intensive care patients have shown that older and more experienced doctors and doctors with religious convictions (i.e., Christians) more often refused to opt for treatment limitations (Christakis and Asch, 1995; Sprung et al., 2003).

Considering our results on varying beliefs about pain perception in DOCs, physicians and healthcare workers' views on pain and symptom management may also be affected. Since nearly half of the interviewed doctors express that VS patients do not feel pain, they could be expected to act accordingly by, for instance, not providing analgesic medication in these patients. These issues become even more important in cases when VS patients are agreed to be withdrawn from life-supporting treatment, such as artificial nutrition and hydration. In these cases (e.g., Terri Schiavo) patients may be left without administration of opioids or other analgesic drugs during their dying process (Fins, 2006; Laureys, 2005a) on the grounds that they are deployed from experiencing suffering from hunger and thirst (Ahronheim and Gasner, 1990). In light of an incomplete picture of pain perception in VS patients, the existing risk for misdiagnosis (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009c), the inconclusive drug-related effects in DOCs (Demertzi et al., 2008) and the limitations in interpreting neuroimaging results (Poldrack, 2008;

Laureys and Boly, 2007), pain prophylaxis and treatment have been proposed for all patients suffering from DOCs (Schnakers and Zasler, 2007; Schnakers et al., 2009b).

The reported discrepancies in opinions about pain perception in VS patients may also be related to the absence of a unanimously accepted definition of pain and suffering. The Multi-Society Task Force on PVS (1994) considered that grimace-like or crying-like behaviors are not likely to reflect conscious awareness of pain or suffering "unless they are consistent, sustained, and definitive in nature." They differentiated between pain and nociception, in that the latter is merely a response to noxious stimulation that can be present without conscious awareness and stated that nociceptive stimulation may elicit unconscious postural responses, as well as other motor, autonomic, and endocrinologic reflexive responses without evoking the experience of pain and suffering if the brain has lost its capacity for self-awareness (Multi-Society Task Force on PVS, 1994). The IASP (1994) definition of pain also refers to cognitive and affective properties of pain, stressing the importance of subjectivity and environmental influences in the experience of pain. Some authors support the view that pain can be regarded as any response to a noxious stimulus (e.g., see Anand and Craig, 1996) — but it is clear that not just any reaction to changes in the environment can be considered as conscious (e.g., brain-death-associated reflexes and automatisms; Laureys, 2005a; Jain and DeGeorgia, 2005). Others have hypothesized, based on observations from children with hydrancephaly (Shewmon et al., 1999) newborns (Anand and Hickey, 1987) and fetuses (Derbyshire, 2008), that midbrain structures may mediate consciousness, supporting the claim that cortical activity is not necessary for conscious perception (Merker, 2007).

In conclusion, our survey shows clear differences in medical professionals' beliefs on pain perception in VS patients as compared to MCS patients. Nearly all respondents considered that MCS patients can feel pain and medical doctors and paramedical professionals largely concur. In contrast, the beliefs on pain perception in VS patients were much more divided. Paramedical professionals, religious participants, and older caregivers reported more often that VS patients may experience pain. In light of many controversies around pain (and hence pain management) in VS and MCS patients, an increase in scientific evidence is essential to enhance our understanding and to permit the development of adapted standards of care and improved clinical guidelines for these challenging and vulnerable noncommunicative patients with DOCs.

Acknowledgments

This work was supported by the Belgian Ministry of Health (SPF Santé Publique), Belgian Fonds de la Recherche Scientifique (FRS), European Commission (DISCOS, Mindbridge, COST), Belgian French Community Concerted Research Action, McDonnell Foundation, Mind Science Foundation, Reine Elisabeth Medical Foundation, and University and University Hospital of Liège. S. Laureys is Senior Research Associate, C. Schnakers and M. Boly are Postdoctoral Researchers, C. Chatelle and M. A. Bruno are Research Fellows, and D. Ledoux is Clinical Associate at FRS.

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Two Distinct Neuronal Networks Mediate the Awareness of Environment and of Self

Audrey Vanhaudenhuyse[1*], Athena Demertzi[1*], Manuel Schabus[2], Quentin Noirhomme[1], Serge Bredart[1], Melanie Boly[1], Christophe Phillips[1], Andrea Soddu[1], Andre Luxen[1], Gustave Moonen[1], and Steven Laureys[1]

Abstract

■ Evidence from functional neuroimaging studies on resting state suggests that there are two distinct anticorrelated cortical systems that mediate conscious awareness: an "extrinsic" system that encompasses lateral fronto-parietal areas and has been linked with processes of external input (external awareness), and an "intrinsic" system which encompasses mainly medial brain areas and has been associated with internal processes (internal awareness). The aim of our study was to explore the neural correlates of resting state by providing behavioral and neuroimaging data from healthy volunteers. With no a priori assumptions, we first determined behaviorally the relationship between external and internal awareness in 31 subjects. We found a significant anticorrelation between external and internal awareness with a mean switching frequency of 0.05 Hz (range: 0.01–0.1 Hz). Interestingly, this frequency is similar to BOLD fMRI slow oscillations. We then evaluated 22 healthy volunteers in an fMRI paradigm looking for brain areas where BOLD activity correlated with "internal" and "external" scores. Activation of precuneus/posterior cingulate, anterior cingulate/mesiofrontal cortices, and parahippocampal areas ("intrinsic system") was linearly linked to intensity of internal awareness, whereas activation of lateral fronto-parietal cortices ("extrinsic system") was linearly associated with intensity of external awareness. ■

INTRODUCTION

Consciousness has two components, arousal and awareness (Zeman, 2001). Arousal refers to the levels of alertness or vigilance and involves the activity of the brainstem reticular formation, hypothalamus, and basal forebrain, whereas awareness refers to the contents of consciousness and is related to the activity of a widespread set of fronto-parietal associative areas. Awareness and arousal are linearly correlated, in the sense that the less aroused we get the less aware of our surroundings and ourselves we become (Laureys, 2005). Furthermore, awareness encompasses two components: awareness of the environment (external) and of self (internal) (James, 1890). We here define external awareness as the conscious perception of one's environment through the sensory modalities (e.g., visual, auditory, somesthetic, or olfactory perception). Internal awareness is defined as encompassing mental processes that do not require the mediation of external stimuli or sensory input (e.g., mind wandering, daydreaming, inner speech, mental imagery; for a review, see Lieberman, 2007). Growing neuroscientific evidence supports that the awareness brain network can be subdivided in two main networks: a fronto-parietal network routinely exhibiting activity increases during attention-demanding cognitive tasks, and a "default network," which has been involved in self-related processes (Fox et al., 2005).

The aim of the present study is to better characterize the subjective cognitive processes inherent to these "external" and "internal" or "default" networks. We first performed a behavioral experiment looking for the relationship between subjective external and internal awareness scores in 31 healthy volunteers. During an eyes-closed resting condition, subjects were asked to score their external and internal awareness levels by button presses after hearing an auditory prompt. Next, we performed an fMRI experiment in 22 subjects looking for the neural correlates of subjective external and internal awareness scores, correlating external and internal awareness intensity to changes in BOLD neural activity.

METHODS

Before each experiment, subjects received the following instruction: "During the next 15 minutes, we ask you to keep your eyes closed and to avoid prolonged structured thinking, such as counting or singing. When you hear a beep, please use the keyboard to communicate the intensity of

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[1]University of Liège, Liège, Belgium, [2]University of Salzburg, Salzburg, Austria

*A. V. and A. D. contributed equally to this work.

‘external awareness’ and ‘internal awareness’ ongoing prior to the beep. ‘External’ is here defined as the perception of environmental sensory stimuli (e.g., auditory, visual, olfactory, or somesthetic). ‘Internal’ here refers to all environmental stimuli-independent thoughts (e.g., inner speech, autobiographical memories, or wandering thoughts).”

Participants

Behavioral data were acquired from 31 healthy subjects [21 women, mean (*SD*) age = 26 (3) years]. Imaging data were acquired from 22 healthy subjects, different from the subjects of the behavioral study [10 women, mean (*SD*) age = 23 (2) years]; one participant was excluded from further analysis due to movement artifacts. None of the participants had any relevant medical history or used any centrally acting medication. All participants gave their written informed consent prior to inclusion in the study, which was approved by the Ethics Committee of the University of Liège.

Behavioral Experiment

Our experimental exploration consists of two parts. First, a behavioral experiment was used in order to determine the relationship between external and internal awareness. External and internal awareness scores were recorded using a keyboard. The experiment took place in a quiet room where the subjects were seated comfortably in a chair facing the keyboard. Subjects placed four fingers of both hands (not the thumb) on the keyboard. For the first behavioral study, for the half of the subjects, the left hand corresponded to external awareness (for the other half, the left hand corresponded to internal awareness; randomized order). All subjects were instructed to start responding by using button presses of their left hand on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = maximal). The subjects’ task was to rate both external and internal awareness (prompted by a 60-dB beep presented via headphones), as defined in the instruction mentioned above. Only when the two scores were given could the next beep be elicited. Interstimulus interval was randomized between 11.3 and 26.8 sec (mean = 19 ± 8 sec). A familiarization session (11 responses) preceded the main experiment (66 responses). Upon completion of the experiment, the content of external and internal awareness was assessed using a semi-structured interview.

Statistical Analysis

The relationship between ratings of external and internal awareness was estimated by calculating Spearman’s r correlation coefficients (two-tailed) for every subject and then estimating the mean correlation within the sample. In terms of temporal dynamics, the frequency of switching between internal and external awareness scores was estimated by first subtracting the external from internal ratings in order to get a unique curve for every subject. The frequency spectrum of these obtained scores was estimated using the Lomb periodogram method for unevenly sampled awareness scores (Press, Flannery, Teukolsky, & Vetterling, 1992; Lomb, 1976).

Imaging Experiment

After having established the relationship between external and internal awareness with the behavioral experiment (using responses from both hands), the fMRI study was performed. Here, in order to reduce the interference with resting state brain function and to reduce motor responses and artifacts to the maximum, behavioral responses were obtained on a single scale reflecting intensity from “more external” to “more internal” awareness. Hence, for the fMRI experiment, awareness scores were recorded with the left hand for all subjects (1 = strongly external, 2 = moderately external, 3 = moderately internal, and 4 = strongly internal). During the scanning period, subjects were asked not to move, to keep their eyes closed, to relax, and to avoid structured thinking (e.g., counting, singing). Subjects were presented an auditory beep, on average, every 20 sec (range = 3–30 sec). After each sound, subjects were asked to evaluate and score by a button press their state of awareness (“strongly external,” “moderately external,” “moderately internal,” and “strongly internal”) for the period preceding the beep. The fMRI study was terminated when on-line analysis showed 15 responses in each state of awareness.

Paired Student’s t tests assessed the differences in reaction times between external and internal awareness states. Similarly to the behavioral experiment, the frequency spectrum of awareness scores obtained during the fMRI data was estimated using the Lomb method for unevenly sampled data (Press et al., 1992; Lomb, 1976).

MRI Acquisition

fMRI time series were acquired on a 3-T head-only scanner (Magnetom Allegra; Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit–receive quadrature head coil. Multislice T_2*-weighted functional images were acquired with a gradient-echo, echo-planar imaging sequence using axial slice orientation and covering the whole brain (32 slices, FoV = 220×220 mm^2, voxel size = $3.4 \times 3.4 \times 3$ mm^3, 30% interslice gap, matrix size = $64 \times 64 \times 32$, TR = 2460 msec, TE = 40 msec, FA = 90°). The three initial volumes were discarded to avoid T_1 saturation effects. For anatomical reference, a high-resolution T_1-weighted image was acquired for each subject [T_1-weighted 3-D magnetization-prepared rapid gradient-echo sequence, TR = 1960 msec, TE = 4.43 msec, inversion time

(TI) = 1100 msec, FoV = 230 × 173 mm^2, matrix size = 256 × 192 × 176, voxel size = 0.9 × 0.9 × 0.9 mm^3].

MRI Analysis

Functional data were preprocessed and analyzed by means of the Statistical Parametric Mapping software SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5/; Wellcome Department of Imaging Neuroscience, London, UK), using a two-steps procedure (random effect analysis) that took into account both within- and between-subject variability, as was published elsewhere (Vanhaudenhuyse et al., 2009; Boly et al., 2007). The first two fMRI volumes were removed to allow for signal equilibration. Preprocessing steps included realignment, spatial normalization, and smoothing (Friston, Ashburner, et al., 1995; Friston, Holmes, et al., 1995). The normalization was performed using a three-step automated procedure (Friston, Ashburner, et al., 1995). Firstly, the structural T1 scan of each subject was segmented and normalization parameters were derived from this step from the subject space to the MNI space. Secondly, the functional data were coregistered to the structural scan. Thirdly, the structural and functional scans were normalized using the normalization parameters (voxel size: 2 × 2 × 2 mm for functional and 1 × 1 × 1 mm for structural images) derived from the first step. Functional data were then smoothed using an 8-mm FWHM Gaussian kernel. Each subject's data were modeled individually with a generalized linear model (Friston, Holmes, et al., 1995) and images of effects of interest were produced. These images were then analyzed with a mixed effects model aimed at showing stereotypical effect in the population from which the subjects are drawn (Penny & Holmes, 2003). The mixed effects model was implemented in two processing steps accounting for fixed and random effects, respectively (Boly et al., 2007; Friston, Stephan, Lund, Morcom, & Kiebel, 2005).

For each subject, a first-level intraindividual fixed effects analysis aimed at modeling the data to partition the observed neurophysiological responses into components of interest, confounds, and errors by using a general linear model (Vanhaudenhuyse et al., 2009; Boly et al., 2007; Friston, Holmes, et al., 1995). We created a design matrix using a block design (lasting 3–30 sec) for every individual subject incorporating answers of subjects ("strongly external," "moderately external," "moderately internal," and "strongly internal") as regressors of interest, time of beeps, reaction time, and movement parameters as supplementary regressors. Reaction times were calculated by subtracting time of answer from time of beep. Movement parameters were derived from realignment of the functional volumes (translations in the x, y, and z directions and rotations around the x, y, and z axes). Reaction times and movement parameters were included as covariates of no interest in the design matrix. A first analysis identified stimulus-induced brain activation in periods rated as "strongly external," "moderately external," "moderately internal," and "strongly internal." These periods were incorporated as regressors of interest in the design matrix using a block design (lasting 3–30 sec). The movements were modeled in supplementary regressors. Movement parameters derived from realignment of the functional volumes (translations in the x, y, and z directions and rotations around the x, y, and z axes) were included as covariates of no interest in the design matrix. High-pass filtering using a cutoff period of 128 sec was implemented in the design matrix to remove low-frequency drift from the time series (Vanhaudenhuyse et al., 2009; Boly et al., 2007; Friston et al., 2000). Serial correlations were estimated using a restricted maximum likelihood algorithm with an intrinsic autoregressive model during parameter estimation. The effects of interest were tested through linear contrasts, generating statistical parametric maps (SPM$\{t\}$) in each subject. Contrasts images were computed, identifying a linear positive correlation with external thoughts (1.5 0.5 −0.5 −1.5 contrast of the general linear model parameters) and a linear positive correlation with internal thoughts (contrast −1.5 −0.5 0.5 1.5). The resulting set of voxel values for each contrast constituted a map of t statistic (SPM$\{t\}$) thresholded at $p < .001$ (Peigneux et al., 2006). We then smoothed the contrast images (6 mm FWHM Gaussian kernel) in order to improve statistic across subjects by increasing the overlap between activated areas of each subject, and balancing the existing intersubject anatomical variability (Mikl et al., 2008; White et al., 2001). These smoothed contrast images were entered in a second-level general linear model, acting as a random effects analysis investigating consistent effects at the population level. Statistical inferences were then obtained after correction for multiple comparison at the voxel level using false discovery rate $p < .05$ (whole head volume) for areas previously reported to be involved in internal awareness (i.e., mesiofrontal/anterior cingulate and precuneal/posterior cingulate cortices; Boly et al., 2007; Laureys, Perrin, & Bredart, 2007; Mason et al., 2007), whereas a small volume (8 mm radius sphere) corrected at $p < .05$ (Worsley, 1996) was calculated for areas previously reported to be involved in external awareness (i.e., bilateral posterior parietal and dorsolateral prefrontal cortex; Boly et al., 2007; Haynes, Driver, & Rees, 2005; Dehaene et al., 2001; Vuilleumier et al., 2001), and internal awareness (i.e., mesiofrontal/anterior cingulate and precuneal/posterior cingulate cortices; Boly et al., 2007; Laureys et al., 2007; Mason et al., 2007).

RESULTS

Behavioral Experiment

We observed a significant negative correlation between external and internal awareness scores at the group level (Spearman's $r = -.44$, $p < .02$, two-tailed). At the subject level, 24 participants showed significant negative correlations between internal and external awareness, one showed a positive correlation, and six participants showed

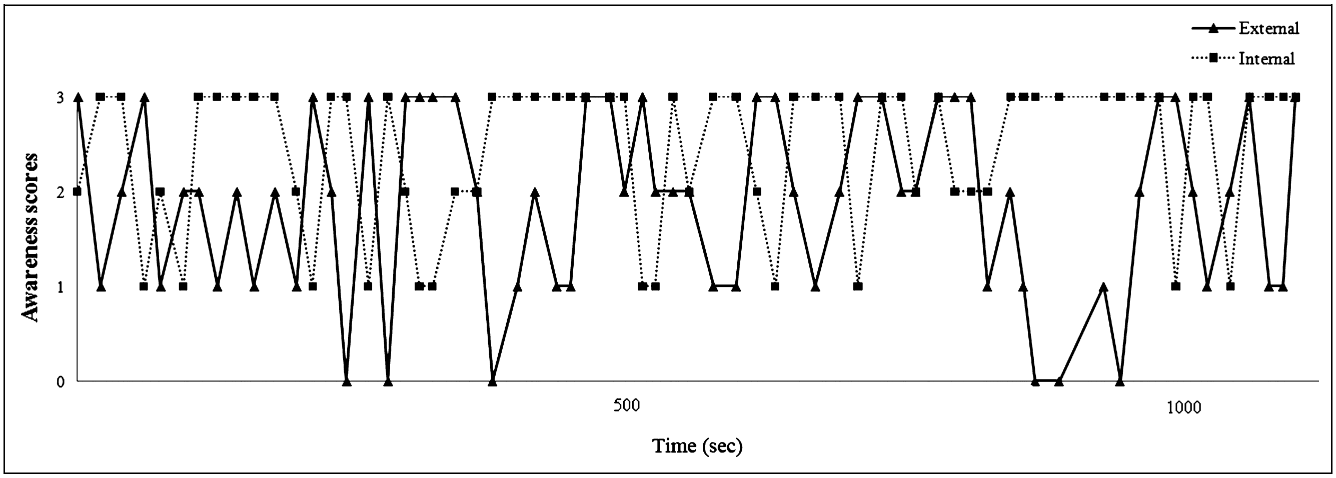

Figure 1. The temporal dynamics of the two components of awareness in a representative subject illustrating that external and internal awareness scores anticorrelate.

nonsignificant correlations. The switching between external and internal awareness was calculated to occur, on average, with a mean frequency of 0.05 ± 0.03 Hz (*SD*) frequency (range = 0.01–0.1 Hz) (Figure 1). External thoughts reported were auditory in 65% of subjects, somesthetic in 58%, olfactory in 13%, and visual in 1%; internal thoughts were experiment-related in 52%, autobiographical in 42%, and inner speech in 13% of subjects. The contents of external and internal awareness are summarized in Table 1.

fMRI Experiment

Scanning was ended when on-line analysis showed at least 15 responses in each state of awareness [meaning 18 ± 2 minutes ($X \pm SD$)]. The intensity of internal awareness intensity correlated linearly with activity in posterior cingulate/precuneal, anterior cingulate/mesiofrontal, and bilateral parahippocampal cortices (whole-brain false discovery rate <0.05; Figure 2, blue areas; Table 2A). The intensity of external awareness scores correlated linearly with activity in the bilateral inferior frontal gyrus and inferior parietal lobule (small-volume correction; Figure 2, red areas; Table 2B). Additional contrasts looking for linear positive correlations with external thoughts only (1.5 0.5 0 0), independently of a linear positive correlation with internal thoughts only (0 0 0.5 1.5), showed similar results.

Reaction times obtained during the fMRI study did not differ when subjects were in "extrinsic" modes as compared to those obtained during "intrinsic" modes of conscious activity [mean (*SD*) 1352 (1132) msec vs. 1427 (837) msec; $t(20) = 0.72$, $p = .48$].The switching between external and internal awareness was calculated (Laguna, Moody, & Mark, 1998) to occur with a mean (*SD*) frequency of 0.03 (0.004) Hz (range = 0.03–0.4 Hz). The mean duration of periods of external [mean (*SD*) = 28 (41) sec] versus internal awareness [29 (66) sec] was not significantly different ($p = .35$).

Table 1. The Contents of the Two Components of Awareness Based on Semi-structured Interview after Completion of the Behavioral Experiment

Content	*Number of Subjects (%)*	*Examples*
External		
Auditory	20 (65)	Hearing sounds from outside the room
Somesthetic	18 (58)	Felt itchiness, uncomfortable body posture
Olfactory	4 (13)	Smelling perfume
Visual	2 (1)	Visual perceptions through closed eyelids
Internal		
Experiment-related	16 (52)	Thoughts related to the length of the study
Autobiographical (future and past)	13 (42)	Vacation, plans for weekend
Inner speech	4 (13)	Instruction to oneself to stay vigilant

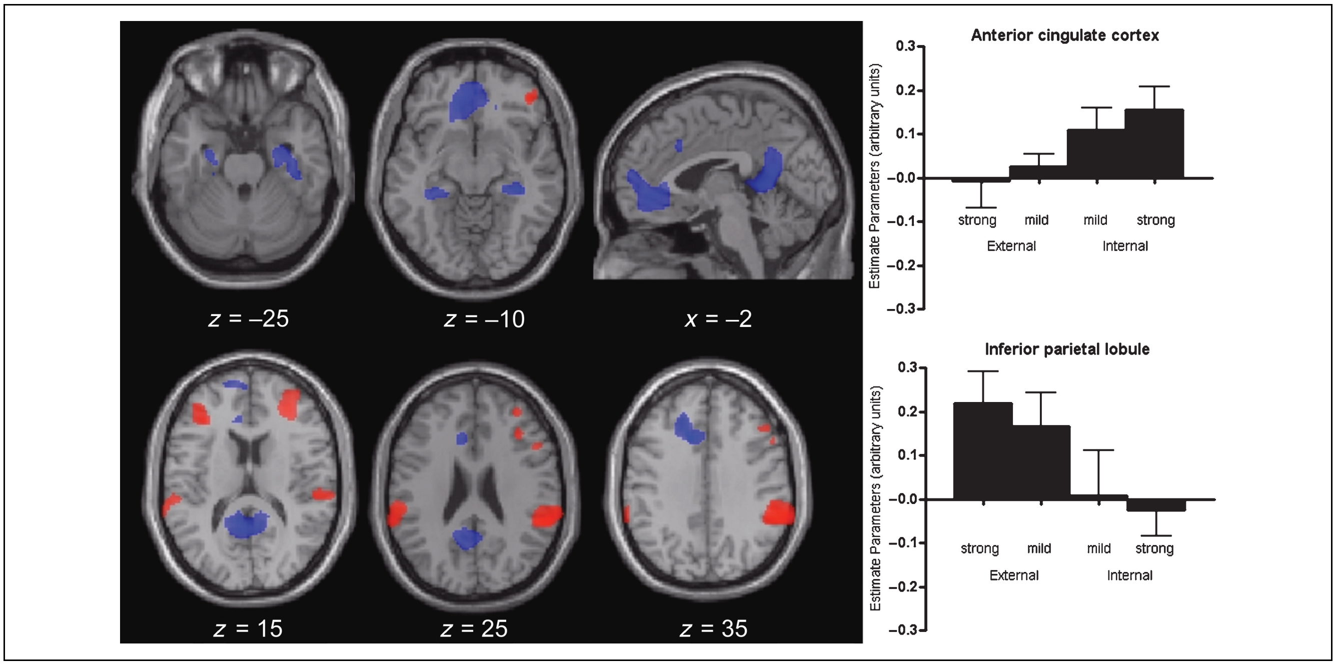

Figure 2. Brain regions showing a correlation between BOLD signal and the intensity of internal and external awareness scores in 22 healthy volunteers. Stronger internal awareness scores correlate with increased activity in anterior cingulate/mesiofrontal, posterior cingulate/precuneal, and parahippocampal cortices (areas in blue). External awareness scores correlate with increased activity in bilateral inferior parietal lobule and dorsolateral prefrontal cortices (in red).

DISCUSSION

Growing neuroscientific evidence supports the idea that the brain's intrinsic or default activity is essential to its global functioning (Raichle & Snyder, 2007). This notion was initially stressed by positron emission tomography studies, which revealed metabolic decreases in specific brain areas (e.g., posterior cingulate/precuneal and anterior cingulate/medial–prefrontal cortices) during performance of specific cognitive tasks as compared to passive resting state (Shulman et al., 1997). Raichle and Snyder (2007) and Raichle et al. (2001) considered these "deactivations" as deviations from an ongoing metabolic/physiologic baseline which characterizes the functionality not only of the aforementioned areas, the so-called default network, but also of most areas of the brain. Searching for joined

Table 2. Peak Voxels of Brain Areas Showing a Positive Correlation with Intensity of External and Internal Awareness

Region	*x (mm)*	*y (mm)*	*z (mm)*	*Z*	*p*
(A) Internal					
PCC/precuneus	−10	−42	8	4.68	<.0001[a]
ACC/mesiofrontal	−12	20	38	5.01	<.0001[a]
Left parahippocampal	−24	−18	−20	3.87	<.0001[a]
Right parahippocampal	38	−30	−10	4.76	<.0001[a]
(B) External					
R Inferior frontal gyrus	38	44	4	2.66	.004[b]
L Inferior frontal gyrus	−36	32	16	2.25	*ns* (.012)
R Inferior parietal	60	−42	32	2.86	.002[b]
L Inferior parietal	−58	−30	22	2.49	*ns* (.006)

R = right; L = left; PCC = posterior cingulate cortex; ACC = anterior cingulate cortex; *ns* = nonsignificant.

[a] False discovery rate corrected.

[b] Small-volume corrected (8 mm radius sphere centered on previously published coordinates).

activations in this "default state," two meta-analyses of positron emission tomography activation protocols with healthy subjects revealed that a network of frontal and parietal heteromodal associative cortices was more active at rest as compared to other cognitive tasks (Mazoyer et al., 2001; Shulman et al., 1997). Such evidence led to the assumption that the brain at rest is not silent. On the contrary, the brain's activity at rest is characterized by spontaneous low-frequency fluctuations, in the range of 0.01–0.1 Hz, which can be detected in the BOLD signal of the fMRI measurement in "resting" conditions. These spontaneous BOLD fluctuations cannot be attributed to peripheral noise (e.g., cardiac and respiratory fluctuations, motion of the subject) but show synchronized activity with other functionally related brain regions (Fox & Raichle, 2007; Cordes et al., 2000). In particular, it is suggested that the brain's baseline activity is organized in two widespread brain networks: "extrinsic" and "intrinsic" (Boly et al., 2007; Fox & Raichle, 2007; Golland et al., 2007; Tian et al., 2007; Fox et al., 2005; Fransson, 2005; Cordes et al., 2000). The extrinsic system encompasses lateral fronto-parietal areas, resembling the brain activations during goal-directed behavior, and it has been linked to cognitive processes of somatosensory (Boly et al., 2007; Bornhovd et al., 2002; Buchel et al., 2002), visual (Fuhrmann, Hein, Tsai, Naumer, & Knight, 2008; Rees, 2007), and auditive (Fuhrmann et al., 2008) external sensory input. The intrinsic system encompasses mainly medial brain areas, is similar to the activity of the default network, and has been associated with cognitive processes such as mind wandering or daydreaming (Mason et al., 2007; McKiernan, D'Angelo, Kaufman, & Binder, 2006), mental imagery (Knauff, Fangmeier, Ruff, & Johnson-Laird, 2003), inner speech and self-oriented thoughts (Goldberg, Harel, & Malach, 2006; Lou et al., 2004).

The present study aimed to bridge the gap between our knowledge on default resting state neural networks as assessed by fMRI and their subjective cognitive counterparts. In our behavioral experiment, we showed a negative correlation between external and internal awareness scores in nearly 80% of the studied subjects (24 out of 31 participants). It should be noted that despite the significant anticorrelation between external and internal modes of conscious processing at the group level, there seems to exist a substantial variability at the individual subject level. Future studies could correlate this variability of conscious content with personality traits (e.g., from normal controls to "schizoid" subjects with dissociative contents of consciousness). We also showed a periodic shift from external to internal awareness occurring, on average, every 20 sec (0.05 Hz), corresponding to the spontaneous low-frequency fluctuations (range of 0.01–0.1 Hz) previously reported (Fox & Raichle, 2007; Cordes et al., 2000). Engagement to demanding self-oriented tasks makes us less receptive to environmental stimuli (James, 1890) and this switch in attention can happen without conscious recognition (Smallwood & Schooler, 2006). In the absence of conscious control, human minds like to wander during both resting periods and heavily loaded cognitive tasks (Giambra, 1995; Antrobus, 1968). Such stimulus-independent thoughts are reported significantly more often during rest than when performing externally oriented tasks (e.g., tone detection task; Filler & Giambra, 1973) and during tasks that are overlearned as compared to novel ones (Goldberg et al., 2006). This unconstrained mental activity was shown to impair signal detection (Giambra, 1995; Singer, 1993), reading (Antrobus, 1968), detailed encoding (Teasdale et al., 1995), and sustained attention tasks (Duval & Wicklund, 1972). In this sense, psychological research suggests that deprivation of external sensory input may result in an increase of internally generated activity (Smallwood, McSpadden, & Schooler, 2008; Schooler, Reichle, & Halpern, 2005; Schooler, 2002; Giambra, 1995). However, clinical cases such as Charles–Bonnet syndrome (i.e., visually impaired patients that experience visual illusions) might counterbalance these findings (Kester, 2009).

Our fMRI study showed a link between the intrinsic and extrinsic brain networks and spontaneous mentation. In the fMRI experiment, subjects' reports of being "strongly externally aware" correlated with activation in the "extrinsic system" (i.e., lateral fronto-parietal areas) and reports of being "strongly internally aware" correlated with activation in the "intrinsic system" (i.e., medial brain areas). Our data are in line with previous studies showing the competing character of the two systems in the sense that these two systems can disturb or even interrupt one another (Tian et al., 2007; Weissman, Roberts, Visscher, & Woldorff, 2006), illustrated also by studies on motor performance (Fox, Snyder, Vincent, & Raichle, 2007), perceptual discrimination (Sapir, d'Avossa, McAvoy, Shulman, & Corbetta, 2005), attention lapses (Weissman et al., 2006), and somatosensory perception of stimuli close to sensory threshold (Boly et al., 2007). These studies have shown that high prestimulus baseline activity in the intrinsic system is associated with a tendency to ignore environmental stimuli, whereas perceived external stimuli were associated with an increased activity in the extrinsic system. The predictive value of the prestimulus baseline activity to behavior has been also shown by studies with EEG (Sapir et al., 2005) and magnetoencephalography (Linkenkaer-Hansen, Nikulin, Palva, Ilmoniemi, & Palva, 2004). It should be noted that, to date, no definite answer can be given as to whether these two systems constitute the causal correlates of internal and external awareness. The sufficiency and necessity of these two components to consciousness remains to be further explored by, for example, transcranial magnetic stimulation lesional protocols or other more invasive methodologies.

Although it has been suggested that the low-frequency fluctuations observed at resting state reflect nothing but vascular processes (Lamme, 2003), others support that they refer to conscious mentation (Goldberg et al., 2006). According to our results, collected via a semi-structured interview, the content of spontaneous thought was preferentially autobiographical and referred to mental images, reminiscent of past experiences and plan making, which correspond to accumulating data that the default network is mediating self-related processes (Golland, Golland, Bentin, & Malach, 2008; Addis, Wong, & Schacter, 2007; Li, Yan, Bergquist, & Sinha, 2007; Mitchell et al., 2007; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Naghavi & Nyberg, 2005; Sapir et al., 2005; Otten & Rugg, 2001). Several other explanations have been introduced for the functional role of the resting state, such that it reflects spontaneous thoughts (Buckner & Carroll, 2007) or that it accounts for the monitoring of the external world (for a review, see Hahn, Ross, & Stein, 2007). Nevertheless, the pervasiveness of the default network after general anesthesia in monkeys (Vincent et al., 2007), in vegetative state (only cortico-cortical connectivity), and its absence in brain death (Boly et al., 2009), reflects a fundamental intrinsic property of the brain's organization that seems to transcend the levels of consciousness (Boly et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008). Future studies could apply the presented methodology to modified states of consciousness such as hypnosis. We hypothesize that in hypnotic resting state, internal and external modes would be dissociated with a predominance of intrinsic network activity.

The critical role of the extrinsic and intrinsic systems to consciousness is well illustrated in cases of impaired conscious states. For example, in the vegetative state (a state of arousal without awareness, Laureys, 2005), systematic metabolic dysfunctions have been identified in a wide fronto-parietal network encompassing the bilateral lateral and frontal regions, the bilateral parieto-temporal and posterior parietal areas, posterior cingulate cortex, and the precuneus (Laureys, 2005; Laureys et al., 1999). In addition, disconnections between latero-frontal and midline posterior areas and between thalamic nuclei and lateral and medial frontal cortices have been also found in vegetative patients (Laureys et al., 1999, 2000). The lack of external and internal awareness is observed not only in these patients but also in slow-wave sleep (Maquet et al., 2005) and in general anesthesia (Kaisti et al., 2003), whereas they resume their functionality during REM sleep (Maquet et al., 2005), supporting our findings.

In conclusion, our data shed light on the neural correlates of awareness' two major dimensions: external or environmental awareness relating to activity in lateral fronto-parietal associative networks and internal awareness relating to midline "default" networks. The study of the functional integrity of these two interdependent brain networks may offer clinical interest in our search for neural markers of awareness in heath and disease (e.g., coma and related "vegetative" states).

Acknowledgments

This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission, the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Fondation Médicale Reine Elisabeth, and the University of Liège. A. V. was funded by ARC 06/11-340, A. D. by the DISCOS Marie-Curie Research Training Network, M. B. is research fellow at the FNRS, Q. N. is a postdoctoral fellow at the FNRS, S. L. and C. P. are senior research associate at the FNRS.

Reprint requests should be sent to Prof. Steven Laureys, Cyclotron Research Center, Sart Tilman-B30, 4000 Liège, Belgium, or via e-mail: steven.laureys@ulg.ac.be.

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E. J. W. Van Someren et al. (Eds.)
Progress in Brain Research, Vol. 193
ISSN: 0079-6123

CHAPTER 20

Hypnotic modulation of resting state fMRI default mode and extrinsic network connectivity

A. Demertzi[†], A. Soddu[†], M.-E. Faymonville[‡], M. A. Bahri[§], O. Gosseries[†],
A. Vanhaudenhuyse[†], C. Phillips[§,¶], P. Maquet[§], Q. Noirhomme[†],
A. Luxen[§] and S. Laureys[†,*]

[†] *Coma Science Group, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liège, Liège, Belgium*
[‡] *Pain Clinic, University Hospital of Liège, Liège, Belgium*
[§] *Cyclotron Research Centre, University of Liège, Liège, Belgium*
[¶] *Department of Electrical Engineering and Computer Science, University of Liège, Liège, Belgium*

Abstract: Resting state fMRI (functional magnetic resonance imaging) acquisitions are characterized by low-frequency spontaneous activity in a default mode network (encompassing medial brain areas and linked to self-related processes) and an anticorrelated "extrinsic" system (encompassing lateral frontoparietal areas and modulated via external sensory stimulation). In order to better determine the functional contribution of these networks to conscious awareness, we here sought to transiently modulate their relationship by means of hypnosis. We used independent component analysis (ICA) on resting state fMRI acquisitions during normal wakefulness, under hypnotic state, and during a control condition of autobiographical mental imagery. As compared to mental imagery, hypnosis-induced modulation of resting state fMRI networks resulted in a reduced "extrinsic" lateral frontoparietal cortical connectivity, possibly reflecting a decreased sensory awareness. The default mode network showed an increased connectivity in bilateral angular and middle frontal gyri, whereas its posterior midline and parahippocampal structures decreased their connectivity during hypnosis, supposedly related to an altered "self" awareness and posthypnotic amnesia. In our view, fMRI resting state studies of physiological (e.g., sleep or hypnosis), pharmacological (e.g., sedation or anesthesia), and pathological modulation (e.g., coma or related states) of "intrinsic" default mode and anticorrelated "extrinsic" sensory networks, and their interaction with other cerebral networks, will further improve our understanding of the neural correlates of subjective awareness.

Keywords: consciousness; hypnotic state; awareness; fMRI; default mode network; functional connectivity.

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*Corresponding author.
Tel.: +32-4-366-23-16; Fax: +32-4-366-29-46
E-mail: steven.laureys@ulg.ac.be

DOI: 10.1016/B978-0-444-53839-0.00020-X

Introduction

Spontaneous brain activity has recently received increasing interest in the neuroimaging community. However, the value of functional magnetic resonance imaging (fMRI) resting-state studies to a better understanding of brain–behavior relationships has been challenged (e.g., Boly et al., 2008). During task-negative conditions, several cerebral networks, characterized by low-frequency dynamic fluctuations, appear to play a potential functional role in sensory and higher cognitive functioning (Damoiseaux et al., 2006). Correlation analysis among these distinct networks has identified functional correlations between distinct somatosensory systems which in turn appear to anticorrelate with an "intrinsic system" or default network (Fox et al., 2005; Tian et al., 2007). More particularly, the "extrinsic" system, encompassing lateral frontoparietal areas, has been linked to processes of externally derived input via somatosensory (Boly et al., 2007; Bornhovd et al., 2002; Buchel et al., 2002), visual and auditory modalities (Fuhrmann et al., 2008; Rees, 2007). The default mode network encompasses midline brain areas and it has been associated with internally oriented cognitive processes, such as mind wandering or daydreaming (Mason et al., 2007; McKiernan et al., 2006), mental imagery (Knauff et al., 2003; Wang et al., 2008), inner speech (Morin and Michaud, 2007), and self-oriented thoughts (Goldberg et al., 2006; Lou et al., 2004). The functional significance of this anticorrelated pattern is not completely understood but there seems to be a link between cerebral function and its conscious behavioral counterpart under healthy situations (Vanhaudenhuyse et al., 2011) and during experimentally manipulated states of unconsciousness, such as anesthesia (Boveroux et al., 2010).

In order to better determine the functional contribution of these anticorrelated networks to consciousness, we sought to transiently modulate their relationship by means of hypnosis. Hypnosis is "a procedure during which a health professional or researcher suggests that a patient or subject experiences changes in sensations, perceptions, thoughts, or behavior" (The Executive Committee of the American Psychological Association—Division of Psychological Hypnosis, 1994) by inducing an altered state of consciousness with a distinct cerebral pattern (Maquet et al., 1999; Rainville et al., 2002). At the phenomenological level, hypnosis is characterized by increased degrees of private processes, such as absorption (i.e., the capacity to remain implicated in a mental state), dissociation (i.e., the mental separation from the environment), disorientation in time, space and person, diminished tendency to judge and censor, whereas it reduces spontaneous thoughts and gives the feeling of one's own response as automatic or extravolitional (Oakley and Halligan, 2009; Rainville and Price, 2003). The experimental manipulation of these basic dimensions of experience is thought to provide leverage to investigate not only the contents of consciousness but also the neural correlates of its background states (Chalmers, 2000).

We here used independent component analysis (ICA) on resting state fMRI acquisitions during normal wakefulness, under hypnotic state and during a control condition of autobiographical mental imagery. The ICA approach to study functional connectivity is a user-independent way to analyze complex signals as it does not require predefined regions of interest or the identification of a seed voxel location and is powerful to separate the neuronal from the global signal and other noise-related signal variations (Beckmann et al., 2005). Hence, the anticorrelations of the resting state cannot be explained as an artifact of the global signal regression, which underlies their biological basis (Fox et al., 2009).

We here hypothesized that, compared to autobiographical mental imagery, subjects under hypnotic state would report a phenomenology of an altered state of consciousness, showing increased "self" absorption, dissociated from decreased external sensory awareness. Recording of "resting state" fMRI networks under hypnosis was predicted to show an altered functional connectivity of both the default mode network and the anticorrelated "extrinsic" system.

Methods

Subjects and procedure

Twelve healthy subjects (4 women, 8 men; mean age 21 years, SD ±3) with no previous neurological or psychiatric history participated in the study after giving written informed consent in accordance with the Ethics Committee of the Faculty of Medicine of the University of Liège. For their inclusion in the study, subjects needed to report an absorption and dissociation level $>6/10$ during a familiarization session with hypnosis which preceded the main experiment. During this session, detailed information about past pleasant life experiences, which the subject wanted to use during hypnotic induction, was obtained through a semi-structured interview as described elsewhere (Faymonville et al., 2003).

The hypnotic state was induced in the same way as in our patients during surgery (Faymonville et al., 1995, 1997, 1999) and as in our previous functional neuroimaging studies with healthy volunteers (Faymonville et al., 2003; Maquet et al., 1999; Vanhaudenhuyse et al., 2009a). The hypnotic instruction encompassed a 3-min induction procedure involving progressive eye fixation and muscle relaxation. Subjects were then invited to reexperience their pleasant autobiographical memories. As in clinical conditions, permissive and indirect suggestions were used to develop and deepen the hypnotic state. Subjects were continuously given cues for maintaining a hypnotic state. The exact words and details of the induction technique and specific suggestions and details during the course of the induction varied depending upon the experimenter's (M.E.F.) observation of subject behavior, and on her judgment of subjects' needs. During the experimental session, the experimenter remained silent.

Data acquisition and analysis

Three scanning sessions were performed: during normal wakefulness, under hypnotic state, and during a controlled condition of mental imagery of autobiographical memories (i.e., the same memories used in hypnotic session but here without the hypnotic induction). In order to exclude carry-over effects, the order of the sessions was randomized across subjects. In all subjects, resting state fMRI data were acquired on a 3T magnetic resonance scanner (Magnetom Allegra; Siemens Medical Solutions, Erlangen, Germany). Three hundred and fifty multislice T_2*-weighted fMRI images were obtained with a gradient echoplanar sequence using axial slice orientation (32 slices, $\text{FoV} = 220 \times 220\ \text{mm}^2$, voxel size $= 3.4 \times 3.4 \times 3\ \text{mm}^3$, 30% interslice gap, matrix size $= 64 \times 64 \times 32$, $\text{TR} = 2460$ ms, $\text{TE} = 40$ ms, $\text{FA} = 90°$). Head movements were minimized using customized cushions. A T1 magnetization prepared rapid gradient echo sequence was also acquired in the same session for coregistration of subject's anatomy with functional data. The most comfortable supine position attainable was sought to avoid painful stimulation related to position. During data acquisition, subjects wore earplugs and headphones through which they were receiving the instructions for the hypnotic induction. After each session, subjects were asked to rate on a 0 (not at all) to 10 (fully) scale their subjective experiences concerning the level of arousal, absorption, dissociation, and external thoughts.

fMRI data were preprocessed and analyzed with "Brain Voyager" software package (Brain Innovation, Maastricht, The Netherlands). Preprocessing of functional scans included 3D motion correction, linear trend removal, slice scan time correction and filtering out low frequencies of up to 0.005 Hz. The data were spatially smoothed with a Gaussian filter of full width at half maximum value of 6 mm. The first three fMRI volumes were discarded to allow for signal equilibration. In two subjects, 197 scans were kept in the analysis due to increased motion across time (i.e., >6 mm). The functional images from each participant were each aligned to the participant's own anatomical scan and warped into the standard anatomical space of Talairach and Tournoux, 1988 by individually defining bounding boxes for the entire brain, using anterior commisure (AC) and posterior commisure (PC) as anchor points for the transformation. ICA, as implemented in "Brain Voyager" (Formisano et al., 2004), was performed using 30 components (Ylipaavalniemi and Vigario, 2008). Then self-organizing ICA (Esposito et al., 2005) permitted a spatial similarity test on single subjects' independent components and an averaged template obtained in seven independent controls (mean age = 48 years, SD ± 13, range: 25–65, 3 females; 300 functional scans acquired on a 3T MR scanner, Trio Tim, Siemens, Germany; gradient echo-planar sequence with axial slice orientation: 32 slices; voxel size: $3.0 \times 3.0 \times 3.75$ mm^3; matrix size: $64 \times 64 \times 32$; repetition time: 2,000 ms, echo time ¼ 30 ms, flip angle: 78°; field of view: 192 mm).

At a first-level analysis, the component of interest (z-map) was transformed into a statistical parametric map (SPM) for each individual subject: the time courses of all components but that of interest (i.e., which contained the z values of the two systems) were used to regress out the initial BOLD signal; the saved residuals represented the BOLD activity of the default mode and the "extrinsic" system. Then by using the time course of the component of interest as a predictor of this residual BOLD activity, the t-maps were obtained. At a second-level analysis, the beta values extracted from the previous step were entered in repeated-measures multiple subjects general linear models (random effects) with three levels (normal wakefulness, hypnotic state, mental imagery). One-sample ANOVAs (FDR corrected $p < 0.05$) were ordered to calculate the mean effects of each level. The contrast between hypnotic state versus mental imagery was ordered. Statistical parametric maps resulting from the voxel wise analysis were considered significant for statistical values that survived a cluster-based correction for multiple comparisons as implemented in Brain Voyager (Goebel et al., 2006) using the "cluster-level statistical threshold estimator" plug-in. This approach to correction for multiple comparisons is based on a 3D extension of the randomization procedure described by Forman and colleagues (Forman et al., 1995). First, voxel-level threshold was set at $t = 2.2$ ($p = 0.05$, uncorrected). Thresholded maps were then submitted to a region of interest (ROI) brain-based correction criterion (masks for the default mode and "extrinsic" systems) that was based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster-level false-positive rates. After 1000 iterations, the minimum cluster size threshold that yielded a cluster-level false positive rate of 5% was applied to the statistical maps. After each session, subjective reports were collected as regards the level of arousal, absorption, dissociation and intensity of external thoughts on a 10-point scale (0: not at all, 10: totally). Wilcoxon's signed-rank tests (SPSS v. 16) were preformed to test the differences in scores within each variable across the three conditions per subject. Results were considered significant at a $p<0.05$ (two-tailed).

Results

Participants reported similar arousal scores during normal wakefulness (6.4 ± 2.0 mean and SD; range 2–10), mental imagery 6.1 ± 1.8 (range 3–8), and hypnotic state (5.3 ± 2.3). Dissociation and absorption scores were higher in hypnotic state as compared to mental imagery and normal wakefulness. Self-reported intensity scores of external thoughts were lower in hypnotic state, as compared to mental imagery and normal wakefulness (Fig. 1).

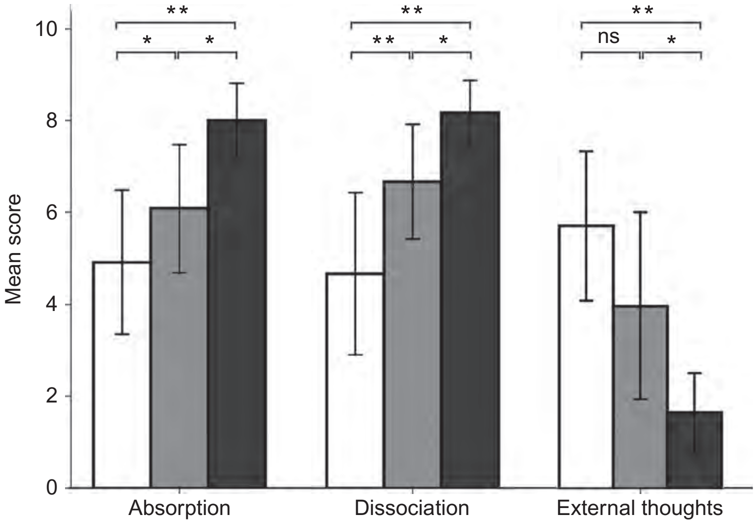

Fig. 1. Absorption, dissociation, and external awareness scores in normal wakefulness (white), autobiographical mental imagery (light gray), and hypnotic state (dark gray) (mean values with 95% confidence intervals; ** $p < 0.01$; *$p < 0.05$).

In normal wakefulness, the identified default mode network encompassed posterior cingulate and adjacent precuneal cortices, anterior cingulate and adjacent medial prefrontal cortices, bilateral angular, middle and inferior temporal, and parahippocampal gyri. The anticorrelated "extrinsic" system encompassed bilateral inferior frontal and supramarginal gyri (Table 1). In autobiographical mental imagery, the identified default mode and anticorrelated "extrinsic" networks encompassed similar areas as described above albeit less widespread (Table 2). In hypnotic state, a further decrease in default mode and "extrinsic" network connectivity extent and intensity was observed, as illustrated graphically in Fig. 2.

The comparison between hypnosis and mental imagery showed an increased connectivity in part of the default network encompassing the middle frontal and bilateral angular gyri whereas the restrosplenial/posterior cingulate and bilateral parahippocampal areas showed a decreased connectivity. The "extrinsic" network did not show any increased connectivity but we identified a decreased connectivity in the right supramarginal and left superior temporal areas in hypnosis as compared to mental imagery (Table 3; Fig. 3).

Discussion

Resting state fMRI acquisitions are characterized by low-frequency spontaneous activity in a default mode network (i.e., relatively decoupled from external input, encompassing medial brain areas and linked to self-related processes; Gusnard and Raichle, 2001) and an anticorrelated "extrinsic" or externally oriented network (i.e., modulated via external sensory stimulation encompassing lateral parietal areas; Damoiseaux et al., 2006; Golland et al., 2007; Raichle et al., 2001). We here aimed to determine how these two networks are influenced by a transient altered conscious state, such as hypnosis. In normal wakefulness, we first identified both networks in accordance to prior studies (Damoiseaux et al., 2006; Fox et al., 2005; Golland et al., 2007; Tian et al., 2007). The relationship between these two

Table 1. Peak voxels of the default mode network and anticorrelated extrinsic system identified in normal wakefulness

	Common names (Brodmann area)	Cluster size (number of voxels)	*x*	*y*	*z*	*t*	*p*
Default mode network							
	Posterior cingulate/precuneus (23, 31, 7)	68,050	−1	−59	24	25.19	<0.001
	Medial prefrontal cortex/anterior cingulate (24, 32, 10)	47,407	−1	40	12	14.89	<0.001
R	Angular gyrus (39)	7287	47	−59	18	11.31	<0.001
L	Angular gyrus (39)	5609	−43	−59	21	8.20	<0.001
R	Middle temporal gyrus (21)	3827	62	−8	−15	6.91	<0.001
L	Middle temporal gyrus (21)	4594	−55	−17	−12	9.66	<0.001
R	Inferior temporal gyrus (38)	521	41	22	−24	5.49	<0.001
L	Inferior temporal gyrus (38)	255	−43	22	−21	5.20	<0.001
L	Postcentral gyrus (2)	313	−13	−29	69	5.97	<0.001
	Medial occipitotemporal gyrus (17)	278	−7	−89	6	4.30	0.001
	Thalamus	421	2	−17	15	4.91	<0.001
	Brainstem	510	−1	−23	−24	7.52	<0.001
	Cerebellar tonsils	252	5	−53	−33	4.95	<0.001
Extrinsic system							
R	Inferior frontal gyrus (45)	10,403	41	1	15	−7.32	<0.001
R	Inferior frontal gyrus (47)	376	47	31	0	−5.10	<0.001
L	Inferior frontal gyrus (47)	12,612	−49	19	−3	−7.98	<0.001
R	Supermarginal gyrus (40)	3971	53	−32	24	−7.02	<0.001
L	Supermarginal gyrus (40)	2923	−67	−29	15	−5.79	<0.001
L	Superior frontal gyrus (9)	1416	−40	37	27	−5.58	<0.001
L	Medial frontal gyrus (32)	4130	−4	7	45	−7.67	<0.001
L	Precentral gyrus (6)	615	−46	−2	45	−5.05	<0.001
L	Inferior occipital gyrus (19)	469	−43	−53	0	−5.21	<0.001
	Anterior cingulate gyrus (24)	437	17	−20	42	−5.44	<0.001

Stereotaxic coordinates are in normalized Talairach space, *p* values are FDR corrected for multiple comparisons at the whole brain level.

networks at conscious resting state has been previously characterized as competing, where one system can disturb or even interrupt the other (Boly et al., 2008; Fox et al., 2005; Golland et al., 2007; Tian et al., 2007) with a consequence on the way we perceive the external world. For example, this ongoing resting activity has been shown to mediate sensory awareness in the sense that increased activity in the "extrinsic" frontoparietal network seemed to facilitate the conscious perception of low-intensity somatosensory stimuli, whereas unperceived intensity-matched stimuli were preceded by increased activity in the default mode network (Boly et al., 2007). Previous studies have also shown that increasing attentional demands in cognitive tasks lead to decreased activity in the default mode network (McKiernan et al., 2003) and lapses in attention were shown to correlate with reduced prestimulus activity in the anterior cingulate and right prefrontal regions, areas involved in controlling attention (Weissman et al., 2006). We recently showed that this opposed functionality of the default mode and anticorrelated "extrinsic" system has a cognitive behavioral counterpart. Explicit subjective reports for increased intensity of "internal" awareness (i.e., self-related stimulus-independent processes) were related to increased connectivity in the default network, whereas increased "external" awareness scores (i.e., perception of the environment) was associated with increased connectivity in the

Table 2. Peak voxels of the default mode network and anticorrelated extrinsic system identified in mental imagery (A) and hypnotic state (B)

Common names (Brodmann area)		Cluster size (number of voxels)	*x*	*y*	*z*	*t*	*p*
A. Mental imagery							
Default mode network							
	Posterior cingulate/precuneus (23, 30, 7)	31,502	–7	–53	12	19.79	<0.001
	Medial prefrontal cortex/anterior cingulate (32)	11,372	2	49	3	14.44	<0.001
R	Angular gyrus (39)	1908	38	–62	21	6.08	<0.001
L	Angular gyrus (39)	2068	–40	–62	27	6.8	<0.001
R	Parahippocampal gyrus (35)	2874	26	–26	–15	10.08	<0.001
R	Middle frontal gyrus (8)	923	23	19	42	6.46	<0.001
L	Middle frontal gyrus (8)	823	–22	19	36	6.67	<0.001
L	Superior temporal gyrus (38)	309	–34	22	–24	5.41	<0.001
R	Middle occipital gyrus (17)	234	17	–89	–3	5.38	<0.001
	Cerebellar tonsil	340	–10	–56	–33	5.45	<0.001
Extrinsic system							
R	Inferior frontal gyrus (44)	4167	47	7	6	–8.05	<0.001
L	Inferior frontal gyrus (6)	3063	–49	4	21	–7.15	<0.001
L	Inferior frontal gyrus (44)	1461	–43	34	18	–5.48	<0.001
R	Supermarginal gyrus (40)	5863	53	–32	36	–7.49	<0.001
L	Supermarginal gyrus (40)	4715	–61	–32	33	–8.17	<0.001
R	Middle occipital gyrus (17)	337	29	–80	9	–5.61	<0.001
B. Hypnotic state							
Default mode network							
	Posterior cingulate/precuneus (31)	14,718	–4	–56	30	17.95	<0.001
	Anterior cingulate/mesiofrontal (32)	8272	–4	28	–9	7.29	<0.001
R	Angular gyrus (39)	3755	44	–59	24	12.75	<0.001
L	Angular gyrus (39)	1598	–49	–56	21	6.85	<0.001
R	Superior frontal gyrus (8)	534	23	19	48	7.04	<0.001
L	Superior frontal gyrus (10)	624	–13	46	18	8.24	<0.001
R	Middle temporal gyrus (38)	216	56	–8	–15	6.51	<0.001
Extrinsic system							
R	Inferior frontal gyrus (45)	440	32	31	9	–7.57	<0.001
L	Inferior frontal gyrus (44)	637	–43	4	6	–6.04	<0.001

Stereotaxic coordinates are in normalized Talairach space, *p* values are FDR corrected for multiple comparisons at the whole brain level.

“extrinsic” system (Vanhaudenhuyse et al., 2011), confirming the functional significance underlying the activity of both resting networks to conscious experience in health and disease (e.g., Laureys et al., 2007; Qin et al., 2010).

The selection of a control condition for hypnotic state remains challenging as, a priori, no cerebral state is close to hypnotic state. Thus, results from studies with hypnosis need to be interpreted based on the chosen control condition because the generation of different types of mental images will be associated with different cerebral activation patterns (e.g., Gardini et al., 2005; Ishai et al., 2000). We here chose to study hypnotic state as we use it in the clinical setting and during surgery (Faymonville et al., 1997,

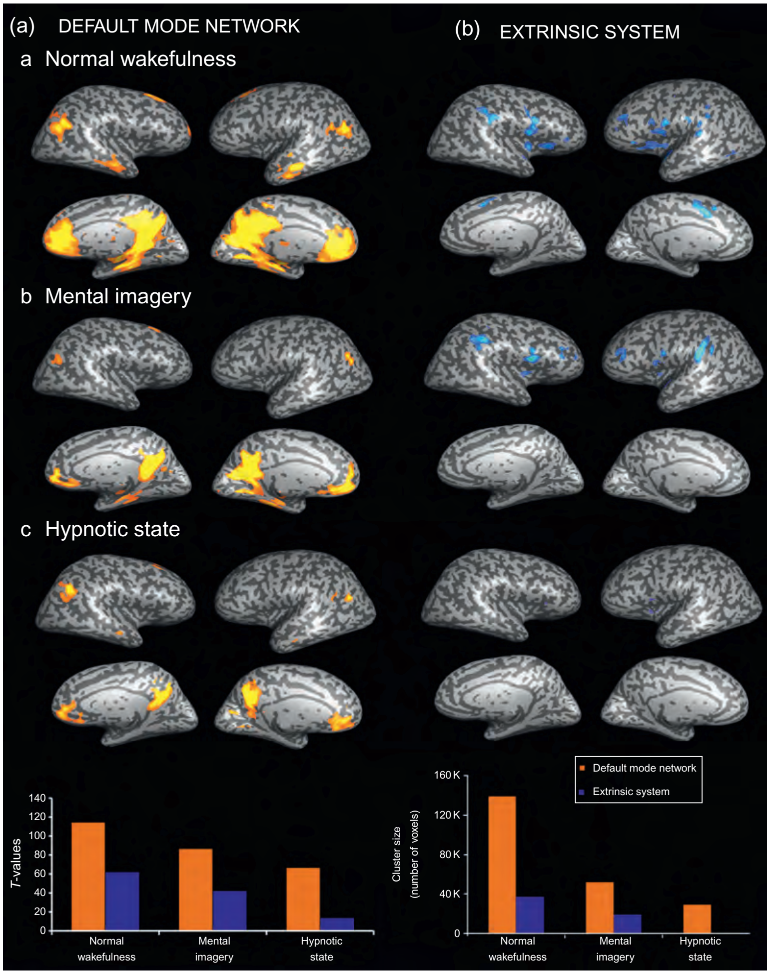

Fig. 2. The default mode network (a) and its anticorrelated "extrinsic" system (b) under normal wakefulness, mental imagery, and hypnotic state. Results are thresholded at whole brain false discovery rate corrected $p < 0.05$. The graphs illustrate the global connectivity strength (left; summed T values of all identified clusters in the random effect analysis) and extend (right; total number of voxels of all identified clusters) in both networks during the three conditions.

2000), asking subjects to revive pleasant autobiographical memories. Hence, our control condition employed mental imagery of pleasant autobiographical memories without induction of hypnosis because it is characterized by a polymodal content (motor, visual, and contextual) of episodic nature (Conway and Pleydell-Pearce, 2000).

We here observed that, in comparison to autobiographical mental imagery, under hypnosis the "extrinsic" system exhibited reduced functional connectivity, whereas the default network showed reduced connectivity in its posterior midline and parahippocampal structures but increased connectivity in its lateral parietal and middle frontal areas. The hypnosis-related increases in cerebral connectivity is in line with previous activation studies showing enhanced functional connectivity of anterior midline structures during hypnotic

Table 3. Peak voxels of areas showing increased and decreased connectivity in (A) the default mode network and (B) extrinsic system in hypnotic state as compared to mental imagery

Common names (Brodmann area)		Cluster size (number of voxels)	*x*	*y*	*z*	*t*	*p*
A. Default mode network							
Increases in connectivity							
R	Medial prefrontal (10)	2417	8	62	18	3.53	0.005
L	Angular gyrus (39)	997	−58	−52	18	3.21	0.008
R	Angular gyrus (39)	775	51	−59	33	3.03	0.011
Decreases in connectivity							
L	Parahippocampal gyrus (35)/ Posterior cingulate (30)	19,088	−25	−23	−18	−6.33	<0.0001
B. Extrinsic system							
Increases in connectivity							
–							
Decreases in connectivity							
R	Supermarginal gyrus (40)	385	47	−39	27	−2.98	0.013
L	Superior temporal gyrus (22)	936	−68	−32	18	−4.64	0.001

Stereotaxic coordinates are in normalized Talairach space, *p* values are cluster level corrected.

analgesia (Faymonville et al., 2003). Frontal increases in regional cerebral blood flow have also previously been demonstrated by positron emission tomography (PET) in the hypnotic state (e.g., Faymonville et al., 2000; Rainville et al., 1999) However, a recent fMRI study showed a hypnosis-related reduction in default mode connectivity in the middle frontal areas (McGeown et al., 2009). These divergent findings may be explained by the distinct suggestion instructions used to induce hypnosis and the different experimental fMRI designs utilized. In our study, we acquired continuous eyes-closed resting state data during each condition where pleasant autobiographical memories were performed during both hypnosis and the control mental imagery task. McGeown et al. (2009) employed a block design comparing an eyes-open visual perceptual task with and without hypnosis. It could also be that the observed persisting activity in the anterior midline part of the default network in our study is due to the chosen less challenging experimental conditions (Greicius and Menon, 2004).

The observed reduction in connectivity of the posterior midline parts of the default mode network during hypnosis might reflect a decreased degree of continuous information gathering from the external world with its relation to oneself (Gusnard and Raichle, 2001). These posterior retrosplenial, cingulate, and precuneal areas of the default network have been previously associated with various cognitive functions, such as visuospatial orientation, episodic memory retrieval, and self-processing (e.g., self-relevance, social cognition, visuospatial perspective taking, and agency; Cavanna and Trimble, 2006) and support functions concerning both orientation within, and interpretation of, the environment (Vogt and Laureys, 2005). The special contribution of the precuneus to consciousness is supported by evidence of its dysfunction in profound unconscious states, such as deep sleep (Horovitz et al., 2009), pharmacological coma (Boveroux et al., in press), and pathological coma and vegetative states (Laureys et al., 1999; Vanhaudenhuyse et al., 2009b) suggesting that it is a critical node in the neural network subserving conscious

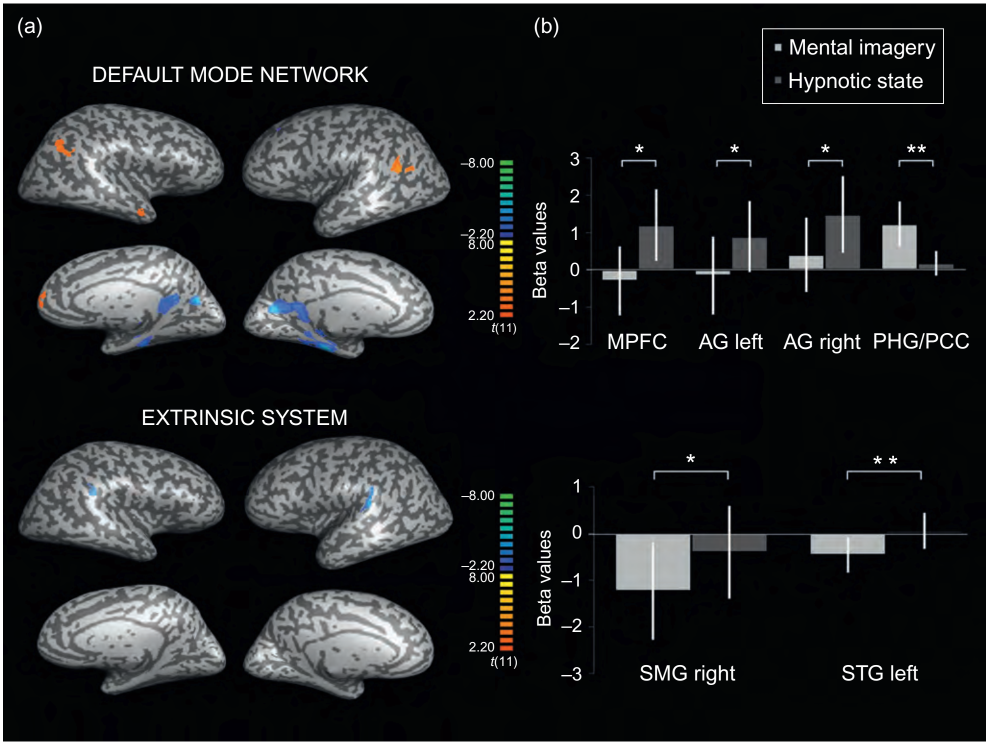

Fig. 3. Increased (in red) and decreased (in blue) functional connectivity in the default mode network and its anticorrelated "extrinsic" system. Results are thresholded at cluster level corrected $p < 0.05$. The graph illustrates the effect size in the medial prefrontal cortex (MPFC), bilateral angular gyri (AG), and parahippocampal gyrus/posterior cingulate cortex (PHG/PCC) for the default mode network and in the temporoparietal cortices (supramarginal gyrus-SMG and superior temporal gyrus-STG) for the extrinsic system (mean beta values and 95% confidence intervals).

experience (Baars et al., 2003). Our results on decreased connectivity of retrosplenial and posterior cingulate cortices extend previous PET studies demonstrating prominent reductions in regional blood flow and metabolism in these posterior midline structures during the hypnotic state (e.g., for review, see Faymonville et al., 2006).

The generation of autobiographical episodic mental images, as evoked in the present study in both normal and hypnotic conditions, is known to involve posterior cingulate, precuneal, and parahippocampal areas (Gardini et al., 2006). The reported reduced connectivity in the latter can be related to posthypnotic amnesia (Barber, 2000), thought to involve a disruption of retrieval processes similar to the functional amnesias observed in clinical dissociative disorders (Kihlstrom, 1997).

The decreased functional connectivity observed in the lateral frontoparietal "extrinsic" system, along with the subjective reports of diminished external awareness, might reflect a blockage of the sensory systems to receive sensory stimuli as a result of hypnotic suggestion which was shown to induce (Derbyshire et al., 2004) or alter somatosensory perceptions (Cojan et al., 2009). Increasing evidence points to the critical role of lateral associative frontoparietal cortical network in the emergence of conscious sensory perception (e.g., Boveroux et al., 2008; Laureys, 2005). The observed hypnosis-induced decreased frontoparietal connectivity could elucidate the clinical finding that patients undergoing surgery during hypnosedation (e.g., Faymonville et al., 1997) show modified phenomenological sensory awareness of their aversive encounters (e.g., see Kupers et al., 2005).

Our results are also in line with a previous suggested framework (Soddu et al., 2009), where it was hypothesized that a hypofunctional "extrinsic" system and a preserved default network activity would account for the participants' subjective experience of disengagement from their external environment leading to a "self-centered absorption" state, translated into a reduced sensory responsivity (i.e., limitation of sensory input or reduced motor output). Indeed, according to the behavioral data, participants reported a higher degree of absorption and dissociation from their surroundings during hypnosis as compared to mental imagery and normal wakefulness. Past phenomenological analysis of reports from subjects in hypnotic state suggests a diminished tendency to judge and monitor, a disorientation in time, space, and person and the experience of one's own response as automatic (Rainville and Price, 2003). Such increased absorption and dissociation levels during hypnotic state account for its antinociceptive effects during various surgical procedures, where hypnosis in combination with local anesthesia and minimal conscious sedation (i.e., "hypnosedation") is used to reduce pain, anxiety, intraoperative use of anxiolytic and analgesic drugs as well as faster recovery of the patient (Faymonville et al., 1998, 2006).

In conclusion, hypnosis-induced modulation of resting state fMRI networks, as compared to mental imagery, seems to result in a reduced "extrinsic" lateral frontoparietal cortical connectivity, possibly reflecting a decreased sensory awareness. The default mode network showed an increased connectivity in bilateral angular and middle frontal gyri whereas its parahippocampal and posterior midline structures decreased their connectivity during hypnosis, putatively related to an altered "self"-awareness and posthypnotic amnesia. In our view, fMRI "resting state" studies of physiological (e.g., sleep or hypnosis), pharmacological (e.g., sedation or anesthesia), and pathological modulation (e.g., coma or related states) of "intrinsic" default mode and anticorrelated "extrinsic" sensory networks and their interaction with other cerebral networks will further improve our understanding of the neural correlates of subjective awareness.

Acknowledgments

This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission (DISCOS, Marie-Curie Actions), the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Fondation Médicale Reine Elisabeth and the University of Liège.

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J Neurol (2011) 258:1058–1065
DOI 10.1007/s00415-010-5882-z

ORIGINAL COMMUNICATION

Attitudes towards end-of-life issues in disorders of consciousness: a European survey

**A. Demertzi · D. Ledoux · M.-A. Bruno ·
A. Vanhaudenhuyse · O. Gosseries · A. Soddu ·
C. Schnakers · G. Moonen · S. Laureys**

Received: 23 July 2010 / Revised: 13 December 2010 / Accepted: 14 December 2010 / Published online: 8 January 2011

Abstract Previous European surveys showed the support of healthcare professionals for treatment withdrawal [i.e., artificial nutrition and hydration (ANH) in chronic vegetative state (VS) patients]. The recent definition of minimally conscious state (MCS), and possibly research advances (e.g., functional neuroimaging), may have lead to uncertainty regarding potential residual perception and may have influenced opinions of healthcare professionals. The aim of the study was to update the end-of-life attitudes towards VS and to determine the end-of-life attitudes towards MCS. A 16-item questionnaire related to consciousness, pain and end-of-life issues in chronic (i.e., >1 year) VS and MCS and locked-in syndrome was distributed among attendants of medical and scientific conferences around Europe ($n = 59$). During a lecture, the items were explained orally to the attendants who needed to provide written yes/no responses. Chi-square tests and logistic regression analyses identified differences and associations for age, European region, religiosity, profession, and gender. We here report data on items concerning end-of-life issues on chronic VS and MCS. Responses were collected from 2,475 participants. For chronic VS (>1 year), 66% of healthcare professionals agreed to withdraw treatment and 82% wished not to be kept alive ($P < 0.001$). For chronic MCS (>1 year), less attendants agreed to withdraw treatment (28%, $P < 0.001$) and wished not to be kept alive (67%, $P < 0.001$). MCS was considered worse than VS for the patients in 54% and for their families in 42% of the sample. Respondents' opinions were associated with geographic region and religiosity. Our data show that end-of-life opinions differ for VS as compared to MCS. The introduction of the diagnostic criteria for MCS has not substantially changed the opinions on end-of-life issues on permanent VS. Additionally, the existing legal ambiguity around MCS may have influenced the audience to draw a line between expressing preferences for self versus others, by implicitly recognizing that the latter could be a step on the slippery slope to legalize euthanasia. Given the observed individual variability, we stress the importance of advance directives and identification of proxies when discussing end-of-life issues in patients with disorders of consciousness.

Keywords Ethics · Vegetative state · Minimally conscious state · Euthanasia · End-of-life · Survey

Introduction

Technological developments in the intensive care led to the survival of severely brain-damaged patients who, until that time, would have died almost instantly from apnea. These patients survive in states of disordered consciousness ranging from coma, vegetative state (VS) and minimally conscious state (MCS). Patients in coma lie with their eyes closed, show no awareness of themselves and their surroundings, and never open their eyes even when intensively stimulated [1]. Patients in VS regain phenomenal sleep-wake cycles but their motor, auditory, and visual functions

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A. Demertzi · D. Ledoux · M.-A. Bruno ·
A. Vanhaudenhuyse · O. Gosseries · A. Soddu ·
C. Schnakers · S. Laureys (✉)
Coma Science Group, Cyclotron Research Centre,
University of Liège, Allée du 6 août no 8,
Sart Tilman B30, 4000 Liège, Belgium
e-mail: steven.laureys@ulg.ac.be

G. Moonen · S. Laureys
Department of Neurology, University Hospital of Liège,
Sart Tilman B-35, 4000 Liège, Belgium

are restricted to mere reflexes [2]. Patients in MCS manifest fluctuating signs of purposeful behavior, may follow simple commands, show gestural or verbal yes/no responses regardless of accuracy, and/or may verbalize intelligibly [3]. In some cases, patients' cognitive abilities are preserved but are not evident due to limited motor capacities, such as quadriplegia or quadriparesis. Such patients are considered to be locked-in [4], and are not among patients with disorders of consciousness although they can be mistaken for unconsciousness [5, 6]. Prolonged survival in these profound unconscious states has been raising medical, ethical, and public policy controversies mainly stemming from how different people regard indefinite survival in such states [7]. By means of a wide European survey among healthcare professionals, we here aimed at updating the end-of-life attitudes towards the VS and determining for the first time in a consistent way the attitudes towards MCS.

Methods

A questionnaire was distributed during lectures at medical and scientific conferences and meetings ($n = 59$) within Europe (data were collected between September 2007 and October 2009). To ensure comparability of responses, participants were first introduced to the clinical definitions of disorders of consciousness and were then asked to provide 'yes' or 'no' answers to 16 questions related to consciousness, chronic VS (i.e., >1 year), chronic MCS (i.e., >1 year) and locked-in syndrome (LIS). We here report the replies obtained in European medical and paramedical professionals to the questions: 'Being in a chronic VS is worse than death for the patient/for the family'; 'Being in a chronic MCS is worse than being in a VS for the patient/for the family'; 'Do you think that it is acceptable to stop treatment (i.e., artificial nutrition and hydration-ANH) in patients in chronic VS?'; 'Do you think that treatment can be stopped in patients in chronic MCS?'; 'Would you like to be kept alive if you were in a chronic VS?'; 'Would you like to be kept alive if you were in a chronic MCS?'. The remaining 10 questions related to consciousness [8] and pain [9] have been reported before. Demographic data including age, gender, nationality, profession, and religious beliefs were recorded. Religiosity was defined as the belief in a personal god belonging to an institutionalized religion (i.e., Christianity, Islam, Judaism) independently of practicing. Nationalities were categorized into three geographic regions based on previous classification criteria [10]: Northern (Denmark, Estonia, Finland, Lithuania, Netherlands, Norway, Poland, Russia, Sweden, UK), Central (Austria, Belgium, Czech Republic, Germany, Hungary, Luxembourg, Moldavia, Romania, Serbia, Slovakia, Slovenia, Switzerland), and Southern Europe (Bulgaria, Croatia, Cyprus, France, Greece, Italy, Portugal, Spain, Turkey, the former Yugoslav Republic of Macedonia). Statistical analyses were performed using SPSS v.16.0 software package. Chi-square tests assessed differences within and between categorical variables. Multiple logistic regressions (enter method) were used to examine and test the associations of the odds for agreement with the questions with five predictor variables (age, profession, European region, religiosity, and gender). Results were considered significant at $P < 0.05$ (two-sided). The study was approved by the ethics committee of the University of Liège. Completion of the questionnaire was voluntary, anonymous, and considered as consent for participation in the survey.

Results

The study sample included 2,475 medical and paramedical professionals coming from 32 European countries (see Table 1 for demographic data). The attitudes towards end-of-life statements for VS and MCS as expressed by the whole sample are summarized in Fig. 1. Respondents more often wished not to be kept alive themselves as compared to accepting to let others die in VS ($P < 0.001$) and MCS ($P < 0.001$) and this dissociation was more important for MCS as compared to VS (interaction analysis; $P < 0.001$). Participants' end-of-life attitudes towards VS and MCS differed based on the three geographic regions (Fig. 2) and religiosity, professional background and gender (Table 2).

Table 1 Demographic characteristics of the studied sample ($n = 2{,}475$)

Age (years), mean ± SD (range)	39 ± 14 (18–88)
Gender, no. (%)	
Women	1,314 (53%)
Men	1,098 (44%)
Missing data	63 (3%)
Respondents by European Region, no (%)	
Northern	402 (16%)
Central	1,213 (49%)
South	855 (35%)
Missing data	5 (0%)
Profession, no. (%)	
Medical professionals	1,608 (65%)
Paramedical professionals	651 (26%)
Missing data	216 (9%)
Religiosity, no. (%)	
Religious respondents	1,407 (57%)
Non-religious respondents	1,004 (40%)
Missing data	64 (3%)

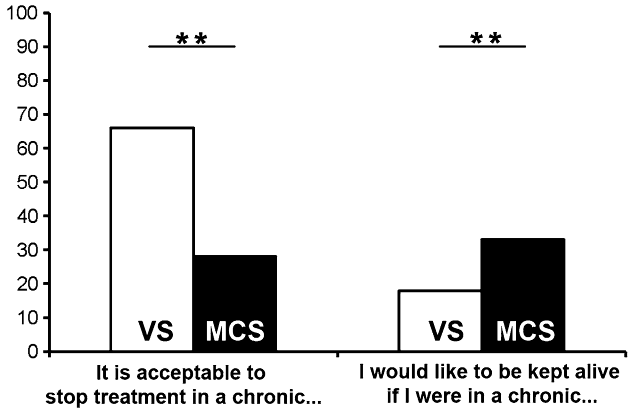

Fig. 1 End-of-life attitudes towards the vegetative state (*VS*) and minimally conscious states (*MCS*) as expressed by 2,475 medical and paramedical professionals. Bars represent % agreement (**$P < 0.001$)

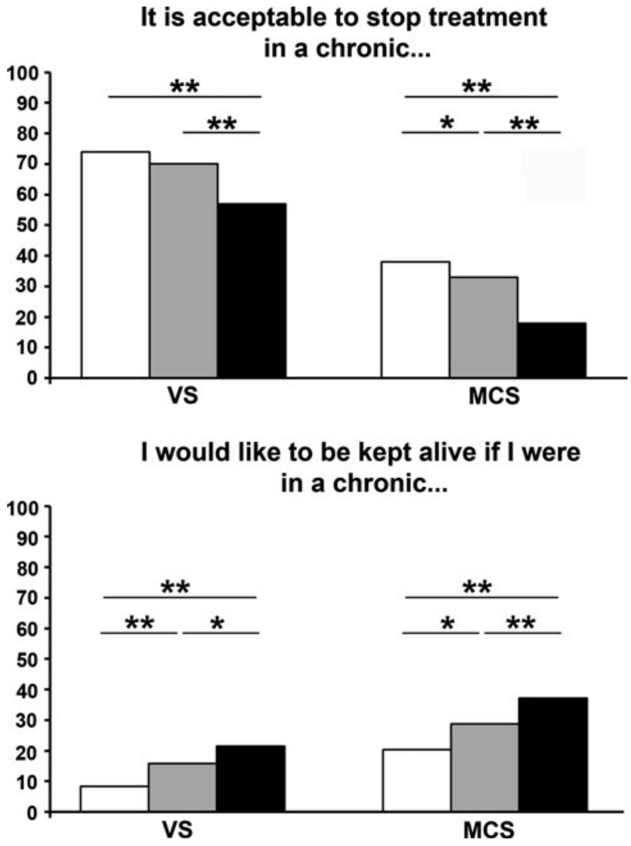

Fig. 2 End-of-life attitudes towards the vegetative state (*VS*) and minimally conscious states (*MCS*) depending on geographic region. Bars represent % agreement (*white*: Northern, *grey*: Central, *black*: Southern Europe; *$P < 0.05$, **$P < 0.001$)

Multiple logistic regression analysis showed that agreement with these questions was mainly associated with geographic region and respondents' religiosity (Table 3).

Chronic MCS was considered worse than VS more so from the perspective of the patient (54%) as compared to that of the family (42%; $P < 0.001$). Inversely, respondents found that chronic VS is worse than death more so from the perspective of the family (80%) as compared to that of the patient (55%; $P < 0.001$).

Discussion

Our attempt to open a discussion on treatment withdrawal from patients with chronic disorders of consciousness (VS, MCS) is not an easy one. We here surveyed end-of-life attitudes of European medical and paramedical professionals ($n = 2{,}475$) towards VS [now called 'unresponsive wakefulness syndrome', 11] and determined, for the first time, attitudes towards the recently defined entity of MCS [3]. Concerning chronic VS (i.e., lasting more than one year and, hence, considered as permanent), two-thirds of the surveyed participants reported that it was acceptable to withdraw ANH from these patients and most (82%) preferred not to be kept alive if they imagined themselves in this condition. These results are in line with surveys from previous decades, where the majority of physicians, despite different cultural background, would generally support ANH withdrawal from VS patients and would not wish life-sustaining treatments for themselves (Table 4). Here, although agreement with withdrawal of treatment was somewhat less as compared to historical data, possibly due to different adopted research methodologies, the surveyed sample expressed similar end-of-life attitudes towards permanent VS despite the recent introduction of the diagnostic criteria for MCS [12], the recent confirmation of potential diagnostic error in VS patients [12], the apparent evidence for residual cognitive processing coming from functional neuroimaging technologies [13, 14] and the potential prognostic value of the latter [15].

Concerning chronic MCS, there were clear differences in opinions as compared to permanent VS: although almost 70% would not wish to be kept alive in this state, recognizing it to be worse than VS, less than one-third of our respondents supported treatment withdrawal from these patients. Such differences in attitudes between VS and MCS are comparable to a previous survey, where 92% of British physicians considered it appropriate to withdraw ANH from patients for whom the predicted outcome was VS and only 22% would think so for patients who were able to communicate simple needs without the capacity for speech production [16]. Our data are opposed to the proposed view that the distinction between MCS and VS is artificial and unneeded [17]. We illustrated that most healthcare professionals hold different views on end-of-life issues for VS as compared to MCS. Similarly, outcome studies [18–20] and neuroimaging studies [21] have stressed the importance to disentangle both clinical entities.

Table 2 End-of-life attitudes towards vegetative (VS) and minimally conscious states (MCS) depending on professional background, religiosity and gender

Question	Type of profession		Religiosity		Gender	
	Medical professionals	Paramedical professionals	Religious respondents	Non-religious respondents	Men	Women
It is acceptable to stop treatment in						
… chronic VS	1,053 (67%)	433 (67%)	844 (61%)	729 (74%)**	739 (68%)	836 (65%)
… chronic MCS	429 (27%)	215 (33%)*	308 (22%)	363 (37%)**	307 (28%)	371 (29%)
I would like to be kept alive if I were in						
… chronic VS	295 (19%)	79 (12%)**	318 (23%)	107 (11%)**	217 (20%)	206 (16%)*
… chronic MCS	552 (35%)	157 (24%)**	570 (41%)	217 (22%)**	383 (35%)	399 (31%)*

VS vegetative state, *MCS* minimally conscious state

* $P < 0.05$, ** $P < 0.001$

Table 3 Logistic regression of agreement vs. disagreement with the four end-of-life related questions on participants' predictor variables

Predictor variable	It is acceptable to stop treatment in chronic VS Odds ratio (95% CI)	It is acceptable to stop treatment in chronic MCS Odds ratio (95% CI)	I would like to be kept alive if I were in chronic VS Odds ratio (95% CI)	I would like to be kept alive if I were in chronic MCS Odds ratio (95% CI)
Age[a]	0.98 (0.97–0.99)**	0.98 (0.98–0.99)**	1.01 (1.01–1.02)*	1.00 (0.99–1.01)
Women	0.79 (0.64–0.97)*	0.91 (0.73–1.13)	0.87 (0.67–1.12)	0.92 (0.75–1.13)
Southern Europe	1	1	1	1
Northern Europe	3.36 (2.38–4.74)**	3.82 (2.79–5.23)**	0.34 (0.21–0.55)**	0.47 (0.34–0.66)**
Central Europe	1.84 (1.49–2.26)**	2.24 (1.77–2.83)**	0.72 (0.56–0.92)*	0.69 (0.56–0.85)**
Medical professionals	1.18 (0.94–1.49)	0.91 (0.73–1.15)	1.18 (0.88–1.59)	1.28 (1.02–1.62)*
Religious respondents	0.45 (0.37–0.55)**	0.46 (0.37–0.55)**	2.20 (1.70–2.85)**	2.24 (1.84–2.73)**

Predicted response: 'agreement'. An odds ratio higher than 1 signifies more agreement with the statement, whereas an odds ratio less than 1 notifies less agreement

VS vegetative state, *MCS* minimally conscious state

* $P < 0.05$, ** $P < 0.001$

[a] For continuous variables, the odds ratio equals the relative change in the odds ratio when the variable is increased by one unit

Additionally, the distinction between personal preferences with private consequences (i.e., 'I would like to be kept alive if I were…') and more objective statements of societal significance (i.e., 'It is acceptable to stop treatment in…') are in accordance with previous findings showing that the majority of surveyed physicians and nurses would refuse treatment for themselves more than for patients [22]. The legal ambiguity which exists around MCS may have influenced the audience to draw a virtual line between expressing preferences for self versus others, by implicitly recognizing that the latter could be a step on the slippery slope to legalize killing [23], a controversial issue around Europe judging from the legislation diversities among European countries [24].

We empirically showed that the majority of our sample (80%) considered chronic VS worse than death and that this was more relevant for the patient's family. It should be noted that this is an emotionally loaded statement which could influence subsequent answers. In principle, we are unable to account with certainty for the sample's responses, especially in the case of MCS where opinions appeared more dissociated. Such results may be due to the different outcome which characterizes VS and MCS [25], or the potential pain perception that the sample ascribes to MCS [9], or the distinct brain activation patterns of these two clinical entities [26]. We preferred, though, to use the present formulation of questioning so as to evaluate in a comparable way our data with past surveys' results [e.g., 22, 27; also Table 4]. Likewise, in order to permit comparisons between items, MCS and LIS questions were formulated in a similar manner as those for VS. The present survey setup (i.e., on the spot data collection as opposed to mailing questionnaires) allowed the audience to ask for clarifications when an item was not well

Table 4 Past surveys on end-of-life attitudes

Statement	Audience (*n*)	Agreement (%)	References
Withdrawal of ANH from patients who will remain in a VS is ethically justified	Physicians (208)	94	[49]
Withdrawal of ANH from patients who will remain in a VS is ethically justified	Physicians (1,027)	94	[37]
It is ethical to withhold or withdraw ANH from PVS patients	Neurologists (169)/Medical directors (150)	88/89	[50]
I am in favour of withdrawing feeding tube from a PVS patient	Internists (326)	80	[51]
I would desire ANH if I were in a PVS	Neurologists (169)/Medical directors (150)	10/13	[50]
I do not wish to be treated if I were in a PVS	Physicians (115)/Nurses (127)	90/89	[22]
I would refuse artificial feeding if I were permanently comatose	Physicians (345)	92	[52]

ANH artificial nutrition and hydration, *VS* vegetative state, *PVS* permanent vegetative state

understood. We also document that significantly more physicians prefer to be kept alive if in chronic MCS as compared to paramedical professionals (Table 2). The reasons for these differences remain speculative and beyond the scope of the present study. Future studies should tackle the importance of the nature of the respondents on end-of-life issues and possible differences between medical caregivers and the general public. Given the observed individual variability in these emotionally highly charged matters we stress the need for advance directives and proxy identification, acknowledging their known limitations such as vague or misleading statements of wishes [28], negation of previously expressed wishes when illness is an actual fact [29] and inconsistency in preferences over time [30]. Finally, it is important to stress that the present study assessed opinions of healthcare professionals. Our sample is, hence, not representative of the general public, which might have different (possibly more positive) views on end-of-life issues than medical and paramedical staff.

End-of-life decisions are not always governed by clinical circumstances and patients' preferences; rather, physicians' characteristics (i.e., age, religion and geographic region) seem to play a critical role for picking such options [31, 32]. In our study, geographic differences as well as religious background were the variables that consistently predicted all four end-of-life statements. Residents from Northern and Central Europe, as compared to Southern Europeans, were more likely to agree with ANH withdrawal in chronic VS whereas religious respondents, older respondents, and women were less likely to find it acceptable. Physicians in Southern Europe have been reported to hold more paternalistic views on medical practice and the presumption to continue to treat is usual [7]. Considering these different attitudes within and out of Europe, it has been suggested that an international consensus regarding standards of care for patients with disorders of consciousness needs to be reached [33]. Additionally, religious affiliation was previously shown to influence the decisions of European intensivists to withdraw treatment [10].

The majority of our sample (80%) considered chronic VS worse than death especially from the family's point of view. In the past, Jennett [27] similarly reported that nearly 90% regarded vegetative survival worse than death, a few commenting that the question was irrelevant for the patient, whereas 95% would consider that the families would regard it worse. Indeed, it was previously shown that families of long-hospitalized VS patients are confronted with an emotional paradox as they cannot adopt a strategy of mourning because their patients are not dead [34]. More recently, it was shown that VS patients' families have been characterized by emotional distress increasing with duration of the disorder, have unsatisfactory family relationships, adopt situation-oriented coping strategies (i.e., efforts aimed at solving and cognitively restructuring the problem or attempting to change the situation), and thoughts of the imminent death of their beloved ones were associated with anxiety and depressive symptoms [35]. Despite these figures, although most families of VS patients were shown to be in favour of interventions for acute complications (e.g., antibiotics), the majority (76%) did not wish their relative to receive cardiopulmonary resuscitation or mechanical ventilation in case needed [36].

It is important to stress that our survey showed differences in opinions on VS and the recently defined MCS [3]. MCS patients are characterized by minimal fluctuating awareness with possible perception of suffering [9, 21], whereas VS patients, by definition, are deprived of such experiences [19]. Similarly, we observed that medical caregivers agreed less to stop treatment in MCS as compared to VS. A previous survey showed that British doctors were more reluctant not to treat or withdraw ANH as the predicted degree of patients' awareness and interaction with the environment increased [37]. It, hence, seems that participants may have considered consciousness as a criterion for making treatment limitation decisions. However, the significance of consciousness as a criterion to withhold treatment has been criticized on the grounds that it may not always be in the patient's best interest to keep on living in a state which may be considered worse than VS; thus, running the risk of acting against the ethical principle of patients' autonomy [38, 39]. In cases of non-communicating patients, like VS and MCS, patients' opinions cannot be obtained, except in the few cases where patients had made advance directives or had indicated an informed surrogate decision maker. However, although advanced directives continue to be widely used in clinical practice [40], one should also consider the empirical fact that the formerly competent person's critical interests do not necessarily reflect her/his experiential interests after incompetency is established irreversibly [29, 41]. Additionally, the literature on traumatic paraplegia and quadriplegia [42] as well as on patients with amyotrophic lateral sclerosis [43] shows that once patients have become accommodated to this state of reduced function, they generally rate their quality of life as satisfactory and are glad to be alive. In cases of legal representation, the proxy decision maker should mediate trying to maximize patients' self-determination and protect their interests on the principles of beneficence (i.e., decisions should be made on patient's best interests and benefits should outweigh the burdens of treatment) and non-maleficence [i.e., ongoing treatment may be judged to be futile on the basis of low likelihood of significant recovery, 44]. Even though for VS patients end-of-life provisions have been introduced [45], for MCS no ethical or legal consensus about withdrawing life support has been formulated [46] and no distributive justice and resource allocation for these patients have yet been determined. Hence, it remains a bioethical debate as to whether and how treatment limitations should be applied for MCS patients [47].

In conclusion, the introduction of diagnostic criteria of MCS in 2002 [3] seems not to substantially change European caregivers' opinions on end-of-life issues on permanent VS. Most of the surveyed participants do not wish to live in this condition and consider it acceptable to stop ANH, even if the observed frequency of agreement seems to be lower as compared to historical data. As for previous surveys, opinions differed between Northern, Central, and Southern European countries and were mostly explained by religious beliefs. For the recently defined MCS, there seems to be a strong dissociation between what we want for ourselves (most caregivers do not wish to be kept alive in this condition) and what we consider acceptable in patients (only a minority considered it acceptable to stop treatment in chronic MCS). Our observation that opinions on treatment withdrawal and personal treatment wishes differ in VS as compared to MCS, stresses the importance to distinguish both clinical entities when preparing advanced directives and discussing personal preferences with proxies. Indeed, 20% of respondents who did not wish to be kept alive if they were themselves VS they preferred to be kept alive if they were in MCS. At present, templates for written instructional directives do not make the difference between vegetative and non-communicative albeit minimally conscious states. Additionally, the finding that healthcare professionals' views are dependent on geographic and religious variables makes the formulation of universal legal and ethical guidelines a challenging task [48]. Despite the prevalent support for the right to die in chronic VS, the observed diversity and complexity around MCS makes us propose to increase efforts promoting advance directives and identification of proxies in tackling the ethical and legal challenges surrounding end-of-life issues in DOC.

Acknowledgments We would like to thank J. Savulescu, D.J. Wilkinson and N. Levy from the Wellcome Centre for Neuroethics, University of Oxford, UK, for the valuable contribution to the discussion on bioethical issues in treatment limitation from patients with disorders of consciousness. This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission (DISCOS, Marie-Curie Actions), the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Fondation Médicale Reine Elisabeth and the University of Liège.

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frontiers in
PSYCHOLOGY

ORIGINAL RESEARCH ARTICLE
published: 07 February 2011
doi: 10.3389/fpsyg.2010.00245

Neural plasticity lessons from disorders of consciousness

Athena Demertzi, Caroline Schnakers, Andrea Soddu, Marie-Aurélie Bruno, Olivia Gosseries, Audrey Vanhaudenhuyse and Steven Laureys*

Coma Science Group, Cyclotron Research Centre and Neurology Department, Sart Tilman, University and University Hospital of Liège, Liège, Belgium

Edited by:
Morten Overgaard, Aarhus University, Aarhus University Hospital, Denmark

Reviewed by:
Ryota Kanai, University College London, UK
Jessica Saenger, Heinrich-Heine-University of Düsseldorf, Germany

****Correspondence:***
Steven Laureys, Cyclotron Research Center, Allée du 6 août No. 8, Sart Tilman B30, 4000 Liège, Belgium.
e-mail: steven.laureys@ulg.ac.be

Communication and intentional behavior are supported by the brain's integrity at a structural and a functional level. When widespread loss of cerebral connectivity is brought about as a result of a severe brain injury, in many cases patients are not capable of conscious interactive behavior and are said to suffer from disorders of consciousness (e.g., coma, vegetative state/unresponsive wakefulness syndrome, minimally conscious states). This lesion paradigm has offered not only clinical insights, as how to improve diagnosis, prognosis, and treatment, but also put forward scientific opportunities to study the brain's plastic abilities. We here review interventional and observational studies performed in severely brain-injured patients with regards to recovery of consciousness. The study of the recovered conscious brain (spontaneous and/or after surgical or pharmacologic interventions), suggests a link between some specific brain areas and the capacity of the brain to sustain conscious experience, challenging at the same time the notion of fixed temporal boundaries in rehabilitative processes. Altered functional connectivity, cerebral structural reorganization as well as behavioral amelioration after invasive treatments will be discussed as the main indices for plasticity in these challenging patients. The study of patients with chronic disorders of consciousness may, thus, provide further insights not only at a clinical level (i.e., medical management and rehabilitation) but also from a scientific-theoretical perspective (i.e., the brain's plastic abilities and the pursuit of the neural correlate of consciousness).

Keywords: neural plasticity, recovery, unresponsive wakefulness syndrome, vegetative state, minimally conscious state, consciousness, functional neuroimaging, deep brain stimulation

Thanks to last decades' technological advances, the study of consciousness has been under the scrutiny of neuroscientific research. The notion that consciousness is supported by and emerged from the brain is well-documented by clinical cases of neurological patients suffering from disorders of consciousness (DOC): in coma, patients are unable to be awakened and hence show no awareness of themselves and of their environment; in the vegetative state (VS) now called unresponsive wakefulness syndrome (UWS; Laureys et al., 2010) there is a dissociation between arousal which is preserved (i.e., clinically evident by eyes opening) and awareness which is abolished (Jennett and Plum, 1972). The recently defined minimally conscious state (MCS) describes patients who show fluctuating signs of awareness but remain unable to communicate (Giacino et al., 2002). Through this lesion paradigm we have the opportunity not only to better understand the neural correlates of consciousness (Tononi and Laureys, 2009) but also to gain insight about the brain's plastic abilities (Laureys et al., 2006a). In the present review, the study of neural plasticity is approached via neurological evidence coming from neuroimaging technologies, such as structural and functional magnetic resonance imaging (MRI), and positron emission tomography (PET), during pathological states and after recovery of consciousness. Altered cerebral functional connectivity, structural reorganization as well as behavioral amelioration after invasive and non-invasive treatments will be discussed as the main indices for plasticity in this challenging population (**Figure 1**).

INTERVENTIONAL STUDIES

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is an interventional surgical procedure which requires the implantation of microelectrodes in deep structures of the brain and the administration of low voltage electricity in these structures. Despite some sparse evidence that DBS may have some ameliorating effects on arousal in VS/UWS patients (Cohadon and Richer, 1993; Yamamoto et al., 2001), in general one cannot argue in favor of this treatment in the VS/UWS population. This is mainly due to the widespread underlying neuropathology of VS/UWS (Adams et al., 2000) which does not permit a straightforward functional re-integration after stimulating the structures of interest in these patients (Schiff and Fins, 2007).

In a more controlled experimental setting, where patients' selection was based on both their neuropathological status (i.e., specific information about the connections between the central thalamus, cerebral cortex, basal ganglia and other subcortical structures) and behavioral profile (i.e., exhibition of preserved arousal and fluctuating behavioral performance), a 38-year-old patient in a MCS more than 6 years after severe traumatic brain injury was selected for DBS treatment (Schiff et al., 2007). Up to the point of DBS treatment, the patient did not show any clinical amelioration despite a 2-year rehabilitation program. However, after applying DBS in bilateral central intralaminar thalamic nuclei (**Figure 2**), the patient showed stimulation-related improved levels of arousal, motor control, and interactive behavior as measured by neuropsychological testing during the DBS "on" periods.

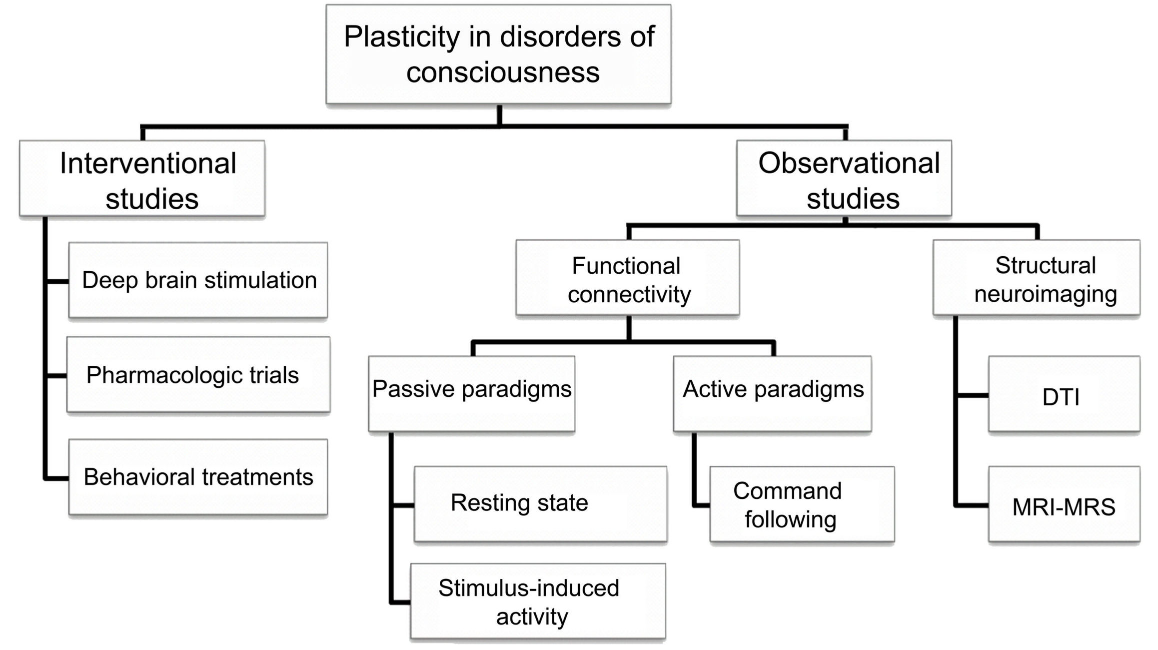

FIGURE 1 | Outline of studies dealing with plasticity issues in patients with disorders of consciousness. DTI, diffusion tensor imaging; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

The effects of DBS were attributed to the recruitable large-scale networks underlying the neuropathology of this MCS patient and were interpreted as a promotion of the patient's arousal regulation via the direct activation of the frontal cortical and basal ganglia systems, innervated by the stimulated thalamic neurons (Schiff et al., 2007; Schiff, 2010).

PHARMACOLOGIC TRIALS

Regarding the effects of pharmacologic trials in patients with DOC, generally speaking no satisfactory results exist (Laureys et al., 2006b). Small-scale pharmacologic studies indicate some exceptional respondents to either stimulant or depressant pharmacologic agents, but for whom no evidence-based recommendations can be made yet (Whyte et al., 2005; Demertzi et al., 2008).

Studies using amantadine, a mixed NMDA and dopaminergic agonist, showed a better outcome in traumatic patients with DOC (Whyte et al., 2005; Sawyer et al., 2008). In addition to behavioral amelioration, a recent PET study of chronic anoxic MCS showed a drug-related increase in fronto-parietal metabolism (Schnakers et al., 2008). Other dopaminergic agents which have been reported to lead to favorable functional outcome are levodopa and bromocriptine (Passler and Riggs, 2001). Clinical improvements has also been reported after administration of baclofen (GABA agonist administered mainly against spasticity; Taira and Hori, 2007) and zolpidem (non-benzodiazepine sedative drug that is used against insomnia in healthy people; for short review see Demertzi et al., 2008). The exact neuromodulating mechanism of these agents is not clear yet. A mesocircuit hypothesis, involving the cortico-thalamo-cortical system as well as projections of the basal ganglia to the central thalamus, has been recently proposed (Schiff, 2010). The dopaminergic agents are thought to either facilitate directly the mesio-frontal cortical neurons, which send excitatory projections to the central thalamus, or modulate the striatum leading to the restoration of the global dynamics of the cortico-thalamic system. On the other hand, zolpidem effects may be explained by a direct action at the level of the global pallidus interna which sends inhibitory projections to the central thalamus; this inhibitory effect could substitute for the normal inhibition of the globus pallidus from the striatum and hence lead to a more stabilized central thalamic activity (Schiff, 2010).

NON-PHARMACOLOGIC INTERVENTIONS

Non-pharmacologic interventions for DOC patients here refer to sensory stimulation techniques and physical therapy, which mainly aim at both preventing complications (i.e., contractures or pressure sore preventions) and/or at enhancing recovery. Sensory stimulation can refer to two types of approaches: multisensory stimulation or sensory regulation (Tolle and Reimer, 2003). The first expresses the principles of behaviorism and holds that enhanced environmental stimulation of the sensory systems is hoped to enhance synaptic re-innervations, whereas the second is based on the principles of information processing and focuses on the enhancement of selective attention by regulating the environment. Concerning physical therapy, there is some evidence that early (Oh and Seo, 2003) and increased intervention (Shiel et al., 2001) leads to better outcome.

PERSPECTIVES

The existing therapeutic nihilism in the field of DOC is currently getting challenged by recent data supporting that some DOC patients could benefit from some rehabilitative interventions (surgical, pharmacologic, or behavioral) reviewed above. Larger-scale

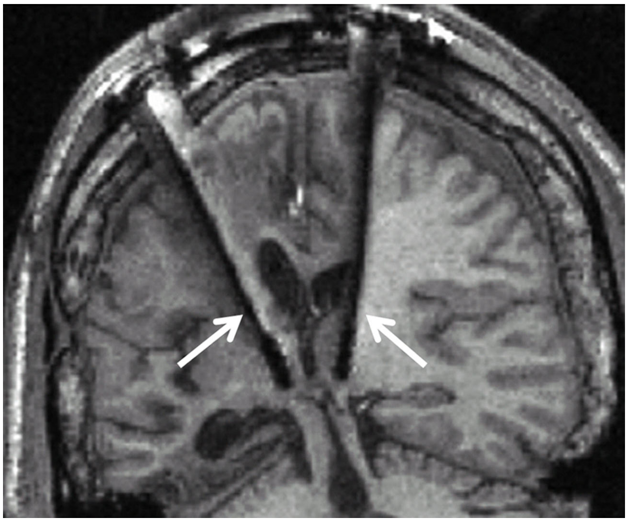

FIGURE 2 | Clinical setup of electrodes implementation in the central thalami bilaterally (white arrows) during deep brain stimulation. Adapted from Schiff et al. (2007).

studies with higher number of patients of various pathologies are ongoing, in order to better comprehend the underlying neuromodulatory effects of DBS and the induced neuroplastic changes in severely injured brains. Currently, the beneficial effects of the pharmacologic and non-pharmacologic approaches described above are not evidence-based and hence are not generally accepted by the medical community (for a systematic review see Lombardi et al., 2002). No unique hypothesis or theoretical framework (Laureys, 2005; Tononi and Laureys, 2009) can at present combine the temporal dynamics and pathophysiological mechanisms of all the aforementioned interventions (e.g., Pistoia et al., 2010) and many questions remain as to the precise mechanisms differentiating spontaneous from therapy-induced cerebral plasticity.

In the therapeutic management of patients with DOC, no "standards of care" do yet exist, mainly due to the limitation of their scientific evidence coming from small-scale studies under suboptimal or uncontrolled settings. Thus, no evidence-based recommendations can be made for a particular treatment option (Demertzi et al., 2008).

OBSERVATIONAL STUDIES

FUNCTIONAL CONNECTIVITY STUDIES

Passive paradigms

Functional neuroimaging does not only allow one to examine the functional segregation (i.e., localizing a function to a cerebral area) but also the functional integration (i.e., assessing the interaction between functionally segregated areas). Current analytical tools permit to assess the functional or effective connectivity between distant cerebral areas in functional imaging. Such analyses explain the activity in one cortical area in terms of an interaction between the influence of another area and some experimental condition (i.e., comparing data obtained during unconsciousness and after recovery). Functional connectivity is defined as the temporal correlation of a neurophysiological index (hemodynamic or metabolic) measured in different remote brain areas, whereas effective connectivity is defined as the influence one neural system exerts over another (Friston, 2002). Based on their experimental design, functional connectivity studies can be reduced to two main categories: passive (i.e., resting state, stimulus-induced activity) and active (i.e., mental task command following) paradigms (Bruno et al., 2010).

Using "resting state" fluorodeoxyglucose PET imaging, decreased global metabolic levels have been identified in VS/UWS patients, with no significant global metabolic resumption after recovery of consciousness. However, "functional disconnections" were identified in a large fronto-parietal network which exhibited regional metabolic restoration in long-range cortico-cortical (between latero-frontal and midline-posterior areas; Laureys et al., 1999) and cortico-thalamo-cortical (between non-specific thalamic nuclei and midline-posterior cortices) after recovery of consciousness from chronic VS/UWS (Laureys et al., 2000b; **Figure 3**). It is hence suggested that fronto-parietal network connectivity is critical in sustaining conscious awareness (Baars et al., 2003; Laureys et al., 2004a), as is also supported by evidence from studies on sensory perception in normal volunteers (Dehaene et al., 2006; Boly et al., 2007).

Positron emission tomography and fMRI studies have identified a "default mode network," defined as a set of areas, encompassing posterior cingulate/precuneus, anterior cingulate/mesio-frontal cortex, and temporo-parietal junctions, which show more activity at rest than during attention-demanding tasks. Recent studies have shown that it is possible to reliably identify this network in the absence of any task, by resting state fMRI connectivity analyses in healthy volunteers (Boly et al., 2008b, 2009). This "default mode network" is considered to be involved in self-related processes (Mason et al., 2007; Buckner et al., 2008; Vanhaudenhuyse et al., 2011) but the functional significance of these spontaneous brain activity fluctuations in pathological states remain only partially understood. It has recently been shown that default mode connectivity decreases during propofol general anesthesia (Boveroux et al., 2010), sleep (Gould et al., 1999), and hypnotic state (McGeown et al., 2009; Demertzi et al., in press). In pathological impaired consciousness, resting state connectivity was shown to disappear in brain death (Boly et al., 2009) and to show a non-linear disintegration in pseudocoma or locked-in syndrome as compared to minimally conscious or relative to unconscious states (VS/UWS or coma; Vanhaudenhuyse et al., 2009; **Figure 4**).

Apart from resting state acquisitions, valuable information is gathered by studies observing the cerebral responses to external sensory stimulation. Using PET, stimulus-induced somatosensory (Laureys et al., 2002; Boly et al., 2008a) and auditory (Laureys et al., 2000a; Boly et al., 2004) activation protocols in VS/UWS patients have identified a cerebral response restricted to primary sensory cortices, whereas MCS patients demonstrated a stronger functional connectivity between sensory and fronto-parietal associative areas in these patients. These findings indicate that the presence of isolated neuronal groups that work in a module-like fashion, are not functionally sufficient for the conscious perception of the world and the generation of conscious behavior (Schiff et al., 2002). Additionally, stimuli with emotional valence like infant cries (Laureys et al., 2004b) or the patient's own name

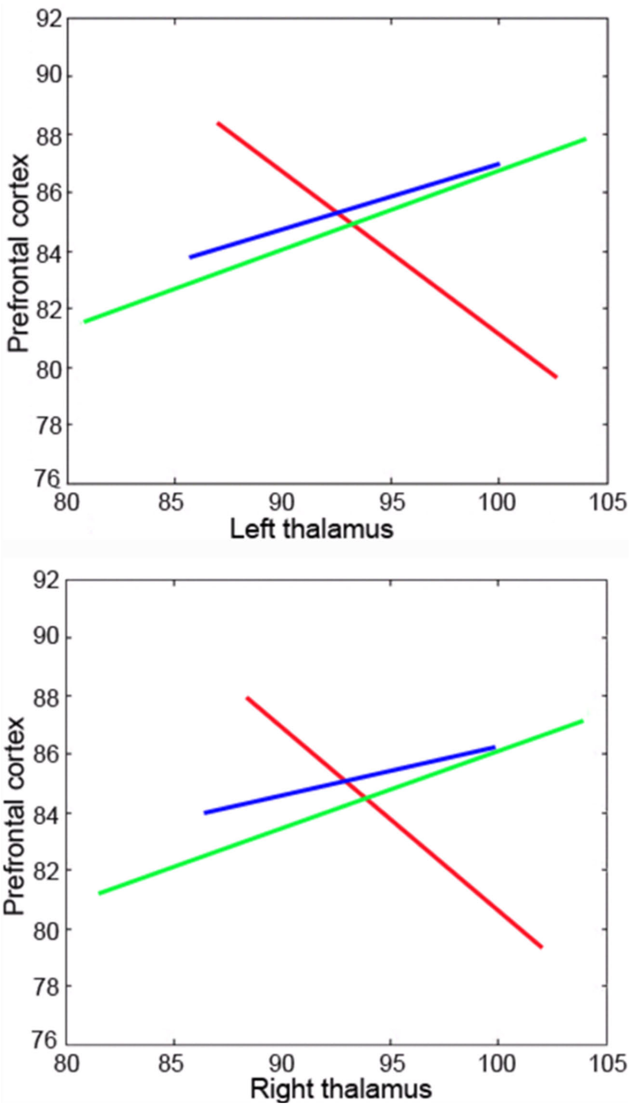

FIGURE 3 | Functional connectivity between the thalami and prefrontal cortex is abolished during pathological unconsciousness (UWS/VS; red regression line) and resumes a near-normal modulation after recovery of consciousness (blue line). The green line illustrates connectivity in healthy controls. Regression lines represent cross-correlation of normalized regional cerebral blood flow as measured by H_2O^{15}-PET. Adapted from Laureys et al. (2000b).

(Di et al., 2007) induced a widespread near-normal activation in MCS. The latter fMRI study also showed to be informative of patients' prognosis and recovery as confirmed by a recent study by Coleman et al. (2007).

Active paradigms

"Active paradigms" in neuroimaging studies, aiming to show command following, constitute a more direct proof to demonstrate conscious awareness, independent of motor activity. If a patient systematically follows a specific mental command, then this subject is expected to activate certain brain areas in a consistent manner and only then one can infer that this subject is conscious. Using this approach, a collaborative study between the Cambridge and Liège imaging centers, we showed in a clinically VS/UWS patient fMRI evidence of obeying to simple commands (i.e., "imagine walking around in your house" or "imaging playing tennis") in specific brain areas (i.e., parahippocampal and supplementary motor areas, respectively) indistinguishable from that observed in healthy controls (Owen et al., 2006). Such activation could not be attributed to automatic recruitment of these areas of interest (Soddu et al., 2009) and thus the patient was considered to be conscious. Of note is that 6 months later, when the patient was clinically re-examined, she recovered visual pursuit of a mirror (Vanhaudenhuyse et al., 2008), indicating her transition to a MCS. The residual brain activity detected via neuroimaging technologies could not be initially identified in the patient's bedside, suggesting that neuronal activation was taking place in absence of any behavioral output.

STRUCTURAL IMAGING

Structural connectivity refers to a network of physical or structural (axonal) connections which bines sets of neuronal populations. In clinical cases, information about the structural architecture of the brain can provide insights about recovery and neural plasticity in anoxic or traumatic brain injury. In chronic DOC, patients will progressively develop diffuse brain atrophy. In these cases, classical morphological MRI may not be a reliable indicator of the severity of the axonal injury and hence of the level of consciousness (Tshibanda et al., 2009). However, tools with higher sensitivity have been introduced which hold promise for studying plasticity in patients with DOC, such as diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS; Tshibanda et al., 2010).

Diffusion tensor imaging assesses the architectural organization of white matter fibers and hence can detect *in vivo* diffuse axonal injury (Arfanakis et al., 2002). In an exceptional case of late recovery from traumatic brain injury, Voss et al. (2006) used DTI to document an increased fractional anisotropy (thought to reflect fiber density) in large, bilateral regions of medial parieto-occipital areas of the white matter paralleling his clinical recovery of speech and motor function 19 years after the acute insult. These findings were contingent to an increased regional metabolism in these areas when measured with PET, similar to the partially restored cortical regions observed in patients who recover consciousness after being in a chronic VS/UWS (Laureys et al., 2000b, 2006a; **Figure 5**). This multimodal posteriomedial associative area has been previously suggested to be part of the human awareness network (Vogt and Laureys, 2005).

Magnetic resonance spectroscopy is another non-invasive technique that can provide *in vivo* quantification of certain biochemical markers such as N-acetylaspartate (heralding information about neuronal density and viability), choline (reflecting cell membrane turnover), and creatine (reflecting cell aerobic energy metabolism; Tshibanda et al., 2009). When information from this technique was combined with morphological MRI in traumatic brain injury, patients could be separated in prognostic subgroups based on the Glasgow Outcome Scale which was not possible when the different imaging techniques were applied separately (Carpentier et al., 2006).

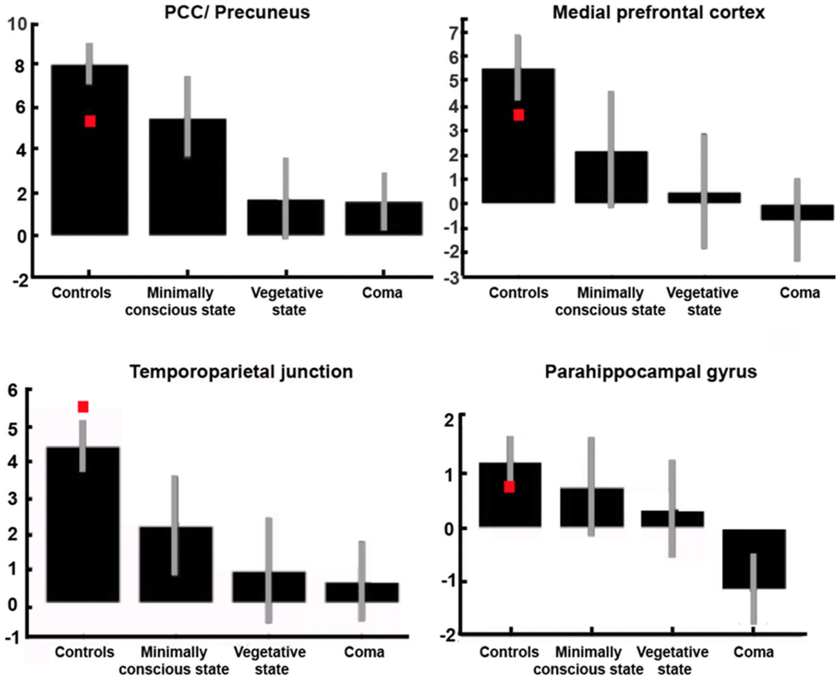

FIGURE 4 | The most representative nodes of the "default mode network" show a decrease in functional connectivity as we move from normal consciousness and locked-in syndrome (red squares) to minimally conscious or unconscious states. Graphs represent connectivity strength (mean *z* scores with 90% confidence intervals). PCC, posterior cingulate cortex. Adapted from Vanhaudenhuyse et al. (2009).

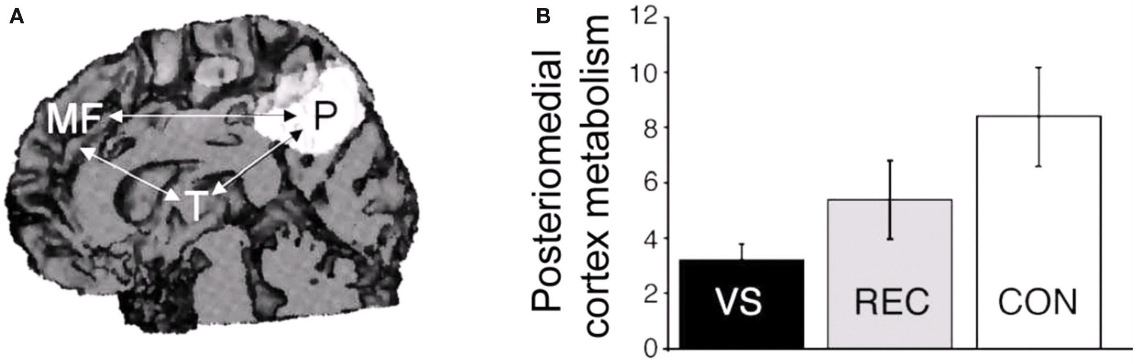

FIGURE 5 | (A) Restoration of glucose metabolism in posteriomedial cortices after recovery from the VS/UWS (area in white; arrows indicate the functional disconnections observed in VS/UWS patients). **(B)** In the same posteriomedial area, lower metabolism was observed in VS/UWS patients (black bar) as compared to those who recovered consciousness (gray bar) and to healthy controls (white bar), suggesting its critical role in the mediation of conscious awareness. Scale represents cerebral metabolic rates for glucose uptake (in mg/100 g/min). Adapted from Laureys et al. (2006a).

PERSPECTIVES

The use of resting state fMRI to study functional recovery and neural plasticity in DOC patients and its clinical routine use as a diagnostic and prognostic tool needs a controlled methodology and inclusion of a larger number of patients as is currently being tackled by multicentric collaborations. Nevertheless, clinicians should be aware of the many limitations and pitfalls intrinsic to "resting state" analyses – especially the challenge to disentangle genuine neural activity from artifactual movement-related fMRI signal in studies on severe brain injury (Soddu et al., in press). Although clinical assessment presently remains the gold standard in diagnosing this challenging population (Majerus et al., 2005), neuroimaging instruments in some exceptional cases of motor-deprived non-communicating DOC patients may be used as a means to establish a reliable communication code (Monti et al., 2010b). The challenge now will be to validate these novel technologies and to define the ethical and legal frameworks redefining cognitive competence in these patients with very limited and technology-dependent communication (Fins et al., 2008). Structural MRI coupled to spectroscopic and DTI techniques are currently being validated as prognostic markers in acute and chronic DOC (e.g., Lescot et al., 2009; Tshibanda et al., 2010). These studies also will improve our understanding of residual neural plasticity in the recovery of consciousness.

CONCLUSION

Most recoveries of consciousness, with or without recovery of social or professional integration, take place within the first 3 months after non-traumatic and after 12 months after traumatic cerebral accidents and survival beyond 10 years remains unusual – albeit depending on the level of medical and nursing care (The Multi-Society Task Force on PVS, 1994; Monti et al., 2010a). However, clinical cases of both late spontaneous recoveries (e.g., Voss et al., 2006; Estraneo et al., 2010) or after invasive interventional treatments (e.g., Schiff et al., 2007) challenge the dogma of temporally fixed periods for possible neuronal plasticity. It is important to stress that the cellular mechanisms underlying recovery of consciousness after severe brain damage remain speculative. Our understanding of possible neurogenesis (known to occur predominantly in associative fronto-parietal cortices in non-human primates; Gould et al., 1999), axonal sprouting and neurite outgrowth, or even apoptosis in this patient population remains very limited. The residual cerebral plasticity during vegetative/unresponsive and MCS patients has been largely overlooked by the medical community and deserves further investigation. We believe that the challenge is now to identify the conditions in which and the mechanisms by which some patients may recover consciousness by use of the latest MRI and PET neuroimaging tools. The absence of large, controlled randomized interventional studies in patients with chronic DOC account for the present lack of evidence-based guidelines and tendency for therapeutic nihilism and can be related to the continuing societal, political, legal, and ethical debates in this field. The study of patients with chronic DOC may hence provide further insights in the medical management and rehabilitation of these patients at the clinical level, as well as increasing our understanding of the brain's long overlooked plastic abilities and the scientific quest for the neural correlates of human consciousness.

ACKNOWLEDGMENTS

This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission (DISCOS Marie-Curie Actions, COST, DECODER), the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Fondation Médicale Reine Elisabeth, and the University and University Hospital of Liège.

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Conflict of Interest Statement: The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 16 October 2010; paper pending published: 19 November 2010; accepted: 24 December 2010; published online: 07 February 2011.

Citation: Demertzi A, Schnakers C, Soddu A, Bruno M-A, Gosseries O, Vanhaudenhuyse A and Laureys S (2010) Neural plasticity lessons from disorders of consciousness. Front. Psychology ***1****:245. doi: 10.3389/fpsyg.2010.00245*

This article was submitted to Frontiers in Consciousness Research, a specialty of Frontiers in Psychology.

Neuroethics
DOI 10.1007/s12152-011-9149-x

ORIGINAL PAPER

Pain Perception in Disorders of Consciousness: Neuroscience, Clinical Care, and Ethics in Dialogue

A. Demertzi · E. Racine · M-A. Bruno · D. Ledoux · O. Gosseries · A. Vanhaudenhuyse · M. Thonnard · A. Soddu · G. Moonen · S. Laureys

Received: 2 August 2011 / Accepted: 15 December 2011

Abstract Pain, suffering and positive emotions in patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious states (MCS) pose clinical and ethical challenges. Clinically, we evaluate behavioural responses after painful stimulation and also emotionally-contingent behaviours (e.g., smiling). Using stimuli with emotional valence, neuroimaging and electrophysiology technologies can detect subclinical remnants of preserved capacities for pain which might influence decisions about treatment limitation. To date, no data exist as to how healthcare providers think about end-of-life options (e.g., withdrawal of artificial nutrition and hydration) in the presence or absence of pain in non-communicative patients. Here, we aimed to better clarify this issue by re-analyzing previously published data on pain perception (Prog Brain Res 2009 177, 329–38) and end-of-life decisions (J Neurol 2010 258, 1058–65) in patients with disorders of consciousness. In a sample of 2259 European healthcare professionals we found that, for VS/UWS more respondents agreed with treatment withdrawal when they considered that VS/UWS patients did not feel pain (77%) as compared to those who thought VS/UWS did feel pain (59%). This interaction was influenced by religiosity and professional background. For MCS, end-of-life attitudes were not

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A. Demertzi and E. Racine contributed equally to the manuscript.

A. Demertzi (✉) · M.-A. Bruno · D. Ledoux ·
O. Gosseries · A. Vanhaudenhuyse · M. Thonnard ·
A. Soddu · S. Laureys
Coma Science Group, Cyclotron Research Center,
University of Liège,
Liège, Belgium
e-mail: a.demertzi@ulg.ac.be

A. Demertzi · M.-A. Bruno · O. Gosseries ·
A. Vanhaudenhuyse · M. Thonnard · A. Soddu ·
G. Moonen · S. Laureys
CHU Neurology Department, University Hospital of Liège,
Liège, Belgium

E. Racine
Neuroethics Research Unit,
Institut de recherches cliniques de Montréal,
Montreal, Canada

E. Racine
Department of Medicine and Department of Social and
Preventive Medicine, Université de Montréal,
Montreal, Canada

E. Racine
Departments of Neurology and Neurosurgery,
Medicine & Biomedical Ethics Unit, McGill University,
Montreal, Canada

D. Ledoux
CHU Department of Intensive Care, University of Liège,
Liège, Belgium

G. Moonen
University of Liège,
Liège, Belgium

influenced by opinions on pain perception. Within a contemporary ethical context we discuss (1) the evolving scientific understandings of pain perception and their relationship to existing clinical and ethical guidelines; (2) the discrepancies of attitudes within (and between) healthcare providers and their consequences for treatment approaches, and (3) the implicit but complex relationship between pain perception and attitudes toward life-sustaining treatments.

Keywords Pain · End-of-life · Vegetative state · Minimally conscious state · Ethics · Attitudes · Survey

Introduction

Pain and pleasure are inherently subjective experiences that can be verbally communicated to others. In the absence of oral communication, we can infer these experiences in others by observing facial expressions of "liking" or "disliking". For example, in newborns the tongue protrusion that can lick the lips can be considered a positive affective expression whereas brow wrinkling and wide-eyes opening are usually considered as facial expressions of negative affect [e.g., 1]. Likewise, in non-communicative severe brain-damaged patients we are limited to infer emotional states by evaluating behavioural responsiveness to external stimuli. Patients in a vegetative state [VS, now called unresponsive wakefulness syndrome/UWS 2] are in a condition of preserved wakefulness with absent volitional behaviour and response to command [3]. Minimally conscious state (MCS) characterizes patients who show discernible but fluctuating signs of awareness without effective communication with their environment [4]. MCS is now subcategorized in MCS- (i.e., showing signs of volitional behaviour that is non-reflex movements like visual pursuit, orientation to pain and contingent motor responses to specific stimuli) and MCS+ (i.e., patients showing response to verbal or written commands) [5]. To date, the management of pain continues to raise controversial issues both at a clinical and ethical level [6, 7]. Clinically, the pharmacological and non-pharmacological therapy of pain in non-communicative patients varies from country to country, mainly depending on the ascription of pain to these patients [8, 9]. For example, the Multi-Society Task Force on PVS [10] rules out the possibility that VS/UWS patients experience pain and hence makes no recommendations for its management. The Royal College of Physicians [11], however, recommends the administration of sedatives after treatment withdrawal, recognizing the possibility of pain and suffering at the end of life. Suffering (which is considered a property of sentient organisms) is an ill-defined term, referring to states of increased distress associated with events threatening the intactness of the person [7, 12]. Suffering in patients with disorders of consciousness raises controversial questions about whether non-responsive patients might have such an experience. The issue of suffering becomes even more challenging when treatment limitation has been agreed upon. End-of-life decisions in patients with disorders of consciousness are not rare but the legal provisions currently differ from country to country [13, 14]. In Europe, there are differences in the way treatment limitation is perceived, especially between Northern and Southern countries [15]. We also showed that opinions on end-of-decisions depend on the diagnosis of the patient (for VS/UWS there is more support for treatment withdrawal as compared to MCS), on the professional status (paramedical workers agree more with treatment withdrawal as compared to medical doctors) and on the cultural background of the clinician making the decision (religious respondents agree less with treatment limitation as compared to non-religious).

Here we aim to summarize available evidence on the study of pain but also of positive emotion and affect in non-communicative patients. We review the assessment tools measuring pain at the bedside and recent functional neuroimaging and electrophysiological studies. Some scholars suggest that when pain perception is suspected in patients with disorders of consciousness, continuation of life-sustaining treatment may be against patients' best interests and harm them by exposing them to unpleasant feelings [16]. Others support that the question should not be about whether or not to withhold or withdraw life sustaining treatment patients with disorders of consciousness but about how much of analgesic care should be administered to them [8]. Here, with a further aim to add at the ethical discussion on end-of-life options with regards to pain perception in these patients, we re-analyzed European survey data on healthcare providers previously published on attitudes on pain perception [6] and end-of life [15] in patients with disorders of consciousness. We assessed whether opinions on end-of-life options associate with beliefs regarding pain perception in patients with disorders of consciousness and identified variables explaining this association. Considering the data, we further discuss (1) the evolving scientific understandings of pain perception and their relationship to existing clinical and ethical guidelines, (2) the discrepancies in attitudes of healthcare workers and their consequences for consistent treatment approaches and (3) the implicit but complex relationship between pain perception and attitudes toward life-sustaining treatments.

Behavioural Assessment of Negative and Positive Affect in Non-communicative Patients

According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience associated with real or potential tissue damage" [17]. This implies that pain has both physical and emotional properties. We will use the term 'nociception' to refer to the physical responsiveness to noxious (harmful) stimulation [18]. Nociception may elicit unconscious postural responses (as well as other motor reflexes, autonomic and endocrinologic responses) without necessarily evoking the experience of suffering, especially when the brain has lost its capacity for self-awareness [e.g. spinal reflexes and lazarus sign in brain death, 10, 19]. As stressed by the IASP, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. As pain can also be present in the absence of noxious stimulation [18], then how can one know whether patients in VS/UWS or in MCS experience pain or suffering? At the bedside, we infer pain perception in these patients by evaluating behavioural responsiveness to noxious stimuli. Three types of motor responses are usually tested: a) stereotypical responses, which are slow extension or flexion movements of the arms and legs, b) flexion withdrawal, where the limb moves away from the point of stimulation and c) localisation responses, where the non-stimulated limb touches the part of the body that received the stimulation. Localisation of pain is the only motor response thought to be a purposeful and intentional act to eliminate a noxious stimulus [4] but one cannot be sure of how specifically painful a stimulation can be or how salient it is to the patient [7]. Hence, pain localization does not necessarily imply that the patient suffers, but this possibility has to be considered. Other observed behaviours resulting from noxious stimulation (i.e., eyes opening, quickening of breathing, increasing heart rate and blood pressure, occasional grimace-like or crying-like behaviours) are considered to be of subcortical origin [also seen in infants with anencephaly, e.g. 20, 21] and do not necessarily reflect conscious perception of pain. Studies in general anesthesia also suggest that motor or autonomic responses are not reliable indicators of consciousness [e.g. 22]. Clinically, noxious-related behaviours are studied by applying pressure to the fingernail, to the joints of the jaw or above the eyes. However, which specific type of noxious stimulation is the most effective at detecting signs of conscious perception still remains to be determined [23]. Numerous scales have been developed for the assessment of pain in non-communicative subjects, especially in newborns (e.g., Neonatal Infant Pain Scale; Faces, Legs, Activity, Cry, Consolability Pain Assessment Tool) and the demented elderly (Pain Assessment in Advanced Dementia Scale; Checklist of Nonverbal Pain Indicators). Only recently a validated scale has been introduced to measure pain in patients with disorders of consciousness. The Nociception Coma Scale (NCS) evaluates motor, verbal, facial and visual responses after noxious stimulation [24]. Its total score ranges between 0 and 12, with 7 indicating perception of pain and hence need for analgesic treatment.

Using the Coma Recovery Scale-Revised (CRS-R) [25] for the clinical assessment of consciousness, the clinician evaluates visual, auditory, motor, oromotor, communication, and wakefulness levels. The manual further proposes the additional evaluation of affective behaviours occurring in the presence of a specific non-noxious stimulus. Smiling, for example, is among behaviours that family members and clinical staff might notice but which can be missed during the formal administration of the scale. Such responses, in order to be considered as non-contingent and meaningful, must occur in the presence of a specific stimulus and not occur when the stimulus is absent. Nevertheless, in clinical practice the behavioural assessment of positive emotions is not yet included in standardized assessments, possibly because they are not as alarming compared to responses to threatening stimuli. Alternative interventions, such as music therapy, could assist in the extraction of positive emotional responses. For example, it was previously shown that a patient initially diagnosed as in VS/UWS was subsequently categorized in MCS because she showed consistent emotional behaviours (changes in facial gestures) to a song of significant personal valence; such response could not be extracted during classical evaluation of consciousness [26]. Compensation for false negatives at the bedside, as a result of patients' physical condition (tetraplegia, spasticity, etc.) or low motivation, is achieved by the assistance of neuroimaging technologies which begin to shed light on the grey zones of consciousness in non-communicative patients [27].

Functional Neuroimaging and Electrophysiology of Negative and Positive Affect in Non-communicative Patients

At present no functional neuroimaging studies have truly assessed positive emotions in patients with disorders of consciousness. However, a number of studies did show that stimuli with emotional valence (as compared non-neutral stimuli) result in higher-level brain processing in severely brain damaged patients. In MCS, infant cries and patient's own name identified that, as compared to meaningless noise, there was more widespread brain activation for the patient's own name, followed by infant cries, comparable to that obtained in controls [28]. Additionally, auditory stimulation with personalized narratives elicited similar-to-controls cortical activity associated with language processing [29]. Residual cognitive processing was also indentified in a MCS patient when he was told stories by his mother [30] or when intimate family pictures were presented [31].

In VS/UWS, emotion-related activity of sound or speech was identified when a patient was told stories by his mother [32]. In another unresponsive patient, the mother's voice elicited a peak EEG frequency at 33 Hz [gamma band, considered to be involved in conscious perception; e.g., 33] parallel to changes in heart rate [34]. Heart rate changes in these patients were also found during the presentation of "positive" and "negative" music [35]. A long-term comatose patient with eyes closed and stereotypical motor behaviour, showed emotional processing as a response to her children's voice followed by her friend's and by an unknown voice [36]. In an emotional oddball paradigm on affective prosody (i.e., a single sad exclamation was presented among four equally probable joyful exclamations) 6 out of 27 VS/UWS and MCS, and 3 patients with locked-in syndrome (LIS),[1] showed a similar-to-controls broadly distributed electrophysiological negativity (N300) after the sad deviant stimulus, considered indicative of an accurate detection of affective mismatch [38].

In the absence of subjective response, one cannot be certain whether such brain responses to emotional entail conscious awareness. What we are interested in, however, is to determine the minimal prerequisites of conscious perception. With regards to pain, previous neuroimaging studies in healthy volunteers showed that pain cannot be localized in an isolated "pain centre" in the brain, but it rather encompasses a neural circuitry [39, 40]. Two distinct brain networks have been implicated in pain perception: (i) a lateral pain system or sensory network processing nociception (lateral thalamic nuclei, primary and secondary somatosensory and posterior parietal cortices); and (ii) a medial pain system or affective network (medial thalamus, anterior cingulate, prefrontal and insular cortices) considered to process the emotional aspects of pain [41]. When noxious stimulation was applied to VS/UWS patients, no evidence of noxious stimulation-related downstream activation beyond primary somatosensory cortex was identified [42]. Instead, cortical activation subsisted as an island, dissociated from higher-order associative cortices that are currently thought to be necessary for conscious awareness [e.g., 43, 44]. However, another study reported additional activation of secondary somatosensory and insular cortices in VS/UWS patients [45], suggesting the possibility of affective experiences of pain in these patients. As opposed to VS/UWS patients, noxious stimulation in MCS patients measured with PET elicited cerebral responses not only in the midbrain, thalamus, and primary somatosensory cortex but also more widespread activation in secondary somatosensory, insular, posterior parietal, and anterior cingulate cortices, comparable to healthy controls [46, 47], strongly

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[1] Patients with locked-in syndrome (LIS) are unable to move body parts, but remain fully conscious of themselves and their environment. In classic cases, LIS patients use their eyes for basic communication with their surroundings (e.g., look up for "yes", look down for "no"). In cases of complete LIS, patients cannot even move their eyelids and, unless carefully assessed, these patients can be erroneously diagnosed as unconscious [37].

suggesting preserved capacity of pain experience in these patients.

Attitudes Towards Well-Being and Pain-Mediated End-of-Life Decisions

In healthy controls, pleasure and well-being depends on the positive affect (hedonia) and on the sense of purposefulness or engagement in life (eudemonia) [48]. Despite the general view that quality of well-being is diminished in disease as a result of limited capacities to functionally engage in everyday living, these attitudes are formulated from a third-person perspective and may underestimate patients' subjective well-being [49]. Indeed, we recently showed that a majority of patients in a chronic LIS, despite self-reporting severe restrictions in community reintegration, professed good subjective well-being [50]. The self-reported happiness status was associated with longer duration in LIS, the ability to produce speech and lower rates of anxiety. In patients with disorders of consciousness, however, self-ratings are impossible to acquire and only estimates about what it is like to be in this situation can be made. An analysis of public media reports on Terri Schiavo [a patient in a VS/UWS; e.g., 51], revealed that in some cases the patient was described as feeling discomfort which was incompatible with her state [52]. In another study, ratings from family members, who are more acquainted with VS/UWS, showed that 90% of families reported, among others, that the patients perceived pain [53]. When clinicians were recently asked to express their opinions on possible pain perception in VS/UWS [6], a significant number of medical doctors ascribed pain perception in VS/UWS (56%) despite formal guidelines suggesting the opposite [e.g., 10]. Analysis of the respondents' characteristics showed that paramedical professionals, religious respondents, and older healthcare providers reported more often that VS/UWS patients may experience pain (as opposed to medical doctors, non-religious and younger respondents). For MCS, there was no discrepancy in opinions and the majority (97%) of respondents found that MCS patients feel pain [6]. Inconsistencies in the medical management of pain have been shown in a recent survey in the United States with (conscious) patients visiting the emergency department with pain-related complaints; the investigators found that patients aged older than 75 years were less likely to receive pain medication as compared to patients aged between 35-54 years [54]. The issue of pain management in non-responsive patients becomes more challenging when withdrawal from life-supporting treatment, such as artificial nutrition and hydration, has been agreed upon [15]. In these cases, VS/UWS patients can be left without administration of opioids or other analgesic drugs during their dying process [19, 55] on the grounds that they are deprived from experiencing suffering due to hunger or thirst [56]. To date, no data exist as to how opinions on pain perception in patients with disorders of consciousness could influence views on end-of-life decisions.

We re-analyzed our previously published survey data [6, 15] looking for possible correlations between healthcare providers' opinions on pain perception in VS/UWS and MCS and views on end-of-life preferences in these patients. A sample of 2259 healthcare professionals coming from 32 European countries (see Table 1 for demographic data) expressed their opinions (yes-no answers) to the questions: "Do you think that patients in a vegetative state can feel pain?"; "Do you think that patients in a minimally conscious state can feel pain?"; "Do you think that it is acceptable to stop treatment (i.e., artificial nutrition and hydration-ANH) in patients in chronic VS?"; "Do you think that treatment can be stopped in patients in chronic MCS?" Recorded demographic data included age, gender, nationality, profession, and religious beliefs[2] (Table 1). For chronic VS/UWS, agreement with treatment withdrawal was negatively correlated with opinions on pain perception in this state; in other words, the more respondents found it appropriate to withdraw treatment from VS/UWS patients, the less they recognized that these patients feel pain (Table 2a; Fig. 1). For chronic MCS, end-of-life attitudes were not mediated by opinions on pain perception (Table 2b, Fig. 1). We then investigated the characteristics of respondents who supported treatment withdrawal when they thought that patients in VS/UWS and MCS feel pain or not. With respect to professional background, for chronic VS/UWS, more paramedical workers than

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[2] Religiosity was defined as the belief in a personal God belonging to an institutionalized religion (i.e., Christianity, Islam, Judaism) independently of practicing.

Table 1 Demographic data of the surveyed clinicians (n=2259)

Age, mean ±SD (range), years	38±14 (18–88)
Gender, no (%)	
Women	1222 (54)
Men	1001 (44)
Missing	36 (2)
Respondents by geographical region, no (%)	
Northern Europe	316 (14)
Central Europe	1148 (51)
Southern Europe	790 (35)
Missing	5 (0)
Profession, no (%)	
Medical professionals	1606 (71)
Paramedical professionals	653 (29)
Religiosity, no (%)	
Religious respondents	1286 (57)
Non-religious respondents	915 (40)
Missing	58 (3)

medical doctors supported treatment limitation when they thought that VS/UWS patients feel pain (Fig. 2a, left panel). For chronic MCS, medical doctors and paramedical professionals' opinions did not differ in terms of pain perception in these patients (Fig. 2b, left panel). With respect to religious beliefs, for chronic VS/UWS, less religious than non-religious respondents supported treatment limitation both when they considered pain perception and not in VS/UWS patients (Fig. 2a, right panel). For chronic MCS, less religious than non-religious respondents agreed with treatment withdrawal when they considered that MCS patients feel pain (Fig. 2b, right panel).

Ethically Salient Questions

The previously discussed points on clinical assessment, neuroimaging/electrophysiology applications and expressed attitudes of laymen and healthcare workers on pain in VS/UWS and MCS patients generate ethically salient questions. Some important questions concern: (1) the evolving scientific understandings of pain perception and their relationship to existing clinical and ethical guidelines; (2) the discrepancies of attitudes within (and between) healthcare providers and their consequences for treatment approaches, and (3) the implicit but complex relationship between pain perception and attitudes toward life-sustaining treatments.

Evolving Scientific Understandings of Pain Perception and their Relationship to Existing Clinical and Ethical Guidelines

The consistency among respondents' opinions that MCS patients are capable for pain perception is supported by both neuroimaging [e.g., 46] and behavioural [4] data, showing a distinct clinical picture from VS/UWS patients. Yet, there is still a minority holding that VS/UWS feel pain. Interestingly, clinicians have

Table 2 Logistic regression (method: enter) results of the agreement with treatment withdrawal in patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS) as predicted by opinions on pain perception in these states. (a) For VS/UWS, agreement with treatment withdrawal was significantly predicted when respondents thought less that VS/UWS patients feel pain. (b) For MCS, agreement with treatment withdrawal was not significantly predicted by opinions on pain perception in these patients

	Odds ratio[a]	95.0% Confidence interval		p value
		Lower	Upper	
a. Treatment can be stopped in VS/UWS				
Patients in VS/UWS can feel pain	0.420	0.348	0.507	<.001
Constant	3.414			<.001
b. Treatment can be stopped in MCS				
Patients in MCS can feel pain	0.658	0.414	1.046	0.077
Constant	0.612			0.034

Predicted response: 'agreement'

[a] An odds ratio higher than 1 signifies more agreement with the statement, whereas an odds ratio less than 1 notifies less agreement

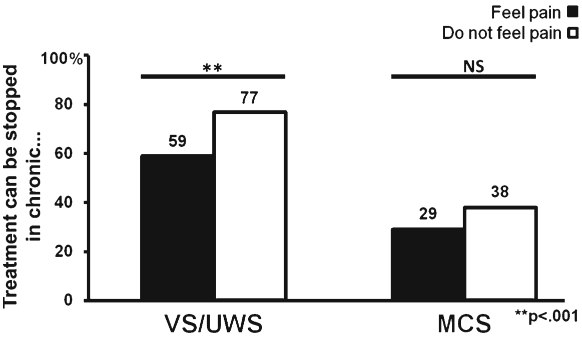

Fig. 1 Attitudes towards treatment withdrawal in VS/UWS are mediated by opinions on pain perception in patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS) but not in minimally conscious state (MCS)

consistently offered ambiguous or mixed answers about pain perception in VS/UWS (or MCS) patients [57]. For example, Payne et al. [57] surveyed 170 physicians from the American Academy of Neurology and 150 from the American Medical Directors Association and reported that 30% believed VS/UWS patients experience pain (interestingly, they found no differences between academic and non-academic physicians). Similarly, an unpublished survey by the American Neurological Association reported that 31% of its members were "uncertain" about whether VS/UWS patients could experience pain (31%) and suffering (26%) [58].

Two possible non-mutually exclusive interpretations of this tension or gap between guidelines and clinicians merit our attention. On the one hand, perhaps clinicians are blatantly wrong, or are what we could call in *disagreement of knowledge* with guidelines, i.e., they are or were wrong because they did not know. In support of this interpretation, research on diagnostic accuracy has shown that clinicians have trouble distinguishing the VS/UWS from MCS [59–61] and even confuse the VS/UWS with more remote states, like brain death and the locked in syndrome [62–64]. Knowledge disagreement could also be explained by the fact that, prior to the 2002 guidelines on MCS [4], MCS patients could have been clustered with VS/UWS patients within the broader category of vegetative patients. On the other hand, perhaps a different kind of disagreement could also be at work, a *disagreement of apprehension or perspective*, entailing that clinicians are or were observing pain perception in some

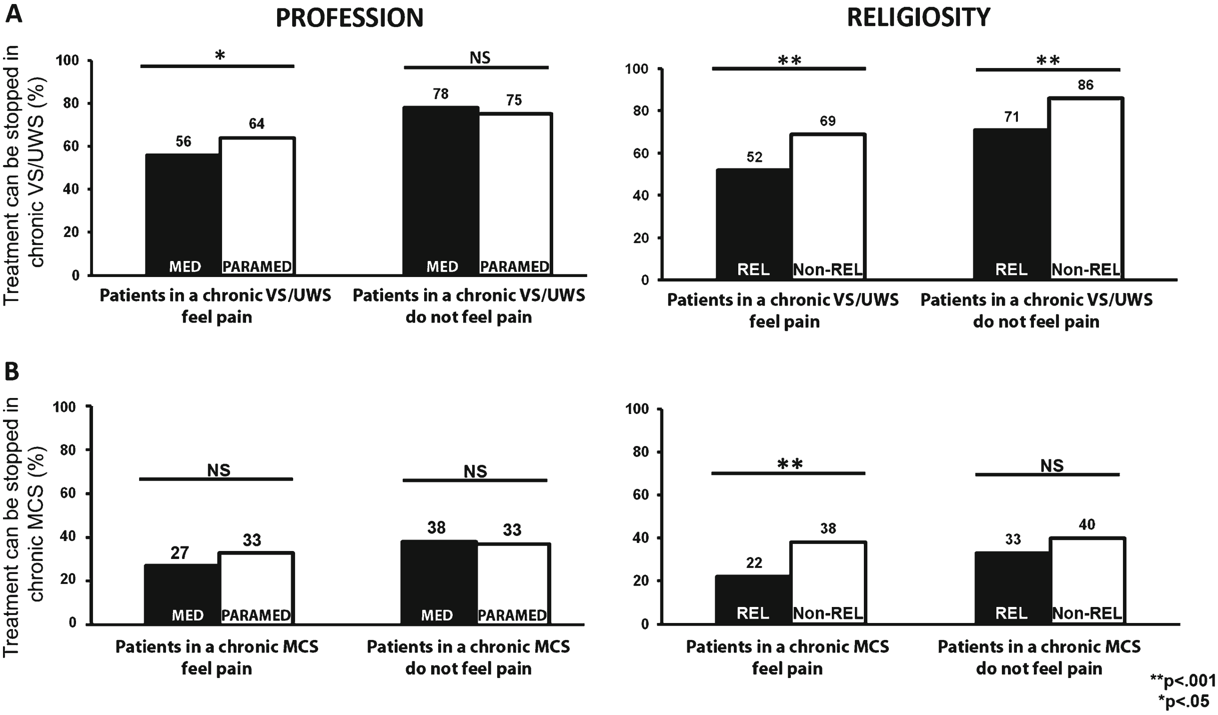

Fig. 2 Attitudes towards treatment withdrawal in patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS; panel **a**) and minimally conscious state (MCS; panel **b**) with regards to pain perception as formulated by professional background and religious beliefs

patients which was not reflected fully in guidelines offered to them. Following this interpretation, clinicians who may have or have not been in *agreement of knowledge* with guidelines may have nonetheless been at odds with them, deliberately or not, because of a difference in apprehension of pain perception. For example, influential guidelines such as the Multi-society Task Force's guidelines on the VS [10] could have under-recognized pain in MCS patients, not well distinguished from VS patients at the time of their publication. Accordingly, perhaps clinicians might have been partly right not to offer answers consistent with the views of major professional societies.

Now that we realize with hindsight that MCS is acknowledged as a distinct diagnostic category and that these patients feel pain, we are invited to greater humility in discussing pain perception (and awareness more generally) in disorders of consciousness. The different interpretations of the disagreement between clinicians and guidelines open up room for a cautionary medico-ethical approach where the perspective of a broad base of clinicians may need to be considered carefully in the development of guidelines as an additional process to establish external validity of diagnostic categories. There is no doubt that some confusion about VS/UWS and MCS exists due to lack of knowledge in healthcare professionals, including specialized clinicians [63]. However, to date, discrepancies have often been considered to be a knowledge gap on the part of clinicians; not a possible misapprehension of the guidelines themselves in spite of unspecific or indirect evidence about capacities like pain perception. In these patients, closer attention to *why* clinicians disagree with common understandings (e.g., through methodologies that allow to capture these information) could be an important ingredient in the development of consensual approaches and guidelines to tease apart disagreements of knowledge and disagreements of apprehension.

Discrepancies in Attitudes of Healthcare Providers and Their Consequences for Consistent Treatment Approaches

Our analysis suggests discrepancies between or within healthcare providers, which merit close attention. For example, respondents' opinions for chronic VS/UWS patients were mediated by professional background (Fig. 2). More paramedical respondents (64%) as compared to medical doctors (56%) were in favor of treatment withdrawal when also thinking that these patients perceive pain. The observed differences based on professional background might be related to many factors including differences in proximity to the patient, time spent at the bedside, sensibilities, and education [65, 66]. Nonetheless, this variability is concerning. Family members may be exposed to various messages about pain perception based on who they talk to [67]. Opinions on pain perception and end-of-life in MCS seemed to be less controversial among respondents, with no differences between physicians and paramedical professionals. In other research, we have found similarly that physician characteristics can shape attitudes toward end-of-life care, judgments about quality of life, and prognosis for post-coma recovery [67]. Several studies have shown differences between medical specialists and various healthcare providers in end-of-life care [65, 68–71].

Religiosity in general (i.e., when both religious and non-religious respondents were taken together) did not mediate the support on treatment withdrawal when comparing opinions about pain perception in VS/UWS patients (Fig. 2). However, some differences were identified between religious and non-religious respondents about withdrawal of life support. Although treatment withdrawal was generally supported less for MCS than for VS/UWS, religious respondents disagreed with treatment withdrawal significantly more than non-religious respondents (Fig. 2). We have previously shown that religious beliefs influence personal philosophical convictions towards dualistic views on the relationship between consciousness and the brain [72]. Such personal beliefs have also been shown to weigh on physicians' clinical decisions [e.g., 73]. In line with our findings on the influence of religion and age on beliefs about pain perception in VS/UWS [6], other studies on, for example, end-of-life decisions in intensive care patients have shown that older and more experienced doctors and doctors with religious convictions (i.e., Christians) more often refused to opt for treatment limitations [74, 75].

The impact of physician- (or other clinicians) dependent variability is not well understood although its existence is now well established. Future research could pay closer attention to this phenomenon in the context of disorders of consciousness a) to better understand the existence of variability between members of healthcare teams; b) to better characterise the impact of variability on family members and proxy decision makers; and c) to develop, if applicable, approaches to mitigate variability or its consequences through, for example, consensual chart notes and team discussion and communication [76].

The Implicit but Complex Relationship Between Pain Perception and Attitudes Toward Life-Sustaining Treatments

The data we reviewed above suggest a connection between beliefs about perception of pain and attitudes toward end-of-life decision-making in VS/UWS. Generally, the more a patient is able to feel pain, the less favorable a clinician is to withdrawal of life support. For instance, treatment withdrawal for chronic VS/UWS was supported more when respondents considered that these patients do not feel pain (77%) as compared to when they thought the patients feel pain (59%; Fig. 1). The high number of participants supporting treatment withdrawal in VS/UWS when considering that pain perception is absent is in line with existing guidelines on pain perception in these patients. However, the overall data suggest conflicting or complex ethical reasoning made by respondents regarding the relationship between pain perception and acceptability of withdrawal of life support.

At first glance, the relationship observed could be justified in as much as a patient with more sentience, and therefore more awareness, could be judged to be apt to be kept alive. Likewise, a patient who does not feel pain could be exhibiting lack of awareness and be allowed to die. We previously discussed that end-of-life opinions referring to patients (as opposed to imagined scenarios of oneself being in a state of disordered consciousness), could be formulated based on evidence of awareness [15]. With a similar rationale, pain as a subjective conscious experience corresponds to a form of conscious awareness. And such evidence, according to some, may give a strong reason to preserve life [77]. For the sake of our discussion we can retain this hypothesis as one possible explanation of the relationship observed in the data and also an approach put forth by some commentators [78] (and criticized by others [79]). We do admit that this is an implicit connection but given its plausibility and consequences, we discuss some of its assumptions further.

The implicit connection between greater pain sentience, greater awareness and therefore for greater reticence to withdrawal of life support resonates with a heavy trend in bioethics exploring the principle of respect for persons in terms of personhood or moral status of the person. This trend or line of argument usually assumes that we respect persons or other moral agents because of their ability or capacity as moral agents or persons. The capacities of persons usually refer to things like sentience and interests [80] or cognitive abilities [81] according to different authors. An enormous literature has examined and discussed if and what conditions or criteria a person or a moral agent must fulfill [e.g., 82], hoping thereby to shed lights on debates related to the beginning or the end of life [83]. In this scheme, evidence of sentience could very well be understood as a proof of being a moral agent. As suggested by Ropper, recent neuroimaging research, if it shows residual cognitive function or pain perception, could easily be interpreted by family members as an indication that treatments should be maintained [78]. Underlying this view is the assumption that some ontological status can be correlated to being a person and, once this state established, respect for that person or moral agent is called for. For the sake of clarity and simplicity, this could be designated as the *ontological understanding* of respect for persons in this paper.

Generally, equating persons with their brains or neurological status has been described in other areas of neuroethics as neuro-essentialism [84] and carries wide-ranging philosophical and practical problems [85]. A closer examination of the ontological understanding of respect for persons reveals specific problems of two different natures. First, at a more practical level, greater sentience or pain perception in MCS could mean greater ability to feel pleasurable states or well-being, which would call for specific therapeutic approaches [79] and an argument in favour of maintaining treatments. But greater sentience could very well mean a greater ability to feel both pain and suffering, i.e., the effects of being in a severely compromised state. In this sense, pain perception does not relate directly or clearly to a specific stance in favour of (or against) maintaining life support. Second, and more fundamentally, respect for persons entails other aspects which are not captured in a canonical (and allegedly simplified for this paper) ontological understanding of respect for persons. On the one hand, the preferences and interests of the person to be maintained in a state of pain sentience could still be argued to depend largely on preferences and interests as defined by the patient herself previously (or as voiced or articulated by a proxy decision-maker). In this sense, the close attention to what the patient would have wanted is crucial and the establishment of pain sentience is not by any standards a surrogate for this. On the other hand, still, the ontological view also causes problems because it does not capture *stricto sensu* non-ontological aspects of the principle of respect for persons. Respect for persons does partly rely on the fact that entities respected are considered to have a moral status or moral agency but also, at the same time, because they have worth and value for (and in relationship to) others. Consider the scenario, of a loved one (e.g., child, parent, spouse) being in a neurologically severely compromised state, and even in a state of disordered consciousness. To treat such a compromised loved one without respect would stir in most if not all strong feelings of disapproval even if one agrees that cognitive capacities have diminished or maybe vanished. This urge for respecting the person is not based on the person's capacities; on the contrary she may have lost them. It is rather a mixture of obligations towards others, respect for human relationship or respect for what a person was before the injury that support this principle. This is a more *relational (or contextual) understanding* of respect for persons and such an understanding is ill-captured by common arguments, which equate the person to a neurological status as found at the basis of the ontological view.

Consequently, the implicit connection between sentience and attitudes favoring life should be examined critically (if it does exist in clinicians as we have supposed for our discussion to better examine it critically). This link is debatable because it may rely on a dubious understanding of respect for persons which does not capture the preferences or wishes of the patient as defined by herself, overly objectifies persons and ontologizes the principle of respect for persons. The ontological view may carry forth a broader reductionist framework which, by strongly linking personhood to some ontological status, does not grasp the relational aspects captured in the principle of respect for persons. By extension, implicit or explicit uses of the ontological understanding in interpretations of recent neuroimaging research should be carefully identified and considered to ensure clarity about the reasons underlying respect for persons. This is reinforced by different studies showing strong appeal of neuroimaging data in the public eye [86–89], which could easily lead to neuroessentialism.

Conclusions

The quantification of pain and suffering as well of possible pleasure and happiness in VS/UWS and MCS patients remains extremely challenging. Functional neuroimanging and electrophysiology studies are offering new ways to better understand the residual cerebral processing of emotional stimuli in patients with disorders of consciousness. We here showed that healthcare providers' beliefs on possible pain perception in these patients influence opinions on end-of-life. More respondents who considered these patients to feel pain also opposed to withdrawing life sustain therapy. This interaction was stronger in religious caregivers and nurses. Recent neuroimaging findings as well as research on attitudes of healthcare providers bring forth important questions about the relationship of this research to clinical guidelines, the discrepancies of attitudes between healthcare providers and the complex relationship between pain perception and attitudes toward life-sustaining treatments. These ethical questions illustrate the need for closer attention to perspectives in research and in clinical care within the development of consensual approaches and guidelines; the need to understand practice variability and to minimize its impact on families; and the careful interpretation of recent neuroimaging findings and their consequences on withdrawal of life support.

Acknowledgments This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission, the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Public Utility Foundation "Université Européenne du Travail", "Fondazione Europea di Ricerca Biomedica" and the University and University Hospital of Liège. Writing of this paper was also supported by the Canadian Institutes of Health Research (New Investigator Award and Operating grant). We would also like to thank Dr. Emily Bell for helpful feedback on a previous version of this manuscript.

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Functional connectivity changes in hypnotic state measured by fMRI

Running page heading: Functional connectivity in hypnosis

Athena Demertzi, Soddu Andrea, Vanhaudenhuyse Audrey, Marie-Elisabeth Faymonville,
Steven Laureys
Coma Science Group, Cyclotron Research Center & Neurology Department, University of
Liège, Belgium

Correspondence to:

Prof. Steven Laureys
Coma Science Group
Cyclotron Research Center & Neurology Department
Allée du 6 août n° 8, Sart Tilman B30, University of Liège
4000 Liège, Belgium
Tel: +32 4 366 23 16
Fax: +32 4 366 29 46
e-mail: steven.laureys@ulg.ac.be

Abstract

Introduction: We here employed functional MRI to better characterize hypnosis-related functional connectivity changes in large-scale cerebral networks. **Methods:** Twelve subjects were scanned in three conditions: (1) normal eyes-closed wakefulness, (2) during mental imagery of pleasant autobiographical memories (i.e., control condition), and (3) during hypnotic state (reviving pleasant autobiographical memories). Seven seed regions were used to identify functional connectivity patterns of the default mode, left and right frontoparietal, salience, sensorimotor, auditory, and visual networks. Behavioral data concerning body sense modification, partial amnesia, and time sense modifications were collected at the end of each fMRI session. **Results:** Behaviorally, more subjects under hypnosis (as compared to the control condition) reported a modified sense of body and time as well as partial amnesia. Compared to the control condition of autobiographical mental imagery, we identified increased within-network functional connectivity for the default mode, left and right frontoparietal, salience, sensorimotor, and auditory networks; an enhanced cross-modal interaction between auditory and visual cortices was further observed. The visual network only showed decreases in functional connectivity in both within and between-network areas (i.e., hippocampus). **Conclusions:** Hypnosis, as compared to a control condition of revivification of pleasant autobiographical memories, leads to increases in functional connectivity in the default mode, left and right frontoparietal, salience, sensorimotor, and auditory networks, potentially reflecting lack of inhibitory cortico-cortical mechanisms. Additionally, hypnosis-related decreases in visual network functional connectivity and increases in cross-modal interaction between auditory and visual networks could be identified, hypothesized to reflect a revivification of hypnotic suggestions and not merely cognitively guided memory retrieval.

Key words: hypnosis, fMRI, resting state networks, connectivity, cross-modal interaction.

1. Introduction

Hypnosis is “a procedure during which a health professional or researcher suggests that a patient or subject experiences changes in sensations, perceptions, thoughts, or behavior” (The Executive Committee of the American Psychological Association - Division of Psychological Hypnosis, 1994). At the phenomenological level, hypnosis is characterized by increased degrees of private processes, such as absorption (i.e., the capacity to remain implicated in a mental state), dissociation (i.e., the mental separation from the environment), disorientation in time, space and person, diminished tendency to judge and censor, whereas it reduces spontaneous thoughts and gives the feeling of one's own response as automatic or extravolitional (Rainville and Price, 2003; Terhune and Cardena, 2010). Functional magnetic resonance imaging (fMRI) is an appropriate means to study hypnosis (Oakley et al., 2007). Such neuroimaging studies have contributed in elucidating the nature of hypnosis (intrinsic studies) and have used hypnosis as a means to explore psychological processes using specific suggestions (instrumental studies) (Oakley and Halligan, 2009).

Previous studies on fMRI resting state connectivity showed that the brain is characterized by coherent low-frequency fluctuations in cerebral blood-oxygen-level-dependent (BOLD) signals. These BOLD fluctuations are organized in large-scale “resting state” networks (RSNs) (e.g., Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006). It has been suggested that RSNs are of behavioral-functional significance because they strongly correlate with subjective reports (e.g., Boly et al., 2007; Ploner et al., 2010; Vanhaudenhuyse et al., 2011) and functional patterns from fMRI activation studies (Laird et al., 2011; Smith et al., 2009). We have previously shown that in normal waking conditions, activity in the “default mode network” (DMN) (encompassing precuneus/posterior cingulate cortex (PCC), mesiofrontal/anterior cingulate (ACC), and temporoparietal junction areas) and an anticorrelated “extrinsic” system (encompassing lateral frontoparietal cortices) corresponds to subjective ratings of internal (self-related mental processes) and external (perception of the environment through the senses) awareness respectively (Vanhaudenhuyse, et al., 2011). By means of hypnosis, we recently determined the functional contribution of these two networks to conscious awareness (Demertzi et al., 2011). As compared to a control condition of autobiographical mental imagery, we showed a hypnosis-related reduction in connectivity in the “extrinsic” system, possibly reflecting a decreased sensory or perceptual awareness. Importantly, the different functions of a brain region cannot be understood in *isolation* (i.e., in terms of functional segregation) but only in conjunction with regions it interacts with (i.e., functional integration) (Seghier et al., 2010). Therefore, in order to better understand the neural correlates of subjective awareness under hypnotic state, we aimed to characterize hypnosis-induced functional connectivity changes in seven previously identified RSNs (i.e., default mode, left and right frontoparietal, salience, sensorimotor, auditory, and visual networks). We here employed a hypothesis-driven functional connectivity analysis using a seed-voxel approach (e.g., Fox et al., 2005; Greicius et al., 2003) to calculate whole-brain voxel-wise functional connectivity maps of covariance with the seed region. The same dataset has previously been analyzed using a data-driven independent component analysis, limited to identifying changes in default mode and anticorrelated networks (Demertzi, et al., 2011).

2. Methods

2.1. Subjects and hypnotic induction

Twelve healthy subjects (4 women, mean age: 21 years ±3 SD) with no previous neurological or psychiatric history participated in the study after giving written informed consent in accordance with the Ethics Committee of the Faculty of Medicine of the University of Liège. A familiarization session with hypnosis preceded the main experiment. Subjects who reported absorption and dissociation level >6/10 on a numeric rating scale were further included in the study. During the familiarization session, detailed information about past pleasant life experiences, which the subject wished to use during hypnotic induction, was obtained through a semi-structured interview as described elsewhere (Faymonville et al., 2003). The hypnotic state was induced in the same way as in our patients during surgery (Faymonville et al., 2000; Faymonville et al., 1999; Faymonville, et al., 2003) and as in our previous functional neuroimaging studies with healthy volunteers (Maquet et al., 1999; Vanhaudenhuyse, Boly, et al., 2009). The hypnotic induction encompassed a 3-min instruction procedure involving progressive eye-fixation and muscle relaxation. Subjects were then invited to re-experience their pleasant autobiographical memories. As in clinical conditions, permissive and indirect suggestions were used to develop and deepen the hypnotic state. Subjects were continuously given cues for maintaining a hypnotic state. The exact words and details of the induction technique and specific suggestions and details during the course of the induction varied depending upon the experimenter's (M.E.F.) observation of subject behavior, and on her judgment of subjects' needs. During the experimental session the experimenters remained silent.

Three scanning sessions were performed: (1) during normal wakefulness, (2) during a control condition of mental imagery of autobiographical memories (i.e. the same memories used in hypnotic session but here without the hypnotic induction) (3) under hypnotic state. In order to exclude carry-over effects, the order of the sessions was randomized across subjects. After each fMRI session, subjective experience was debriefed on a 10-point numeric rating scale concerning emotion levels. Additional subjective reports were acquired using dichotomous (yes-no) scales measuring body sense modification (e.g., one arm felt longer than the other), partial amnesia and time sense modification (i.e., the session felt longer/shorter).

2.2. Functional data acquisition and preprocessing

Functional MRI time series were acquired on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany). Multislice T2*-weighted functional images were acquired with a gradient-echo echo-planar imaging sequence using axial slice orientation and covering the whole brain (32 slices, FoV = 220x220 mm^2, voxel size 3.4×3.4×3 mm^3, 30% interslice gap, matrix size 64x64x32, TR = 2460 ms, TE = 40 ms, FA = 90°). The three initial volumes were discarded to avoid T1 saturation effects. Head movements were minimized using customized cushions. A T1 magnetization prepared rapid gradient echo sequence was acquired in the same session for coregistration with functional data. Data preprocessing was performed using Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm) and encompassed reorientation, realignment, coregistration, segmentation, normalization, and smoothing (8-mm full width at half-maximum). Further motion correction (for small, large and rapid motions, noise spikes, and spontaneous deep breaths) was performed using ArtRepair toolbox for SPM (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm).

2.3. Extraction of resting state networks and statistical analysis

The identification of resting state networks was done in three steps as reported elsewhere (Boly et al., 2009; Boveroux et al., 2010; Fox, et al., 2005). First, the six motion parameters were used to regress in the initial signal in order to create a "dummy" BOLD signal, from which the regions of interest (ROIs) would be extracted. A high-pass filter of 128s was used to remove very low frequency fluctuations (.008 Hz). Second, time courses of interest were computed as the first principal component of the BOLD signal in 8-mm spherical ROIs centered on a priori coordinates from published studies: DMN [6 -42 32], left frontoparietal network [-44 36 20], right frontoparietal network [44 36 20], auditory network [-40 -22 8], visual network [-4 -84 8]

(Boveroux, et al., 2010), salience network [38 26 -10] (Seeley et al., 2007), and sensorimotor network [-2 -12 44] (Greicius et al., 2008). For the executive control network, we opted for both left and right network ROI analyses due to a lateralized pattern in functional connectivity reported in previous resting state studies (e.g., Damoiseaux, et al., 2006; Smith, et al., 2009). Similar time course extractions were performed for two other voxels of interest, located in white matter [-22 16 32] and lateral ventricles [-6 20 10]. Third, a design matrix (per subject, per network, per condition (normal waking, control condition of autobiographical mental imagery, hypnotic state) was created with the ROI's time course and 12 nuisance covariates (time courses in white matter, lateral ventricles, global signal and their derivatives, and the six movement parameters). Serial correlations were then estimated with a restricted maximum likelihood algorithm using an intrinsic autoregressive model during parameter estimations. The effects of interest were tested by linear contrasts, generating statistical parametric T maps for each subject. A contrast image was computed for each subject, for each network and for each condition, identifying regions correlating with the selected seed-region after removal of sources of spurious variance.

For each network, individual summary statistical images were entered in a second-level analysis, corresponding to a random effects model which estimates the error variance across subjects (Holmes and Friston, 1998). These second-level analyses consisted of repeated measures analyses of variance (ANOVA) with 3 regressors representing the three experimental conditions (normal wakefulness, control condition, and hypnotic state) and 12 extra regressors modeling the subject-effects for each condition. The error covariance was not assumed to be independent between regressors, and a correction for nonsphericity was applied. One-sided T contrasts tested for connectivity effects in all analyses. After model estimation, a first T contrast searched for areas correlated with each selected seed region during normal wakefulness.

Increased connectivity in hypnotic state was estimated by a conjunction analysis between normal wakefulness and the mental imagery < hypnotic state contrast. Decreased connectivity in hypnotic state was estimated by a conjunction analysis between normal wakefulness and the mental imagery > hypnotic state contrast. Results were corrected for multiple comparisons at the whole brain level using family wise corrections or cluster level corrections thresholded for significance at p<.05. Small volume corrections for multiple comparisons were only accepted in previously identified networks in the normal waking condition (i.e., identifying within network hypnosis-induced connectivity changes using an 8 mm sphere radius). Behavioral data were analyzed with SPSS v.16. Wilcoxon's sign rank tests was used to test differences between conditions for the numerical rating scale. Chi-square tests were used to test differences between conditions for the dichotomous scale. Results were considered significant at p<.05.

3. Results

Under hypnosis, more subjects reported body sense modification (n=7), partial amnesia (n=10) and time sense modification (n=9) as compared to the control condition (Figure 1). Emotional state ratings were not different under hypnosis (mean and SD 5.8±2.7) as compared to the control condition (i.e., autobiographical mental imagery) (mean and SD 5.1±2.7, p=.068).

The identified DMN during normal wakefulness encompassed precuneus/posterior cingulate cortex (PCC), mesiofrontal/anterior cingulate cortex (ACC), bilateral temporoparietal junctions, bilateral middle frontal gyri, parahippocampal gyrus, and thalamus (Table 1, green areas in Figure 2). In hypnosis (as compared to the control condition), increased within-network connectivity was observed in mesiofrontal cortex, bilateral temporoparietal junctions, bilateral middle frontal gyri, and bilateral thalami (Table 1, red areas in Figure 2). No areas showed hypnosis-related decreases.

The left frontoparietal network identified during normal wakefulness encompassed bilateral inferior and superior frontal gyri, bilateral inferior parietal lobes and ACC/supplementary motor area (SMA) (Table 1, green areas in Figure 2). In hypnosis (as compared to the control condition), increased within-network connectivity was observed in the right dorsolateral prefrontal cortex and middle occipital gyrus (Table 1, red areas in Figure 2). Decreased within-network connectivity was observed in most areas of the network (i.e., left inferior parietal lobe, contralateral middle frontal gyrus, left superior frontal gyrus/SMA, and ACC; Table 1, blue areas in Figure 2).

The right frontoparietal network identified during normal wakefulness encompassed bilateral inferior frontal gyri and bilateral inferior parietal lobes, ACC/supplementary motor area (SMA) and bilateral insular cortices (Table 1, green areas in Figure 2). In hypnosis, increased within-network connectivity was observed in bilateral inferior parietal lobes, the ACC and bilateral insular cortex (Table 1, red areas in Figure 2). No areas showed hypnosis-related decreases in functional connectivity.

The salience network identified during normal wakefulness encompassed insula, superior, inferior and middle frontal gyri, ACC, bilateral inferior parietal lobes, right middle temporal gyrus and bilateral globus pallidus (Table 1, green areas in Figure 2). In hypnosis, increased within-network connectivity was observed in the left insula, left inferior and middle frontal gyrus, and the ACC. Additional functional increases were identified in midcingulate cortex, right parahippocampal gyrus and right thalamus (Table 1, red areas in Figure 2). Decreased connectivity was observed in right dorsolateral prefrontal cortex (Table 1, blue areas in Figure 2).

The sensorimotor network identified in normal wakefulness encompassed SMA/midcingulate cortex, bilateral primary motor cortex and middle frontal gyri (Table 1, green areas in Figure 2). In hypnosis, increased within-network connectivity was observed in ACC and left middle frontal gyrus. Additional increases were identified in bilateral premotor cortices, left superior temporal gyrus and left inferior frontal gyrus (Table 1, red areas in Figure 2). Decreased within-network connectivity was observed in midcingulate cortex (Table 1, blue areas in Figure 2).

The auditory network identified in normal wakefulness encompassed bilateral superior temporal gyri/insular cortex, bilateral premotor, primary motor/somatosensory cortices, midcingulate cortex, bilateral thalami, left globus pallidus, and the brainstem (Table 1, green areas in Figure 2). In hypnosis, increased within-network connectivity was observed in bilateral middle and superior (spreading to fusiform area) temporal gyrus. Additional functional increases were identified in left inferior frontal gyrus and primary visual cortex (Table 1, red areas in Figure 2). The effect sizes of the observed cross-modal interaction between the primary auditory and primary visual cortex in the three conditions are displayed in Figure 3. Decreased within-network connectivity was observed in the bilateral globus pallidus and the brainstem (Table 1, blue areas in Figure 2).

The visual network identified in normal wakefulness encompassed primary and extrastriate visual cortices. No areas showed hypnosis-related increases. Decreased within-network connectivity was observed in the extrastriate visual cortex; additional functional decreases were observed with the left hippocampus (Table 1, blue areas in Figure 2).

4. Discussion

We here used hypnotic suggestion of pleasant autobiographical memories to investigate fMRI seed-based functional connectivity changes in seven functional “resting state” networks (RSNs). Subjects were invited to revive pleasant autobiographical memories as we use it in the clinical setting and during surgery (Faymonville, et al., 2000; Faymonville et al., 1997;

Faymonville, et al., 2003). At the behavioral level, significantly more subjects reported modifications in body sense, time sense and partial amnesia. Such experiential changes are commonly reported by hypnotized subjects who recognize an inability to judge, monitor and censor incoming information, with subsequent experiences that their own responses are automatic, characterized by suspension of usual orientation toward person, time, and location (Cardena, 2005; Rainville and Price, 2003). Emotional ratings were similarly high both in hypnosis and the control condition of autobiographical mental imagery, in contrast to previous studies showing higher emotional levels in hypnosis (Cardena, 2005). We should note here that the selection of the control condition to hypnosis remains challenging because in principle no cognitive state is comparable to hypnotic state. Past studies used subtraction analyses from baseline (e.g., Rainville et al., 2002) or mental imagery tasks (e.g., Derbyshire et al., 2004; Szechtman et al., 1998) to study hypnosis-related effects.

fMRI analyses overall showed more important hypnosis-related *increases* in functional connectivity (both within- and between- network) in six of the seven studied RSNs (i.e., DMN, right and left frontoparietal, salience, sensorimotor, and auditory networks); whereas the visual network was characterized by functional connectivity *decreases* in hypnosis (as compared to the control condition). These results extend previous positron emission tomography (PET) studies showing that hypnosis increases blood flow in the prefrontal cortex, right inferior parietal lobe, ACC, precentral regions, thalamus and brainstem, while decreasing activity in left inferior parietal lobe, precuneus/posterior cingulate, and occipital areas (Rainville, et al., 2002; Rainville et al., 1999). Similar increases and occipital decreases in functional connectivity during hypnosis were also observed after the application of noxious stimulation (Faymonville, et al., 2003; Vanhaudenhuyse, et al., 2009).

At the network-level, our identified DMN connectivity in normal waking conditions, classically encompassing precuneus/PCC, mesiofrontal/ACC, and bilateral temporoparietal junctions, corroborates previous studies in normal healthy controls (e.g., Fransson, 2005; Golland et al., 2007; Greicius, et al., 2003; Gusnard et al., 2001; Soddu et al., 2011). Albeit not systematically reported but in line with other studies, we also identified middle frontal (Greicius, et al., 2008; Laird et al., 2009), parahippocampal gyri (Greicius, et al., 2003; Vanhaudenhuyse, Noirhomme, et al., 2009), and thalami (Boveroux, et al., 2010; Fransson, 2005; Uddin et al., 2009) as part of the DMN in normal waking conditions. Under hypnosis (compared to the control condition), we observed within-network functional increases in most areas of the DMN (i.e., mesiofrontal/ACC, bilateral temporoparietal junctions, middle frontal gyri, and thalami). Such increases in connectivity might account for enhanced recollection of autobiographical information, previously shown to include medial prefrontal areas, medial and lateral temporal and retrosplenial/PCC, and temporoparietal junction (Svoboda et al., 2006). The hypnotized subjects might also have been more intensely involved in other self-related cognitive processes to which DMN activity has been classically linked, such as mind wandering (Mason et al., 2007), task-unrelated thoughts (McKiernan et al., 2006), introspection (Goldberg et al., 2006), and monitoring of the “mental self” (Lou et al., 2004). Indeed, we previously showed that hypnotized subjects self-rated increased absorption and dissociation levels parallel to diminished intensity of external thoughts, corroborating phenomenological studies where subjects’ scores during hypnosis were distributed across two response patterns, suggesting a dissociate type and an inward attention profile of experiencing hypnotic state (Terhune and Cardena, 2010). These findings can be discussed in light of a generally preserved functional connectivity in the DMN while the anticorrelated to DMN lateral frontoparietal network (broadly linked to perceptual awareness) showed reduced functional connectivity (Demertzi, et al., 2011). Other studies with hypnosis reported preserved connectivity in the precuneus/PCC next to cortical deactivations in the mesiofrontal part of the DMN during hypnosis, thought to mediate suspension of spontaneous non-goal directed cognitive activity (McGeown et al., 2009). Observed differences in functional patterns may be attributed to the different experimental protocols employed (i.e., guided mental imagery vs. resting state epochs from block and event-related designs) and the conditions under which the data have been collected. The choice of rest condition (eyes open, eyes closed) for instance, seems to influence cerebral spontaneous activity, as it was shown for visual areas (Bianciardi et al., 2009; Marx et al., 2004).

In activation studies with healthy controls, the left frontoparietal network has been often identified together with the right frontoparietal network (e.g., Dosenbach et al., 2008; Shulman et al., 2002). However, spatial similarity analysis between RSNs extracted with data-driven independent component analyses and those emerging from activation studies revealed that the right and left frontoparietal networks correlate with different activation datasets: the left frontoparietal corresponding to cognitive and “language” paradigms and the right frontoparietal corresponding to perceptual, somesthetic and nociception paradigms (consistent with the identification of the insula) (e.g., Boveroux, et al., 2010; Damoiseaux, et al., 2006; Laird, et al., 2011; Smith, et al., 2009). Due to this lateralized profile extracted with independent components analyses, here we studied functional connectivity separately for each network. During normal wakefulness, the identified left frontoparietal network encompassed bilateral inferior and superior frontal gyri, bilateral inferior parietal lobes, and ACC/supplementary motor area (SMA), similar to the aforementioned studies with independent component analysis. Under hypnosis (compared to the control condition), we found increased functional connectivity in the right dorsolateral prefrontal cortex and occipital middle gyrus (areas not part of the initially identified network). Such increased connectivity between occipital and frontal areas has been recently shown to contribute to the maintenance of visual short-term memories - evidenced as electrical oscillatory synchronization in non-human primates (Liebe et al., 2012). It could be hypothesized that the observed increases in connectivity of the left frontoparietal with occipital regions and the dorsolateral prefrontal cortex accounts for an enhanced ability of the subjects to retain more efficiently the suggested visual-related autobiographical hypnotic suggestions. We also observed a hypnosis-induced decreased connectivity in the left inferior parietal lobe, left middle frontal and superior frontal gyrus/SMA, and ACC. Altered activation of these areas, particularly of the left inferior parietal lobe, has been suggested to contribute to an altered monitoring of external time (Coull and Nobre, 1998; Wiener et al., 2010), consistent with our subjects' behavioral reports of time sense modification under hypnosis.

The right frontoparietal network during normal wakefulness encompassed bilateral inferior frontal gyri, bilateral inferior parietal lobes, ACC/SMA, and bilateral insular cortex similar to previous studies (Boveroux, et al., 2010; Damoiseaux, et al., 2006; Smith, et al., 2009). In healthy conditions, the right posterior parietal cortex mediates body-related visuospatial abilities and is suggested to exert inhibitory activity over the contralateral homologous areas (Koch et al., 2011). In hypnosis, we observed increased within-network connectivity in the right frontoparietal network (bilateral inferior parietal lobe, ACC, bilateral insular cortex) and no decreases in functional connectivity. Similar cerebral blood flow increases in right inferior frontal and right inferior parietal gyri were also previously shown for hypnotic state using PET (Rainville, et al., 2002). In hypnosis, it can be that enhanced connectivity in the right frontoparietal network might account for increased inhibitory processes on the left hemisphere (by "imposing" its visuospatial abilities) parallel to an altered state of bodily self-awareness. Such modified bodily senses, like altered sense of agency and out-of-body experiences, have also been linked to similar activity increases - especially in the right temporoparietal junction area (Blanke et al., 2002).

The identified regions of the salience network in normal wakefulness encompassed bilateral insular/ superior-inferior-middle frontal and ACC areas, as classically reported (Menon and Uddin, 2010; Ploner, et al., 2010; Seeley, et al., 2007; Sridharan et al., 2008; Wiech et al., 2010). Additionally, we also identified bilateral inferior parietal lobes, right middle temporal gyrus, and bilateral globus pallidus also in accordance with previously published work (e.g., Seeley, et al., 2007). In normal conditions, activation of the insula and ACC are commonly observed in conflict monitoring, information integration, and response selection (e.g., Cole and Schneider, 2007; Roberts and Hall, 2008). The salience network is also thought to be involved in interoception and pain (Laird, et al., 2011).We here found that in hypnosis (as compared to control condition) there was increased activity in most areas of the salience network (e.g., ACC, bilateral insular cortex) and reduced connectivity in the dorsolateral prefrontal cortex. Altogether, these observations can be interpreted as a decreased capacity of hypnotized subjects to cognitively control (i.e., requiring dorsolateral prefrontal cortex) conflicting incoming information (i.e., requiring ACC). Indeed, previous findings measuring Stroop task performance under hypnosis showed increased conflict-related activity in the ACC and unmodulated cognitive control-related lateral frontal cortex activity and this activation pattern further correlated with the Stroop error-rate (Egner et al., 2005). The ACC and insula have also been implicated in the processing of emotional aspects of noxious stimuli (e.g., Ploner, et al., 2010; Wiech, et al., 2010). Therefore, their increased coupling under hypnosis may reflect an enhanced emotional state, as it was previously reported that hypnotic suggestions for creating pain experiences led to activation of ACC and insula (Derbyshire, et al., 2004). Conversely, hypnosis-induced analgesia with suggestions of pleasant memories, failed to elicit ACC responses to noxious stimuli as compared to normal wakefulness (Vanhaudenhuyse, et al., 2009). We also identified hypnosis-induced increased connectivity between right insula and midcingulate cortex, right parahippocampal gyrus, and thalamus. Concerning the midcingulate cortex, similar connectivity increases with the insula have been previously identified by our group during hypnosis-induced analgesia towards noxious stimulation (Faymonville, et al., 2003). During normal wakefulness, the midcingulate cortex was also found functionally connected to the insular cortex (Taylor et al., 2009). The authors interpreted this connectivity pattern as contributing to the integration of interoceptive information with emotional salience in order to form a subjective representation of the body. Hence, an enhanced increased insular-midcingulate connectivity in hypnosis might account for experiences of an altered emotional state (mediated by the emotionally-related midcingulate cortex, Shackman et al., 2011) concerning the representation of the body (mediated by insula and ACC) (Damasio, 1994) including interoceptive awareness (Khalsa et al., 2009). This interpretation fits with our recorded subjective reports for a modified body sense in hypnotic state. Concerning the right parahippocampal gyrus, increases in functional connectivity in hypnosis may account for a vivid mental imagery, usually reported by hypnotized subjects (Pekala et al., 2010). Indeed, the right parahippocampal gyrus has been shown to mediate the formulation of prototypical mental images (Gardini et al., 2005). Concerning the thalamus, increased connectivity in the thalamus was previously suggested to maintain stable levels of performance in low arousal levels (e.g., occurring after sleep deprivation), hence preventing a generalized thalamocortical synchronization that would lead to sleep (Portas et al., 1998). The importance of thalamocortical connectivity to consciousness is further highlighted by its systematic absence in consciousness pathologies, like in vegetative state patients (eyes open, no signs of awareness of self and environment, Laureys et al., 2000).

The identified sensorimotor network (in normal wakefulness) encompassed supplementary motor area (SMA),/midcingulate cortex, bilateral primary motor cortex and bilateral middle frontal gyri, as in previous studies (Biswal et al., 1995; Cordes et al., 2000; Greicius, et al., 2008; Mannfolk et al., 2011). In hypnosis (as compared to the control condition) we found increased connectivity in most areas of the sensorimotor network (i.e., ACC, left middle frontal gyrus, bilateral premotor cortex) but also in right superior temporal and left inferior frontal gyrus. Decreased connectivity was observed in midcingulate cortex. Previous studies with hypnosis also identified increases in motor-related areas (precentral and premotor) considered to reflect muscular relaxation (Maquet, et al., 1999; Rainville and Price, 2003). Other studies using hypnosis to study this network also reported increases in functional connectivity. For example, hypnotic suggestions for left or right hand paralysis observed increased coupling between precuneus and primary motor cortex (Cojan et al., 2009) or other cortical areas (i.e., right dorsolateral prefrontal cortex, angular gyrus, Pyka et al., 2011). The authors considered their evidence suggestive of enhanced self-monitoring processes or modified cerebral representation of self during hypnosis. In normal resting state, the sensorimotor network has been related to action-execution and perception-somesthesis paradigms (such as action imagination, preparation, and visual motion) (Laird, et al., 2011; Smith, et al., 2009). It could then be that the observed enhanced connectivity under hypnosis reflects vivid motor-related mental imagery. Concerning the midcingulate cortex, previous studies showed that, together with the motor network, they are involved in monitoring response conflicts (as in go-trials, Huster et al., 2011). A decreased connectivity in the midcingulate cortex during hypnosis could imply a diminished capacity to monitor similar conflicts, corroborating phenomenological reports of hypnotized subjects experiencing their responses as automatic and extravolitional (Rainville and Price, 2003). Indeed, a previous study measuring regional cerebral blood flow indicated increased connectivity between the midcingulate cortex and pre-SMA during hypnotic analgesia (Faymonville, et al., 2003). However, the pre-SMA is thought to be involved in inhibitory mechanisms but not in the processing of conflicts per se (Huster, et al., 2011).

The auditory network during normal wakefulness encompassed bilateral superior temporal gyri/insular cortex, bilateral thalami, and left globus pallidus as is classically described (Cordes, et al., 2000; Eckert et al., 2008). We additionally identified motor-related areas (i.e., bilateral premotor and primary motor/somatosensory cortices) as well as midcingulate cortex, and brainstem also in accordance with previous findings (Martuzzi et al., 2010). In hypnosis, increased within-network connectivity was observed in bilateral middle temporal and superior temporal gyrus (spreading to the left fusiform area). Additional increases in functional connectivity were identified in left inferior frontal gyrus and primary visual cortex. The observed increased cross-modal connectivity between the primary auditory and primary visual cortex is confirmed by anatomical tracer studies in nonhuman primates (e.g., Clavagnier et al., 2004). Such cross-modal interaction is also present in controls during normal wakefulness (Eckert, et al., 2008) and disappeared during deep propofol anesthesia (Boveroux, et al., 2010). Behaviorally, such cross-modal interaction was shown in subjects who underwent hypnotic suggestions for having grapheme-color synesthesia, similar to what was observed in congenital grapheme-color synesthetes. The authors interpreted these findings as evidence for decreased inhibition processes between brain areas (Cohen Kadosh et al., 2009). Similarly here, the enhanced cross-modal interaction between low-level auditory and visual cortices in hypnosis could reflect increased cortical disinhibition during hypnosis, corroborating subjective reports of a dream-like state of consciousness of rich mental imagery (Cardena, 2005; Rainville and Price, 2003). Decreased connectivity was observed in bilateral globus pallidus and brainstem. As regards the auditory system in normal wakefulness, globus pallidus was shown to respond to auditory feedback of sensorimotor sequences (Prodoehl et al., 2008). A decreased functional connectivity with the auditory cortex in hypnosis could be indicative of a selective “neglect” to environmental auditory stimuli, consistent with subjects’ reports on having less external (i.e., environmental) thoughts in hypnotic state (Demertzi, et al., 2011). Finally, decreased connectivity of the auditory cortex with the brainstem might imply a lower-level processing of neural impulses generated in the inner ears (Langers et al., 2005), in line with hypnotized subjects’ self-reports on their experienced phenomenology dissociating from the external world.

The visual network (identified during normal wakefulness) encompassed medial posterior occipital areas and included primary, secondary, and tertiary visual cortices as in previous studies (Lowe et al., 1998). Occipital activation in normal conditions is commonly detected in retrieval of nonverbal material (Cabeza and Nyberg, 2000) and during recollection of scenes (Johnson and Rugg, 2007). In “resting state” conditions, it has been associated to viewing simple visual stimuli (Laird, et al., 2011). The visual network was the only RSN showing hypnosis-induced decreases in functional connectivity in extrastriate visual areas and the left hippocampus. Similar occipital decreases under hypnosis have been observed in hypnosis-induced analgesia with pleasant autobiographical suggestions as studied by PET (Faymonville, et al., 2003). A previous fMRI study with posthypnotic suggestion to forget autobiographical long-term memories (i.e., scenes of a previously watched movie) also showed pronounced diminished activity in the extrastriate occipital lobes in the subjects who underwent the posthypnotic amnesia suggestion as compared to those who did not (Mendelsohn et al., 2008). In combination with an observed decrease in the hippocampus, a structure classically related to the encoding and retrieval of long-term memories (Kolb and Whishaw, 2003), it can be hypothesized that subjects in hypnosis do not merely retrieve stored memories, but rather revive them by following the experimenters instruction. This pattern may also account for the observed significant increase of amnesia after the hypnotic state as compared to our control condition.

In conclusion, as compared to a control condition of pleasant autobiographical memories, we here mainly identified increased within-network functional connectivity for the default mode, left and right frontoparietal, salience, sensorimotor, and auditory networks, potentially reflecting lack of inhibitory cortico-cortical mechanisms. This hypothesis is further supported by an increased cross-modal interaction between primary auditory and primary visual cortex in hypnosis as compared to the non-hypnosis conditions. The visual network only showed decreases in functional connectivity in both within and between-network areas (i.e., hippocampus), possibly reflecting a free revivification of hypnotic suggestions and not mere memory retrieval.

Acknowledgments

This work was supported by the Belgian National Funds for Scientific Research (FNRS), the European Commission, the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Public Utility Foundation "Université Européenne du Travail" , "Fondazione Europea di Ricerca Biomedica" and the University and University Hospital of Liège.

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Figure captions

Figure 1. Subjective ratings during normal wakefulness, autobiographical mental imagery, and hypnotic state. More subjects reported body sense modification, partial amnesia, and time sense modification during hypnotic state as compared to autobiographical mental imagery and normal wakefulness (*p<.05).

Figure 2. Identified functional connectivity during normal wakefulness (green areas) in seven large-scale resting state networks. Compared to control condition, resting state networks mainly exhibit hypnosis-related increases in functional connectivity (red areas) with some areas showing decreased functional connectivity (blue areas). Of note is the visual network which exhibits only within-network hypnosis-related functional connectivity decreases. Results are displayed on a structural T1 magnetic resonance template. Normal wakefulness results are thresholded at family wise error rate corrected p<.05 (whole brain) and, for display purposes, functional connectivity increases/decreases in hypnosis are shown at uncorrected p<.001 (x, y and z values indicate the Montreal National Institute coordinates of represented sections).

Figure 3. Increased cross-modal interaction between auditory network (seed) and identified visual network (shown in yellow) in hypnotic state (as compared to the control condition). For display purposes, data are thresholded at uncorrected p<.001 superimposed on a structural T1 magnetic resonance template. Effect sizes (expressed as group mean and 90% CI) are shown in the right panel, reflecting for connectivity between auditory and visual cortices during normal wakefulness, autobiographical mental imagery, and hypnotic state.

Table 1. Peak voxels of the seven resting state networks identified in normal wakefulness and after contrasting hypnotic state with a control condition of autobiographical mental imagery.

	x	y	z	Z value	p value
Default mode network					
Normal wakefulness					
Precuneus/posterior cingulate cortex (7/31)$^+$	9	-49	37	inf	<.001***
Mesiofrontal/Anterior cingulate cortex (10/32)	3	47	-5	6.53	<.001***
L Temporoparietal junction (39)	-45	-64	25	7.37	<.001***
R Temporoparietal junction (39)	51	-58	19	7.24	<.001***
L Middle frontal gyrus (8)	-21	20	43	5.95	<.001***
R Middle frontal gyrus (6)	24	20	52	6.39	<.001***
L Parahippocampal gyrus	-24	-28	-14	4.64	.046***
R Thalamus	9	-13	7	4.63	.048***
Hypnosis > control					
Precuneus/posterior cingulate (7/31)$^+$					
Mesiofrontal/Anterior cingulate cortex (10/32)	15	41	10	5.67	<.001***
L Temporoparietal junction (39)	-48	-61	19	5.43	.001***
R Temporoparietal junction (39)	51	-55	13	4.71	.041***
L Middle frontal gyrus (8)	-24	14	37	4.20	.013**
R Middle frontal gyrus (6)	30	11	22	4.17	.016**
L Thalamus	-12	-10	7	4.48	<.001*
R Thalamus	15	-10	7	3.61	.007*
Hypnosis < control					
No areas identified					
Left frontoparietal network					
Normal wakefulness					
L Inferior frontal gyrus (9/46/13)$^+$	-45	35	19	Inf	<.001***
R Inferior frontal gyrus (9/46/13)	45	41	13	Inf	<.001***

(continued)	x	y	z	Z value	p value
Left frontoparietal network					
Normal wakefulness					
L Inferior parietal lobe (40)	-57	-43	43	6.45	<.001***
R Inferior parietal lobe (7)	36	-58	46	5.13	.007***
L Superior frontal gyrus (6)	-21	8	52	5.35	.002***
R Superior frontal gyrus (6)	24	8	61	5.29	.003***
Anterior cingulate cortex/ Supplementary motor area (32/6)	-9	20	37	5.64	<.001***
Hypnosis > control					
L Inferior frontal gyrus (9/45) +	-54	20	16	5.30	.003***
R Dorsolateral prefrontal cortex (9)	42	8	28	5.28	.003***
L Middle occipital gyrus (19)	-42	-85	16	4.43	.001**
Hypnosis < control					
L Inferior parietal lobe (40)	-51	-46	49	3.91	.002*
R Middle frontal gyrus (10)	33	47	13	4.54	.006**
L Superior frontal gyrus/Supplementary motor area (8/6)	-15	17	43	3.97	.036**
Anterior cingulate cortex (32)	15	35	16	3.82	.004*
Right frontoparietal network					
Normal wakefulness					
R Inferior frontal gyrus (9/46) +	45	35	19	Inf	<.001***
L Inferior frontal gyrus (9/46)	-45	26	25	inf	<.001***
L Inferior parietal lobe (40)	-42	-55	40	inf	<.001***
R Inferior parietal lobe (40)	36	-55	40	inf	<.001***
Anterior cingulate cortex/ Supplementary motor area (32/6)	9	20	43	7.01	<.001***
R insula	33	17	-8	6.86	<.001***
L insula	-30	17	1	5.25	.004***
Hypnosis > control					
R Inferior frontal gyrus (9/46) +	45	35	19	Inf	<.001***

(continued)	x	y	z	Z value	p value
Right frontoparietal network					
Hypnosis > control					
L Inferior parietal lobe (40)	-54	-46	34	3.70	.038**
R Inferior parietal lobe (40/39)	57	-46	43	4.28	.001**
Anterior cingulate cortex (32)	9	23	40	4.74	.039***
L Insula	-24	14	1	3.80	<.001*
R Insula	27	11	1	4.53	<.001*
Hypnosis < control					
No areas					
Salience network					
Normal wakefulness					
R Insula/Superior-Inferior-Middle frontal gyrus (6/9/10)$^+$	39	23	-11	Inf	<.001***
L Insula/Superior-Inferior-Middle frontal gyrus (6/9/10)	-33	26	-14	Inf	<.001***
Anterior cingulate cortex (32)	6	20	40	6.43	<.001***
L Inferior parietal lobe (40)	-66	-43	22	5.19	.005***
R Inferior parietal lobe (40)	51	-43	31	5.36	.002***
R Middle temporal gyrus (21)	51	-25	-8	5.49	.001***
L Globus pallidus	-15	5	-2	5.20	.005***
R Globus pallidus	15	8	1	5.67	<.001***
Hypnosis > control					
R Insula$^+$	39	23	-11	Inf	<.001***
L Insula/Inferior frontal gyrus/Middle frontal gyrus (47/10)	-39	-13	-8	4.84	.023***
Anterior cingulate cortex (32)	9	35	19	3.82	.004*
Midcingulate cingulate cortex (24)	3	8	40	3.52	.050**
R Parahippocampal gyrus	27	-22	-5	4.04	.001**
R Thalamus	9	-28	-5	3.93	.001**
Hypnosis < control					

(continued)	x	y	z	Z value	p value
Salience network					
Hypnosis < control					
Dorsolateral prefrontal cortex (9)	33	50	16	4.95	.015***
Sensorimotor network					
Normal wakefulness					
Supplementary motor area (SMA)/Midcingulate cortex (24)$^+$	-3	-33	43	Inf	<.001***
L Primary motor cortex (4)	39	-13	40	7.45	<.001***
R Middle frontal gyrus (4)	-27	-28	46	inf	<.001***
L Middle frontal gyrus (9)	-30	35	25	5.13	.007***
R Dorsolatreral prefrontal cortex (9)	30	38	28	4.79	.030***
Hypnosis > control					
Supplementary motor area (SMA) $^+$	-3	-13	43	Inf	<.001***
Anterior cingulate cortex (32)	0	29	22	4.65	.002**
L Middle frontal gyrus (9/10)	-27	44	22	4.29	.027**
L Premotor cortex (6)	-51	-4	40	4.33	.003**
R Premotor cortex (6)	48	-1	46	5.28	.003***
R Superior temporal gyrus (22)	45	-37	1	4.51	.020**
L Inferior frontal gyrus (45)	-39	20	4	4.53	.010**
Hypnosis < control					
Midcingulate cortex (24)	-12	2	37	4.08	.033**
Auditory network					
Normal wakefulness					
L Superior temporal gyrus (22/41)$^+$/Insula	-39	-22	7	Inf	<.001***
R Superior temporal gyrus (41)/Insula	48	-25	13	inf	<.001***
L Premotor cortex (6)	-6	-10	70	4.97	.043***
R Premotor cortex (6)	15	-4	70	5.11	.007***
L Primary motor/somatosensory cortex (4/5)	-18	-22	70	6.37	<.001***

(continued)	x	y	z	Z value	p value
Auditory network					
Normal wakefulness					
R Primary motor/somatosensory cortex (4/5)	24	-31	67	5.83	<.001***
Midcingulate cortex (24)	-3	5	37	6.32	<.001***
L Thalamus	-15	-22	1	5.02	<.001***
R Thalamus	15	-19	-2	5.81	<.001***
L Globus pallidus	-18	2	-5	5.45	.001***
Brainstem	6	-25	-20	5.59	.001***
Hypnosis > control					
L Superior temporal gyrus (22) $^{+}$	-39	-25	7	Inf	.001***
L Middle temporal gyrus (21)	-54	-7	-17	4.17	<.001*
R Middle temporal gyrus (21)	57	2	-17	4.32	<.001*
L Superior temporal gyrus (22)/Fusiform gyrus (37)	-54	-52	7	4.46	.003**
R Superior temporal gyrus (22)	51	-43	4	4.05	.008**
L Inferior frontal gyrus (47)	-39	29	-5	4.92	.018***
Primary visual cortex (17)	-6	-82	13	3.58	.001**
Hypnosis < control					
L Globus pallidus	-24	-10	-2	3.93	<.001**
R Globus pallidus	18	-4	-5	3.84	.038**
Brainstem	3	-25	-20	4.16	<.001*
Visual network					
Normal wakefulness					
Primary visual cortex (17)$^{+}$	0	-85	7	Inf	<.001***
Extrastriate visual cortex (18/19)	18	-76	10	inf	<.001***
Hypnosis > control					
No areas identified					
Hypnosis < control					

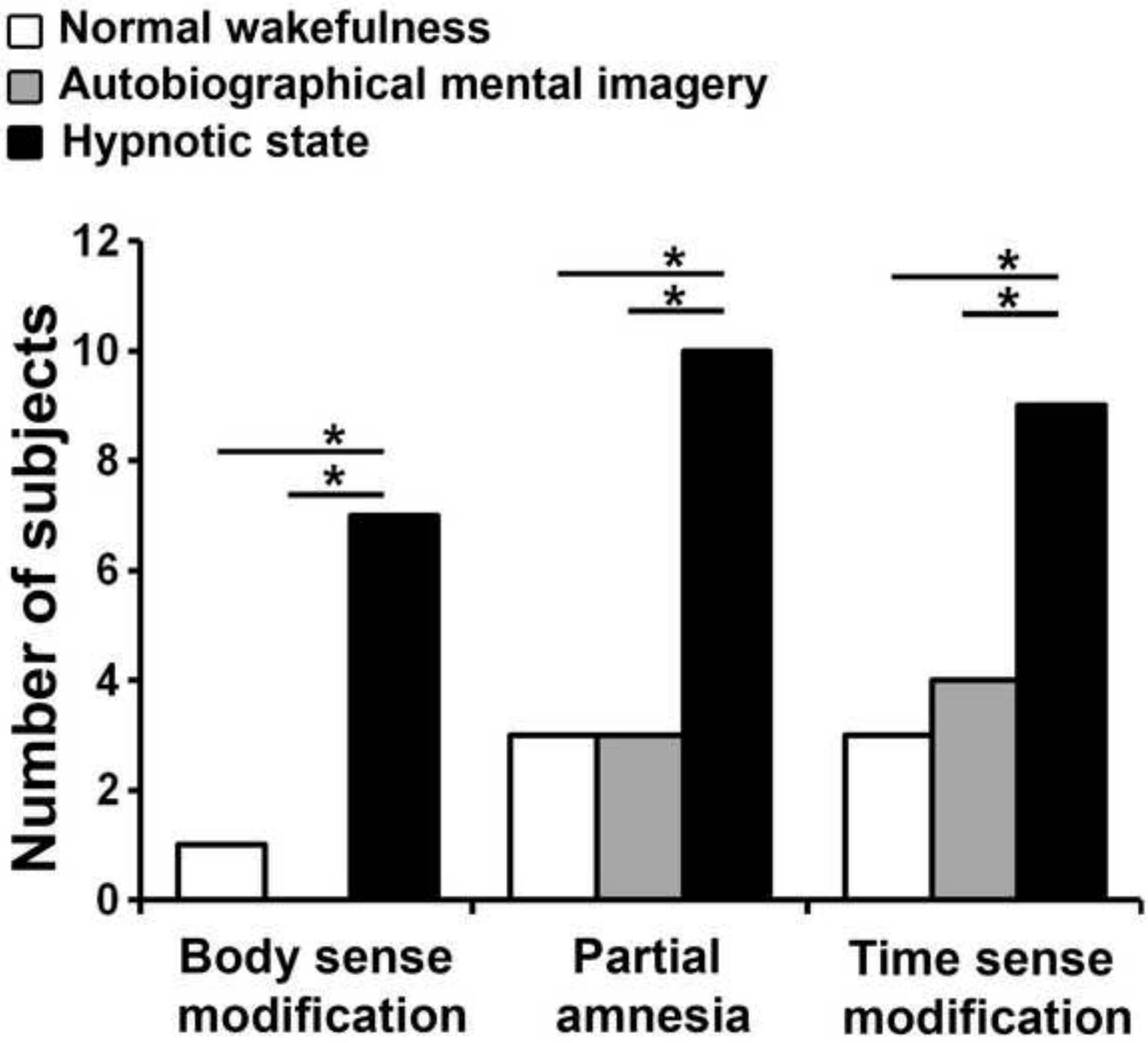
(continued)	x	y	z	Z value	p value
Visual network					
Hypnosis < control					
Primary visual cortex (17)$^+$	0	-85	7	Inf	<.001***
Extrastriate visual cortex (19)	-33	-61	7	4.29	<.001*
Hippocampus	-27	-28	-8	4.13	.005**

*** Family wise error rate corrected p value

**Cluster-level p value

*Small-volume (8mm sphere) corrected p value

$^+$ Seed area


Normal wakefulness
Autobiographical mental imagery
Hypnotic state
Number of subjects
0
2
4
6
8
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12
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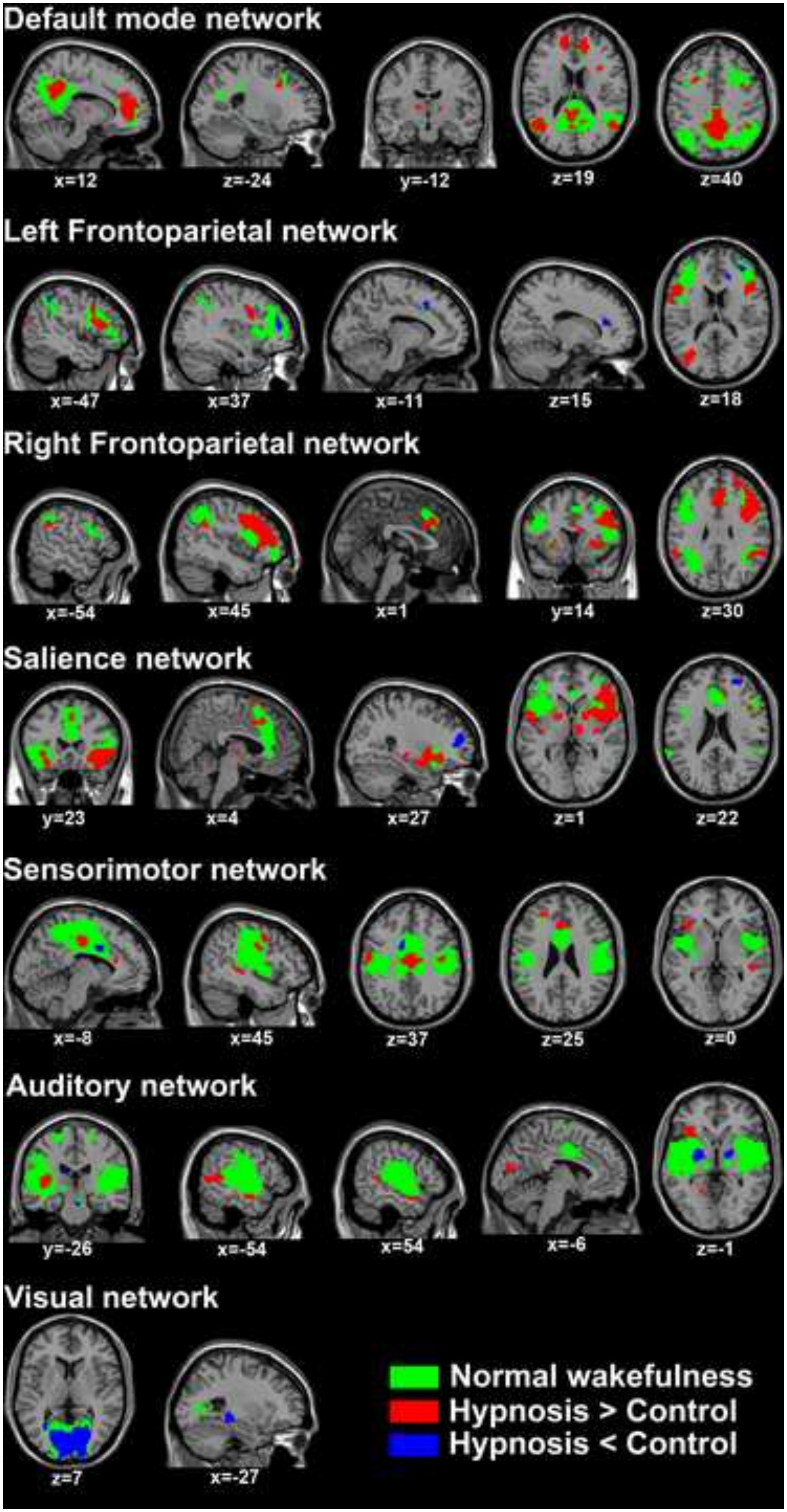
Body sense modification
Partial amnesia
Time sense modification

Figure_2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Left Frontoparietal network
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Right Frontoparietal network
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y=14
z=30
Salience network
y=23
x=4
x=27
z=1
z=22
Sensorimotor network
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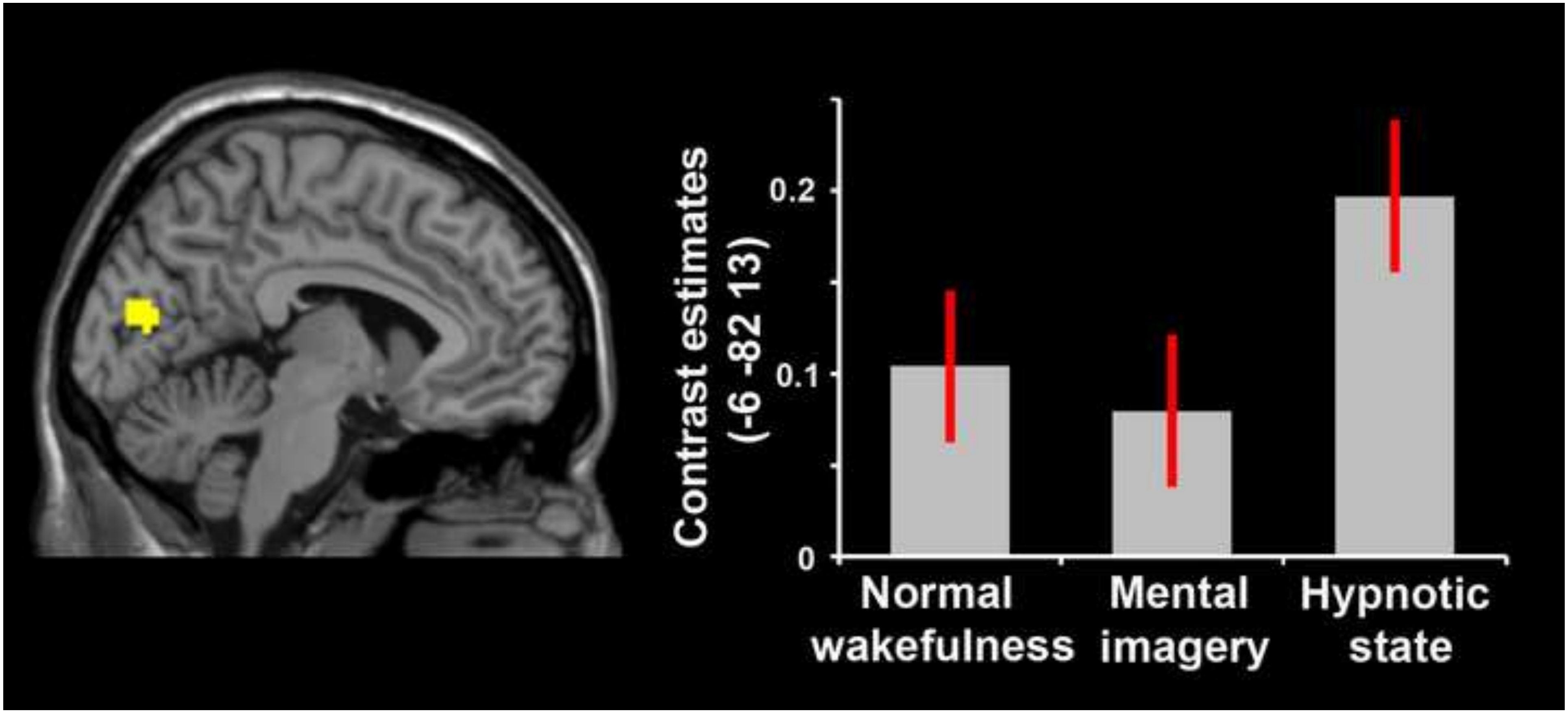
x=45
z=37
z=25
z=0
Auditory network
y=-26
x=-54
x=54
x=-6
z=-1
Visual network
z=7
x=-27
🟩 Normal wakefulness
🟥 Hypnosis > Control
🟦 Hypnosis < Control

Figure_3


Contrast estimates
(-6 -82 13)
0.2
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Normal wakefulness
Mental imagery
Hypnotic state

Ethics in Disorders of Consciousness

A. Demertzi, S. Laureys, and M.-A. Bruno

Introduction

The introduction of the mechanical ventilator in the 1950s and the development of intensive care in the 1960s permitted many patients to sustain their vegetative functions and survive severe injuries. Despite such advances, in many cases patients were found to suffer from altered states of consciousness which had never been encountered before as these patients would normally have died from apnea [1]. The imminent ethical impact of these profound states of unconsciousness was reflected in the composition of the first bioethical committees discussing the redefinition of life and the concept of therapeutic obstinacy. In 1968, the Ad Hoc Committee of Harvard Medical School published a milestone paper for the redefinition of death as irreversible coma and brain failure [2]. The committee was comprised of ten physicians, a theologian, a lawyer and a historian of science, betokening the medical, legal and societal debates that were to follow. We will here give a brief overview of some ethical issues related to the concept of consciousness and the medical management of patients with disorders of consciousness, such as comatose, vegetative and minimally conscious states that may be encountered in the intensive care setting. We will emphasize the problem of pain management and end-of life decision-making.

Ethical Issues in Clinical Management

Confusions and controversies are often related to the way we define things. One such multifaceted term is consciousness, which has many divergent connotations [3]. The way we define consciousness is crucial, as it may govern our attitudes towards medical management of disorders of consciousness. For example, in a survey among medical and paramedical professionals (n = 1858), compared to a student population (n = 250), we recently found that although the majority of health-care workers denied a distinction between consciousness and the brain, more than one-third of medical and paramedical professionals still regarded the mind and brain as separate entities (**Fig. 1**). Such dualistic opinions may have implications in the formulation of scientific questions about the nature of consciousness, in the clinical management of disorders of consciousness, and in the reception of both by the general public [4]. We here adopt a perspective where consciousness is clinically defined as having two components, wakefulness and awareness [5]. Under this definition, many variant altered states of consciousness may be hosted. The most transient and most familiar to us all is the transition

J.-L. Vincent (ed.), *Annual Update in Intensive Care and Emergency Medicine 2011*
DOI 10.1007/978-3-642-18081-1, © Springer Science+Business Media LLC 2011

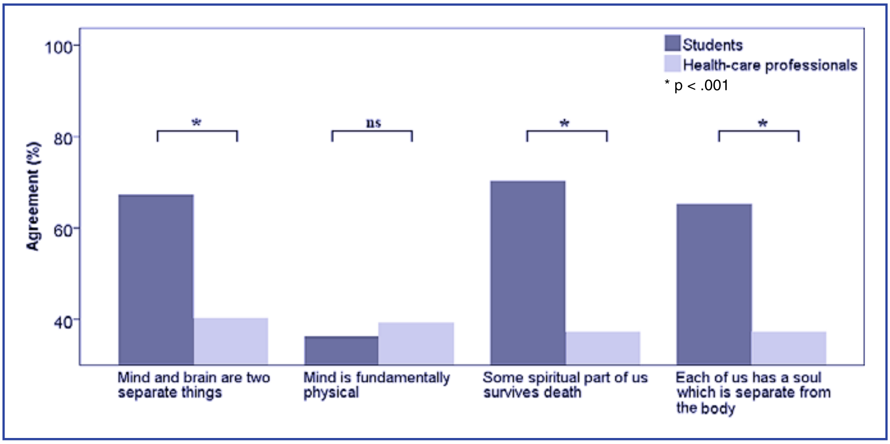

Fig. 1. Dualistic attitudes towards the mind-brain relationship among students (Edinburgh survey, n = 250) and health-care professionals (Liège survey, n = 1858). Adapted from [4] with permission.

from conscious wakefulness to deep sleep; the drowsier we become, the less aware we get of our surroundings and of ourselves. This implies that patients in coma and under anesthesia (i.e., pharmacological coma) are unaware because they cannot be awakened, even after noxious stimulation. The vegetative state is defined as 'wakefulness without awareness', in which patients may open their eyes but will never exhibit non-reflex voluntary movements [6]. A patient in a minimally conscious state may show some signs declaring awareness (e.g., visual pursuit, orientation to pain or non-systematic command following) but is unable to communicate his or her thoughts or feelings [7]. Because these behavioral signs of consciousness are often small and fluctuating in time, this condition may be challenging to diagnose and differentiate from vegetative state [8]. It has been suggested that once conscious awareness has been identified and its quality is estimated in a non-communicating patient (e.g., see [9, 10]), this may well be a good reason to preserve life-sustaining aids [11]. However, the moral significance of preserved consciousness has been questioned on the grounds that it may not always be in a patient's best interest to continue a severely handicapped life [12].

One challenging issue in this debate is the conscious perception of pain in these patients. As defined by the Multi-Society Task Force on persistent vegetative state (PVS), 'pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that may emanate endogenously from the depths of human self-perception' [13]. Thus, pain constitutes a conscious experience with a physical (nociception) and a psychological counterpart (suffering), suggesting that nociception by itself is not sufficient to cause suffering. The management of pain in patients with disorders of consciousness is challenging because patients in a vegetative or minimally conscious state cannot verbally or non-verbally communicate their feelings or experiences [1]. This is reflected in how clinicians perceive pain in these patients. According to recently surveyed attitudes among health-care professionals, there was unanimous support that patients in a minimally conscious state (96 %) perceived pain whereas opinions were less clear for the patients in a vegetative state (56 %) [14]. Considering these results on varying beliefs about pain perception in disorders of consciousness, physicians and health-care workers' views on analgesia and symptom management may also be affected. Since nearly half of the surveyed doctors stated that vegetative state patients do not feel pain, these physicians could be expected to act accordingly, for instance, by not providing analgesic medication to these patients during care or during the dying process after withdrawal of artificial hydration and nutrition [15], the latter on the grounds that these patients do not experience suffering from hunger or thirst [16].

How are clinicians supposed to determine whether patients in a vegetative or minimally conscious state feel pain or suffering? At the patient's bedside, we are limited to evaluating the behavioral responsiveness to pain: If patients show no signs of voluntary movement (i.e., localizing the source of pain) in response to a noxious stimulus, it can be concluded that they do not experience pain. Conscious but paralyzed 'locked-in syndrome' patients, who classically show absent or 'decerebration' (i.e., stereotyped extension) or 'decortication' (i.e., stereotyped flexion) movements, teach that this need not necessarily be the case. In response to noxious stimulation, patients with disorders of consciousness will frequently show increased arousal levels (evidenced by opening or widening of the eyes), quickening of breathing, increased heart rate and blood pressure, or grimace-like or crying-like behavior. As all these abilities are also seen in infants with anencephaly [17], they are considered to be of subcortical origin and not necessarily reflecting conscious perception of pain. However, the absence of a behavioral response cannot be taken as proof of the absence of conscious perception [18] and the inference of pain and suffering merely by observing behavioral responses may be misleading. Repeated clinical examinations by experienced examiners with standardized tools such as the recently proposed 'coma nociception scale' (e.g., [19]) are paramount for the behavioral assessment of pain. Additional information coming from functional neuroimaging studies may assist in the formulation of a clearer clinical picture. For example, in a positron emission tomography (PET) study, it was shown that patients in a vegetative state may show cerebral processing of the incoming noxious stimulus (activation of primary somatosensory areas), but the observed neural activity was isolated and disconnected from higher-order associative brain areas which are considered necessary for conscious perception of pain [20]. It is important to stress that very different results were obtained in patients in a minimally conscious state in whom functional neuroimaging studies have shown more widespread activation in the cerebral network compared to patients in vegetative state, but similar to healthy controls, suggesting potential pain perception these patients [21]. In light of the incomplete picture of pain perception in patients in vegetative state, the existing risk for misdiagnosis [8], the inconclusive drug-related effects in disorders of consciousness [22], and the limitations of interpreting neuroimaging results [23], pain prophylaxis and drug treatment have been proposed for all patients suffering from disorders of consciousness [24].

In intensive care settings, medical doctors and assisting staff are confronted daily with situations where clinical decisions are still more critical, such as continuing or withdrawing life sustaining treatment. Treatment limitations can be viewed as having two directions depending on whether the decision is made preoperatively or after an intervention [25]. In the former case, it may come as a refusal of cardiopulmonary resuscitation (CPR) in case of cardiopulmonary arrest; in the latter case, it most usually comes as a decision to withdraw treatment, such as the artificial respirator or artificial nutrition and hydration. CPR is almost automatically performed as an emergency therapy in order to restore heartbeat and ceased breathing, unless the patient or the legal representative have refused it in advance in a form of a do-not-resuscitate order (DNR). Nevertheless, it should be noted that DNR orders do not necessarily prohibit other therapies; they rather authorize the physician to act on this specific manner of therapy [26]. When the clinical condition of a patient has been stabilized and denoted as irreversible, decisions about artificial nutrition and hydration limitation may come into play. From a bioethical standpoint, withdrawing artificial nutrition and hydration is comparable to withdrawing mechanical ventilation, even if emotionally these two actions may be perceived differently. In the intensive care unit (ICU) setting, the majority of deaths are the result of a medical decision to withhold or withdraw treatment [27]. Such decisions are evidence-based and rely on validated clinical or paraclinical markers of bad outcome ([e.g., for anoxic coma see [28]). Despite the controversy as to whether artificial nutrition and hydration constitutes a medical treatment [29] and thus should never be withdrawn from patients [30], most of the medical community (especially Anglo-Saxon) would agree with its being a medical therapy which can be refused by patients and surrogate decision makers [31]. Such decisions in vegetative state patients are only justified when a case is denoted as irreversible [32]. Guidelines with regard to temporal determination of a definitive outcome in vegetative state currently state that if no recovery is observed within 3 months after a non-traumatic or 12 months after a traumatic accident, the condition of the patient can be denoted as permanent [13].

The controversies around the clinical management at the end-of-life in patients with disorders of consciousness were reflected in a recent European survey (n = 2475), where the majority of health-care professionals (66 %) agreed to withdraw treatment from chronic vegetative state patients whereas only 28 % agreed to do so for chronic minimally conscious state patients; additionally, most clinicians wished not to be kept alive if they imagined themselves in a chronic vegetative state (82 %) and a similar proportion (67 %) agreed if they imagined themselves in a chronic minimally conscious state [33]. Geographical region and religion were among the factors that explained most of the variance in the responses and these results are in line with previous surveys in which physicians' characteristics (i.e., age, religion and geographic region) seem to play a critical role in governing such options [34]. The detected differences between the two states could be due to the existing legal ambiguity around minimally conscious state which may have influenced the surveyed participants to differentiate between expressing preferences for self versus others, by implicitly recognizing that the latter could be a step on the slippery slope to euthanasia.

Clinicians' opinions appear much more uniform with regard to brain death [35]. As mentioned earlier, the Ad Hoc Committee of the Harvard Medical School went on to the redefinition of death as a consequence of the technological advancements in intensive care, where patients could sustain severe injuries but maintain the function of vital organs [2]. It was, therefore, possible to dissociate between cardiac, respiratory and brain functions which in turn required an alternative definition of death, moving from a cardiorespiratory towards a neurocentric formulation (i.e., irreversible coma). According to the latter, death can be viewed either as death of the whole brain or of the brainstem [36] or as neocortical [37]. The first two are defined as the irreversible cessation of the organism as a whole, differing in their anatomical interpretation [38], whereas the last solely requires the irreversible loss of the capacity of consciousness and social interaction but has never convinced medical or legal scholars. The main utility of the introduction of brain death is that it permitted vital organ procurement for transplantation with the application of ethical restrictions, such as the dead donor rule (i.e., a patient has to be declared dead before the removal of life-sustaining organs). Based on the neocortical definition of death, however, both vegetative and minimally conscious state patients can be declared dead. It has been argued that the neocortical definition is conceptually inadequate and practically unfeasible, especially with the lack of a complete understanding of higher-order conscious functioning; hence, patients with disorders of consciousness are not dead [27] and organ donation options in these patients should be excluded since they violate the dead donor rule [39] – despite opposing opinions to abandon this ethical axiom [40].

Legal Issues in Disorders of Consciousness

Disorders of consciousness have posed not only medical challenges but in many cases they required the mediation of legal authorities in order to regulate ambiguous and controversial issues, such as end-of-life decisions. When end-of-life wishes have not been earlier formulated in the form of an advanced directive (i.e., written statement completed by a competent person in anticipation of her/his future incompetence, expressing personal treatment preferences and formal surrogacy appointment), then a surrogate decision maker is eligible to take responsibility for the patient’s clinical management. The way the legal representative should act on behalf of the patient is a progressive one. The surrogate should first attempt to follow the wishes of the patient as closely as possible, in the way in which they were expressed before the accident, either orally or in the form of advance directives. When the wishes are unknown and an advance directive is not available, the surrogate decision maker should try to reproduce the patient’s preferences based on their history and personal values. When this is not possible, decisions should rely on more objective markers that determine the patient’s best interest (e.g., likelihood of recovery, pain management, impact on family) [25, 41]. The proxy decision maker should mediate trying to maximize the patient’s self-determination and protect their interests using the principles of beneficence and non-maleficence [42].

The use of advance directives could also be considered as a means to regulate cost savings in the end-of-life; once the wishes of a terminal patient are known, care can be taken to constrain extraordinary means and spare the available resources for other urgent cases. However, no such rationale corresponds to the reality and advance directives, together with hospice care and the elimination of futile care, have not contributed to the effective regulation of the economics of dying [43]. Treatment resources are not unlimited and despite care for a good death sometimes physicians need to make do with the means they have available. The allocation of resources and the economics at the end-of-life have not yet been fully determined for patients with disorders of consciousness. In intensive care medicine, some unwritten rules can facilitate decisions as to who is to be treated, like the ‘first come’ principle or ‘who will most likely benefit from intensive care’ [44]. However, for chronic disorder of consciousness cases, information on resource allocation is often lacking. This may be due to the nature of patients with chronic vegetative or minimally conscious state. These are severely brain-damaged patients for whom the dilemma on treating becomes crucial either because treatments are not guaranteed as successful (i.e., the condition is too bad to be treated) or unkind (i.e., the quality of life of those surviving is not acceptable) which may lead to an unwise way to allocate available resources [44].

The legal provisions concerning end-of-life issues in disorders of consciousness differ from country to country. In the United States, where a patient-centered medical framework has been adopted, the patient is allowed to participate in the regulation of her/his own course of the disease. In the case of disorders of consciousness, legal representatives in close collaboration with the clinical staff and in line with the patient's previously expressed wishes may decide together about the long-term care of irreversibly comatose patients. There are times, however, when conflicts of interests arise while making such decisions, either between family and physicians, such as in the Quinlan case [45], or among family members, like the more recent Schiavo case [46]. As most often such cases require the mediation of the court, they may have a wider publicity in which public opinion can come into play and may lead to societal movements on pro-life versus right-to-die action groups [47]. In Europe, there are more subtle differences in the way treatment limitation is perceived, especially between Northern (more right-to-die oriented) and Southern (more pro-life positioned) European countries [33]. In general, decisions for treatment limitation (usually concerning artifical nutrition and hydration) need to be taken after reference to the court. Exceptions are the Netherlands, Belgium, Switzerland and Scandinavian countries where no court mediation is needed for limiting treatment in disorders of consciousness [48]. Considering these different attitudes within and out of Europe, it has been suggested that an international consensus regarding standards of care for patients with disorders of consciousness needs to be reached [49].

Conclusion

The ethical issues accrued from the study and management of patients with disorders of consciousness are variant and multi-faceted. Medical, legal and public controversies are partly shaped by how different people think about these issues and in many cases are country-dependent. It is, therefore, evident that a uniform ethical framework needs to be shaped to guide clinicians and caregivers in terms of clinical outcome, prognosis, and medical management.

Acknowledgments: This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission (DISCOS, Marie-Curie Actions), the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11–340), the Fondation Médicale Reine Elisabeth and the University of Liège.

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Manuscript classification: Article

Global fMRI resting state connectivity breakdown in patients with disorders of consciousness

Athena Demertzi (PhD)[1] Andrea Soddu (PhD)[1] Audrey Vanhaudenhuyse (PhD)[1] Francisco Gómez (PhD)[1] Camille Chatelle (MSc)[1] Luaba Tshibanda (MD)[2] Mélanie Boly (PhD)[1] Marie Thonnard (MSc)[1] Vanessa Charland - Verville (BSc)[1] Olivia Gosseries (PhD)[1] Marie - Aurélie Bruno (PhD)[1] Aurore Thibaut (MSc)[1] Murielle Kirsch (MD)[3] Steven Laureys (MD, PhD)[1]

[1]Coma Science Group, Cyclotron Research Center & Neurology Department, University of Liège, Belgium
[2]Department of Radiology, CHU University Hospital, University of Liège, Belgium
[3]Department of Anesthesiology, CHU University Hospital, University of Liège, Belgium

Number of characters in the title (including spaces and punctuation): 92
Number of words in abstract: 249
Number of words in main text: 3045
Number of references: 40
Number of tables: 1
Number of figures: 2

Corresponding author
Steven Laureys, MD, PhD
Coma Science Group, Cyclotron Research Center & Neurology Department
Allée du 6 août n° 8, Sart Tilman B30
University of Liège, 4000 Liège
Tel: +32 4 366 23 16, Fax: +32 4 366 29 46
e - mail address: steven.laureys@ulg.ac.be

Email addresses of co-authors: a.demertzi@ulg.ac.be; andrea.soddu@ulg.ac.be; avanhaudenhuyse@ulg.ac.be; fagomezj@gmail.com; camille.chatelle@ulg.ac.be; l.tshibanda@chu.ulg.ac.be; mboly@student.ulg.ac.be; marie.thonnard@ulg.ac.be; v.charland@ulg.ac.be; ogosseries@ulg.ac.be; ma.bruno@ulg.ac.be; athibaut@ulg.ac.be; murielle.kirsch@chu.ulg.ac.be

Statistical analysis was completed by Athena Demertzi, Andrea Soddu and Steven Laureys (Coma Science Group, Cyclotron Research Center & Neurology Department, University of Liège, Belgium)

Supplemental Table, electronic file name: Demertzi_Article_Supplemental_tables

Search terms: [18] Coma; [121] fMRI; [222] Pain; Crossmodal interaction; Resting state

Author contributions and disclosures

Dr. A. Demertzi was involved in study concept and design, acquisition of data, analysis and interpretation. She reports no disclosures.

Dr. A. Soddu was involved in analysis and interpretation and in critical revision of the manuscript for important intellectual content. He reports no disclosures.

Dr. A. Vanhaudenhuyse was involved in acquisition of data. She reports no disclosures.

Dr. F. Gómez was involved in analysis and interpretation. He reports no disclosures.

Ms C. Chatelle was involved in acquisition of data. She reports no disclosures.

Dr. L. Tshibanda was involved in acquisition of data. He reports no disclosures.

Dr. M. Boly was involved in critical revision of the manuscript for important intellectual content. She reports no disclosures.

Ms M. Thonnard was involved in acquisition of data. She reports no disclosures.

Ms V. Charland - Verville was involved in acquisition of data. She reports no disclosures.

Dr. O. Gosseries was involved in acquisition of data. She reports no disclosures.

Dr. M-A Bruno was involved in acquisition of data. She reports no disclosures.

Ms A. Thibaut was involved in acquisition of data. She reports no disclosures.

Ms M. Kirsch was involved in acquisition of data. She reports no disclosures.

Prof. S. Laureys was involved in study concept and design, analysis and interpretation, and study supervision. He reports no disclosures.

Abstract

Objective: By use of resting state fMRI we first aimed to investigate connectivity changes within and between multiple cerebral systems and then to assess residual pain - related processing in the absence of external stimulation in patients with disorders of consciousness. **Methods:** Functional connectivity in the default mode, left and right frontoparietal, salience, sensorimotor, auditory and visual networks was evaluated with seed - region approach. Behavioral Nociception Coma Scale scores were used as regressors of the salience network's functional integrity, which is shown to mediate pain – related processes. **Results:** Data were obtained from 22 controls, 2 locked - in syndrome, 11 minimally conscious, 12 "vegetative"/unresponsive and 5 comatose patients (15 non - traumatic, 7 anoxic etiology). Between - group comparisons showed intra - network decreases in functional connectivity as a function of the level of consciousness. A disruption in crossmodal interaction between visual and auditory networks was further observed. "Vegetative"/unresponsive and minimally conscious patients' Nociception Coma Scale scores showed a positive correlation with the salience network functional connectivity. **Conclusions:** Our results demonstrate a global breakdown in cortico - cortical connectivity in both sensory/ sensorimotor and "higher - order" networks, possibly accounting for patients' limited capacities for conscious cognition. The observed positive correlation between the Nociception Coma Scale scores and the salience network connectivity reflects nociception - related processes measured in the absence of an external stimulus. Our results point to the utility of resting state analyses in clinical settings where short and simple setups are preferable to activation protocols.

Introduction

Study protocols during resting state (i.e. eyes closed, no task performance) do not require sophisticated setup and surpass the need for patients' active participation. Therefore, this paradigm is a suitable means to study patients with disorders of consciousness (DOC), such as patients in coma, vegetative state/ unresponsive wakefulness syndrome (UWS)[1] and minimally conscious state (MCS). Past studies in these patients using resting state functional magnetic resonance imaging (rsfMRI) have shown reduced connectivity in a default mode network (DMN) as a function of the level of consciousness.[2, 3] Importantly, however, the functions of a brain region can be better understood in conjunction with other brain areas with which it interacts. Therefore, we here aimed to assess rsfMRI functional connectivity in DOC patients by investigating various large - scale cerebral networks (including the DMN), such as the left and right frontoparietal, salience, sensorimotor, auditory and visual networks.[4] Data from two patients with locked - in syndrome (LIS; awake and conscious with/without means of producing speech, limb or facial movements) were used as further control on patients' data. We hypothesized that rsfMRI functional connectivity strength in these different networks will be related to the level of consciousness.

As the issue of pain in the study of coma and related states continues to raise clinical and ethical concerns,[5] we further aimed to assess residual pain - related processing during resting state conditions, in the absence of noxious stimulation. For this purpose, we correlated clinical "pain" scale scores, i.e. Nociception Coma Scale,[6] with the functional integrity of the salience network, given that previous studies have correlated salience network connectivity with pain - related processes.[7-9]

Methods

Patients

We prospectively assessed patients in MCS, VS/UWS, coma and LIS following severe brain damage studied at least 5 days after the acute brain insult. Clinical examination was performed using the Coma Recovery Scale - Revised (CRS - R).[10] Exclusion criteria were contraindication for MRI (e.g. presence of ferromagnetic aneurysm clips, pacemakers), MRI acquisition under sedation or anesthesia, uncertain clinical diagnoses, large focal brain damage (>50% of total brain volume) and the presence of head movements (i.e., >10mm displacement). Healthy volunteers were free of psychiatric or neurological history. The study was approved by the Ethics Committee of the Medical School of the University of Liège. Informed consent to participate in the study was obtained from the healthy subjects and from the legal surrogates of the patients.

Functional data acquisition and preprocessing

In all patients and controls, functional MRI time series were acquired on a 3T head - only scanner (Siemens Medical Solutions, Erlangen, Germany). Three hundred multislice T2* - weighted functional images were acquired with a gradient - echo echo - planar imaging sequence using axial slice orientation and covering the whole brain (32 slices; voxel size: 3×3×3 mm; matrix size 64×64×32; repetition time = 2000 ms; echo time = 30 ms; flip angle = 78°; field of view = 192 mm). The three initial volumes were discarded to avoid T1 saturation effects. For anatomical reference, a high-resolution T1-weighted image was acquired for each subject (T1 - weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence).

Data preprocessing was performed using Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm) and encompassed reorientation, realignment, coregistration, segmentation, normalization, and smoothing (8 - mm full width at half - maximum). Further motion correction (for small, large and rapid motions, noise spikes, and spontaneous deep breaths) was applied using ArtRepair toolbox for SPM (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm).

Extraction of resting state networks and statistical analysis

The identification of resting state networks was done in three steps as employed in previous studies.[11, 12] First, the six motion parameters were used to regress in the initial signal in order to create a "dummy" BOLD signal, from which the regions of interest (ROIs) would be extracted. A high - pass filter of 128s was used to remove very low frequency fluctuations (<.008 Hz). Second, time courses of interest were computed as the first principal component of the BOLD signal in 8mm spherical ROIs centered on a priori coordinates: DMN [6 -42 32], left frontoparietal network [-44 36 20], right frontoparietal network [44 36 20], auditory network [-40 -22 8], visual network [-4 -84 8],[12] salience network [38 26 -10],[7] and sensorimotor network [-2 -12 44].[13] Similar time course extractions were performed for two other voxels of interest, located in white matter [-22 16 32] and lateral ventricles [-6 20 10]. Third, a design matrix (per subject, per network) was created with the ROI's time course and 12 nuisance covariates (time courses in white matter, lateral ventricles, global signal and their derivatives, and the six movement parameters). The effects of interest were tested by linear contrasts, generating statistical parametric T maps for each subject. A contrast image was computed for each subject and for each network identifying regions correlating with the selected seed - region after removal of sources of spurious variance.

For each network, contrast images were entered in a second - level random effects analysis (one - way ANOVA with four levels: controls, MCS, VS/UWS and coma patients). A correction for non - sphericity was applied to account for potentially unequal variance across groups. In controls, one - sided T contrast searched for areas correlating with each selected seed region in each network. Assuming that patients with DOC show similar brain activity as compared to controls, we used an exponential one - tailed T contrast searching for decreases in functional connectivity as a function of the level of consciousness (controls, MCS, VS/UW, coma) in each network.[2] Data of the two LIS patients were not included in the design matrices but their contrast estimates per network were displayed for visual comparison to the data of controls and patients with DOC. For the T contrasts in controls, results were considered significant at $p<.05$ corrected for multiple comparisons at family wise error (FWE) rate for the whole brain volume. For the between - group contrasts, results were considered significant at FWE $p<.05$ calculated at the whole brain level or after small volume correction (SVC; 10mm - radius sphere) around a priori expected coordinates taken from an independently - assessed group of healthy individuals (n=12; 4women; mean age 21±3 years; 350 scans acquired on a 3T head - only scanner (Siemens Medical Solutions, Erlangen, Germany); 32 slices, FoV = 220x220 mm^2, voxel size 3.4×3.4×3 mm^3, 30% interslice gap, matrix size

64x64x32, TR = 2460 ms, TE = 40 ms, FA = 90°; see Supplemental table e-1 for group mean effects for each network).

For the salience network, a regression analysis was performed with the available Nociception Coma Scale (NCS)[6] total scores in 13 patients (3 coma, 7 UWS, 3 MCS). As a control to this regression analysis, we opted to use the same NCS scores as predictors of the functional connectivity in the auditory network. The choice of this network was based on the fact that this system also encompasses ACC and insular cortices in healthy volunteers.[14] For the NCS – salience network regression analysis results were considered significant at $p<.05$ SVC (10mm - radius sphere) around a priori expected coordinates taken from the healthy control group. For the auditory network - NCS regression analysis, results were considered significant at uncorrected $p<.001$ for the whole brain volume.

Results

Between April 2008 and July 2011, 145 patients underwent MRI scanning out whom 59 were excluded due to fMRI scanning under sedation, 27 due to presence of ambiguous clinical signs or uncertain diagnosis or change of diagnosis within a week after scanning, 12 due to large focal brain damage (>50% of total brain volume), 6 due to presence of functional communication, 6 due to motion artifacts (i.e., >10mm displacement) and 5 due to technical reasons. Twenty - eight patients (11 MCS, 12 VS/UWS, 5 coma) were eventually included for further analysis (11 women; mean age 52±17 years, range 20 - 87; 6 traumatic, 22 non - traumatic of which 7 anoxic); 18 patients were assessed in the chronic setting (>1 month post - insult). Data from 2 LIS patients were used for visual comparison with controls' values. Supplemental table e-2 summarizes the patients' demographic and clinical characteristics. Patients' data were compared with an age - matched healthy volunteer group (n=22; 8 women; mean age 46±17 years; range 20 - 75).

All rsfMRI networks were successfully replicated across the group of healthy controls (red areas in figure 1; Supplemental table e-3). Group - level exponential contrasts showed consciousness - level dependent connectivity breakdown in all areas of the identified networks (blue areas in figure 1; table 1). More specifically, the DMN showed a drop in functional connectivity strength in precuneus/PCC, mesiofrontal/ACC, bilateral temporoparietal junction, left middle frontal gyrus when comparing controls, MCS, VS/UWS and coma patients. For the regions anticorrelating to the DMN, a functional connectivity breakdown as a function of the level of consciousness was identified in bilateral inferior frontal gyri, right middle frontal gyrus, bilateral inferior parietal lobes, and supplementary motor area/midcingulate cortex. In the left and right frontoparietal network, between - group comparisons showed decreases in connectivity strength in bilateral inferior frontal and inferior parietal lobes. In the sensorimotor network there were between - group decreases in connectivity strength in SMA and the claustrum. In the auditory network between - group decreases in connectivity were observed in bilateral superior temporal gyri/insular cortices, ACC, and right claustrum. In the visual network between - group decreases in connectivity were observed in primary visual cortex; additional decreases in functional connectivity were observed in left primary auditory cortex and left insula, areas not initially identified in the group of healthy controls.

The between - group comparisons in the salience network showed decreases in connectivity strength in bilateral insula and ACC; additional drops in functional connectivity were found in left pars opercularis (Broca's area), left superior temporal gyrus (primary auditory cortex and up to Wernicke's area), areas not initially identified in the group of healthy controls (table 1, figure 1). Nociception Coma Scale total scores showed a positive correlation with functional connectivity of the salience network's ACC (z = 3.26, p=0.001 SVC; x=0, y=20, z=37), left insula (z = 4.04, p<.001 SVC; x= - 39, y= - 16, z=7), and right insula (z = 2.99, p=.001; SVC ; x=36, y=5, z= - 2) (figure 2). For the control auditory network regression analysis, no correlation between functional connectivity in pain - related areas and NCS scores was identified (Supplemental table e-4).

Discussion

We here investigated fMRI functional connectivity of seven large - scale cerebral networks in 28 patients with DOC, 2 patients with LIS and 22 healthy controls in resting state conditions. Overall, the studied networks (reliably replicated across controls) showed a consciousness level - dependent breakdown in connectivity ranging from controls and LIS, MCS VS/UWS and coma patients.

For the DMN, which is classically linked to self - related processes,[15] our results corroborate previous fMRI[2] and PET studies[16] and are in line with other studies in altered states of consciousness, such as deep sleep,[17, 18] midazolam sedation[13] and propofol anesthesia.[12] We also identified a connectivity breakdown in areas anticorrelating to the DMN. Similar reductions in the anticorrelated system have been identified for hypnosis,[19] sleep,[17] propofol anesthesia[12] and a VS/UWS patient[20] suggesting an important role of this system to conscious awareness. We recently showed that this anticorrelated to the DMN fMRI activity (encompassing bilateral frontoparietal regions) corresponds to overt subjective reports of “external awareness”, namely that it reflects conscious perception of the environment through the senses.[21] Taken together, our results for the DMN and its anticorrelated network in DOC could imply that these patients have limited capacities for self - related mentation. Nevertheless, our limited understanding of the dynamic neural complexity underlying consciousness and its resistance to quantification in the absence of communication[22] makes it difficult to establish strong claims about the self - consciousness in non - communicative patients.

We also observed a breakdown in connectivity strength in the left (involved in cognitive and “language” paradigms) and right frontoparietal network (relating to perceptual, somesthetic and nociception processing)[4, 23] as a function level of consciousness. Activity in these frontoparietal areas has been considered a necessary condition for conscious reportable perception.[24] Here, our findings are in line with previous PET studies showing a bilateral frontoparietal metabolic impairment in MCS patients which is more profound and widespread in VS/UWS.[16, 25] fMRI results from light sleep[26] and propofol anesthesia[12], however, support a generally preserved resting state functional connectivity pattern in these frontoparietal networks. Overall, our results suggest that the reduced rsfMRI connectivity in these frontoparietal networks reflects a reduced level of “external” awareness in patients with DOC, as previously hypothesized.[27]

For the salience network, which has been linked to conflict monitoring, information integration, response selection as well as to emotional, interoception and pain - related processes[4, 7-9] we found consciousness - level dependent decreases in connectivity both within the network (i.e. in ACC and bilateral insula) and in language - related areas (i.e. extending to Broca's and Wernicke's areas) which were not initially identified in controls. Similar altered rsfMRI connectivity in salience network was recently reported for deep sleep.[28] Altogether, our findings might account for a decreased capacity of patients with DOC to respond to salient stimuli, including auditory[29, 30] and noxious. Here, the identified correlation between salience network connectivity and NCS scores suggests that salience network rsfMRI can be used as a tool to assess residual attentional resources to salient stimuli, including possible pain processing in DOC, in the absence of noxious stimulation. The necessity of a paraclinical marker for pain assessment is highlighted by studies showing that clinical examination alone may under - or overestimate the capacity of non - communicative patients for pain.[31]

For the sensorimotor network (linked to action - execution and perception - somesthesis paradigms[4, 23]), the between - group comparison showed a drop in connectivity strength in the claustrum and the SMA as a function of the level of consciousness. In normal wakefulness, the claustrum was suggested to permit the binding of disparate perceptual, cognitive and motor events into a single conscious percept[32] and the SMA was thought to relate to voluntary intentional motor planning[33]. Hence, a disruption of this network in DOC is in line with these patients' incapacities for conscious (motor) cognition. Our results are in contrast to what is observed in rsfMRI studies under light midazolam sedation[13] or during light sleep[26] where generally no significant reductions in sensorimotor network connectivity could be identified.

The between - group connectivity decreases in the auditory network, which has been associated with tone and pitch discrimination, music, speech, phonological and oddball discrimination,[34] corroborate previous activation studies in VS/UWS patients showing restricted auditory responses to primary auditory cortices, dissociated from higher - order auditory areas.[29] Auditory stimulation in MCS patients, in contrast, recruits stronger connectivity between the secondary auditory cortex and temporal and prefrontal association cortices, thought to be necessary for the gain of conscious auditory perception.[35] Our results here are different from what has been observed under propofol anesthesia, where intra - network connectivity is generally preserved.[12] Importantly, we here also report an inter - network connectivity decrease between auditory and salience systems, suggesting a decoupling between these networks in DOC in the absence of salient auditory stimulation. Similar inter - network fMRI connectivity changes have been reported for deep sleep[28] and propofol anesthesia,[36] highlighting the functional importance of such inter - system connectivity to conscious awareness.

For the visual network, we also show a consciousness - level dependent breakdown of both intra - and inter - network connectivity in DOC. Studies in rsfMRI in light sleep, however, show preserved or increased functional connectivity for the visual system,[26, 37] a pattern also observed in propofol anesthesia.[12] Interestingly, we here further observed an impaired crossmodal interaction between visual - auditory networks when comparing normal controls, LIS, MCS, VS/UWS and coma patients. Such visual - auditory crossmodal interaction was previously described in normal conscious conditions[14] and is considered relevant to multisensory integration which subsequently enhances visual awareness.[38] Our findings are also in line with data from propofol anesthesia in healthy volunteers showing decreased crossmodal interaction as a function of pharmacologically - induced unconsciousness.[12]

In summary, we here show a consciousness - level dependent breakdown of rsfMRI connectivity in “lower - level” sensory (auditory and visual) and sensorimotor and in “higher - order” associative networks (default mode, right and left frontoparietal and salience) when comparing controls, LIS, MCS, VS/UWS and coma patients. As previously proposed, these types of networks support conscious awareness by making incoming information (via sensory systems) globally available to multiple brain systems via long - range neurons (associative systems).[24] In that respect, our results account for the disrupted conscious awareness characterizing patients with DOC. In contrast to pathological coma, under propofol anesthesia functional connectivity was shown to be decreased in “higher - order” networks (DMN and bilateral frontoparietal) next to relatively preserved functional connectivity in the sensory systems (visual and auditory) possibly accounting for the after - anesthesia recovery of consciousness.[12] These differences between anesthesia and pathological coma could be partially explained by the fully preserved structural connectivity shown in healthy subjects undergoing anesthesia. It is indeed well known that part of the measured functional connectivity in resting state EPI paradigms reflects structural (white matter) connectivity as, for example, shown by diffusion tensor imaging studies.[39] The precise mechanisms underlying the reversible unconsciousness of anesthesia and the disrupted consciousness in patients with DOC need to be further documented.[40]

In conclusion, resting state functional connectivity in the default mode and its anticorrelated regions, left and right frontoparietal, salience, sensorimotor, auditory and visual networks were reliably identified in controls and showed reduced connectivity in patients with DOC. A reduced crossmodal interaction between visual and auditory cortices was further observed. In patients, the salience network correlated with Nociception Coma Scale scores reflecting nociception - related processes measured in the absence of external noxious stimulation. Our results point to the utility of resting state analyses in clinical settings where short and simple setups are preferable to activation protocols with somatosensory, visual, and auditory stimulation devices. The challenge now is the clinical translation of this approach as a routine para - clinical marker. We think that such evolution will bring relevant ancillary information on patients' residual brain function adding to their medical care and management.

Acknowledgments

This work was supported by the Belgian National Funds for Scientific Research (FNRS), the European Commission, the James McDonnell Foundation, the European Space Agency, Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC - 06/11 - 340), the Public Utility Foundation "Université Européenne du Travail", "Fondazione Europea di Ricerca Biomedica" and the University and University Hospital of Liège. The authors have no conflicts of interest and no disclosures of financial interest to report.

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Table 1. Areas (peak voxels) of the resting state networks showing connectivity breakdown as a function of the level of consciousness, ranging from healthy controls and locked - in syndrome patients, to minimally conscious state, “vegetative”/ unresponsive and patients in coma.

Area		x	y	z	z value	Corrected p value
Default mode network						
	Precuneus/ Posterior cingulate cortex (7/31)	0	- 55	25	5.58	<.001
	Anterior cingulate cortex/ Mesiofrontal cortex (24/10)	3	38	4	4.88	.006
L	Temporoparietal junction (39)	- 51	- 64	25	5.29	.001
R	Temporoparietal junction (39)	54	- 55	28	3.56	<.001•
L	Middle frontal gyrus (8)	- 30	23	46	3.41	<.001•
Anticorrelations default mode network						
L	Inferior frontal gyrus (46/9)	- 45	38	7	4.02	<.001•
R	Inferior frontal gyrus (9)	42	5	34	4.34	.050
R	Middle frontal gyrus (6)	48	5	43	3.92	<.001•
L	Inferior parietal lobe (40)	- 42	- 31	40	5.18	.002
R	Inferior parietal lobe (40)	45	- 28	43	3.42	<.001•
	Midcingulate cortex (24)	- 3	17	28	3.32	<.001•
	Supplementary motor area (6)	0	2	58	3.20	<.001•
Left frontoparietal network						
L	Inferior frontal gyrus (46)	- 48	41	7	4.34	.050
R	Inferior frontal gyrus (46)	48	38	10	4.50	.027

L	Inferior parietal lobe (40)	- 33	- 43	34	4.48	.030
R	Inferior parietal lobe (40)	39	- 49	46	3.18	<.001•
Right frontoparietal network						
L	Inferior frontal lobe (46/9)	- 45	44	7	4.49	.028
R	Inferior parietal lobe (40)	48	- 43	46	3.28	<.001•
L	Inferior parietal lobe (40)	- 45	- 52	49	4.67	.014
Salience network						
R	Insula	36	23	- 2	3.84	<.001•
L	Insula	- 36	17	1	4.97	<.001•
	Anterior cingulate cortex (24/32)	9	23	25	3.43	<.001•
L	Pars opercularis (Broca's area 44)	- 42	5	7	5.98	<.001
L	Superior temporal gyrus (primary auditory cortex 41)	- 42	- 34	16	5.23	.001
L	Superior temporal gyrus (Wernicke's area 22)	- 51	- 10	10	6.29	<.001
Sensorimotor network						
	Supplementary motor area (6)	3	- 13	55	4.56	.024
R	Claustrum	36	- 13	- 2	4.49	.031
Auditory network						
R	Superior temporal gyrus (22)/ Insula	45	- 10	- 8	3.74	<.001•
L	Superior temporal gyrus (Wernicke's area 22)	- 60	- 16	25	3.80	<.001•
	Anterior cingulate cortex (24)	0	26	16	3.92	.039
R	Claustrum	36	5	- 8	5.08	.002
Visual network						

	Primary visual cortex (17)	3	- 79	13	5.11	.002
L	Primary auditory cortex (41)	- 48	- 25	10	4.37	.049
L	Insula	- 42	- 13	10	4.37	.035

P values are corrected for multiple comparisons at family wise error rate p<.05 for the whole brain volume or using an 10mm radius spherical small volume correction ($^\bullet$) centered on a priori coordinates identified in an independently assessed group of healthy individuals.

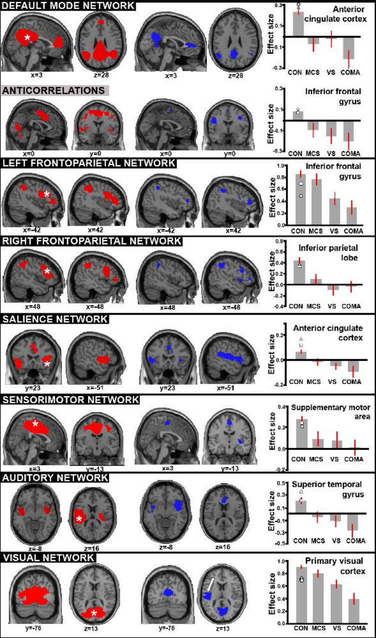
Figure titles and accompanying legends

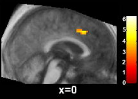
Figure 1. **Decreases in fMRI resting state connectivity as a function of the level of consciousness.**

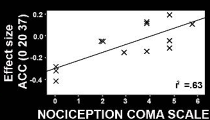
Large - scale resting state functional connectivity is identified in “higher - order” and sensory - sensorimotor networks in healthy controls (red areas; asterisks indicate the position of seed region). Between - group contrasts showed a connectivity breakdown as a function of the level of consciousness (blue areas). Note the decreased crossmodal interaction between visual and auditory cortices (indicated with an arrow) that parallels the decreases in consciousness level. Graphs represent contrast estimates with 90% confidence interval for a representative area of each resting state network in the group of healthy controls (CON), minimally conscious state (MCS), vegetative/unresponsive state (VS) and comatose patients. The effect size for two locked - in syndrome patients is illustrated by a square and a triangle. Results for controls are thresholded at family wise error rate corrected $p<.05$ (whole brain volume). For the anticorrelations with the default mode network and the between - group contrasts, results are thresholded for display purposes at uncorrected $p<.001$. Statistical maps are rendered on a structural T1 magnetic resonance template (x, y and z values indicate the Montreal National Institute coordinates of represented sections).

Figure 2. Salience network connectivity reflects nociception processing in patients with disorders of consciousness.

The figure illustrates increased functional connectivity between the right insula and anterior cingulate cortex (ACC) (small volume corrected $p<.05$) as a function of increased total score on the Nociception Coma Scale. The scatter plot summarizes regression results in 13 patients with disorders of consciousness. The statistical map is rendered on a mean structural T1 magnetic resonance of the patients (x indicates the Montreal National Institute coordinate of represented sections).


DEFAULT MODE NETWORK
x=3
z=28
x=3
z=28
Anterior cingulate cortex
Effect size
0.3
0.1
-0.1
-0.3
CON
MCS
VS
COMA
ANTICORRELATIONS
x=0
y=0
x=0
y=0
Inferior frontal gyrus
Effect size
0.1
-0.1
-0.3
CON
MCS
VS
COMA
LEFT FRONTOPARIETAL NETWORK
x=-42
x=42
x=-42
x=42
Inferior frontal gyrus
Effect size
1.0
0.8
0.6
0.4
0.2
CON
MCS
VS
COMA
RIGHT FRONTOPARIETAL NETWORK
x=48
x=-48
x=48
x=-48
Inferior parietal lobe
Effect size
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
CON
MCS
VS
COMA
SALIENCE NETWORK
y=23
x=-51
y=23
x=-51
Anterior cingulate cortex
Effect size
0.2
0.0
-0.2
CON
MCS
VS
COMA
SENSORIMOTOR NETWORK
x=3
y=-13
x=3
y=-13
Supplementary motor area
Effect size
0.4
0.2
0.0
-0.2
CON
MCS
VS
COMA
AUDITORY NETWORK
z=-8
z=16
z=-8
z=16
Superior temporal gyrus
Effect size
0.5
0.3
0.1
-0.1
-0.3
-0.5
CON
MCS
VS
COMA
VISUAL NETWORK
y=-76
z=13
y=-76
z=13
Primary visual cortex
Effect size
1.0
0.8
0.6
0.4
0.2
CON
MCS
VS
COMA


6
5
4
3
2
1
0
x=0


Effect size
ACC (0 20 37)
0.2
0.0
-0.2
-0.4
0
1
2
3
4
5
6
r² =.63
NOCICEPTION COMA SCALE

Supplemental Table e-1. Peak voxels (FWE p<.05, whole-brain level) of the resting state networks identified in an independently assessed group of healthy controls (n=12).

Area	**x**	**y**	**z**	**z value**	**p value**
Default mode network					
Precuneus/ Posterior cingulate cortex (7/31)	9	-49	37	Inf	<.001
Anterior cingulate cortex/ Mesiofrontal cortex (32/10)	3	47	-5	6.53	<.001
L Temporoparietal junction (39)	-45	-64	25	7.37	<.001
R Temporoparietal junction (39)	42	-58	28	7.11	<.001
L Dorsolateral prefrontal cortex (6/9)	-33	11	31	5.97	<.001
R Dorsolateral prefrontal cortex (6/9)	24	20	52	6.39	<.001
Anticorrelations default mode network					
L Inferior frontal gyrus (47)/Insula	-39	-1	-2	6.80	<.001
R Inferior frontal gyrus (47)/Insula	45	5	-11	7.61	<.001
L Inferior parietal lobe (40)	-48	-10	49	5.90	<.001
R Inferior parietal lobe (40)	63	-25	25	5.57	.004
Supplementary motor area/Midcingulate cortex (6/24)	-18	17	28	6.11	<.001
Anterior cingulate cortex (24)	12	5	70	6.03	<.001
Mesiofrontal cortex (10)	-36	44	25	5.53	.001
R Superior Temporal gyrus (21)	39	-46	-35	4.87	.019
L Fusiform gyrus (37)	-54	-67	-14	5.87	<.001
R Fusiform gyrus (37)	57	-61	-8	5.32	.002
Extrastriate cortex (18)	30	-85	-2	5.23	.004
L Cerebellum	-27	-55	-23	5.27	.003
R Cerebellum	18	-73	-23	5.88	<.001
Left frontoparietal network					
L inferior frontal gyrus (46)	-45	35	19	Inf	<.001
R inferior frontal gyrus (46)	45	41	13	Inf	<.001

L inferior parietal lobe (40)	-57	-43	43	6.45	<.001
R Inferior parietal lobe (40)	36	-58	46	5.13	.007
L Dorsolateral prefrontal cortex (6)	-21	8	52	5.35	.002
R Dorsolateral prefrontal cortex (6)	24	8	61	5.29	.003
Anterior cingulate cortex (32)	-9	20	37	5.64	<.001
Right frontoparietal network					
R inferior frontal gyrus (9/46/47)	45	35	19	Inf	<.001
L inferior frontal gyrus (9/46/47)	-45	26	25	Inf	<.001
R Inferior parietal lobe (40)	36	-55	40	Inf	<.001
L Inferior parietal lobe (40)	-42	-55	40	inf	<.001
Anterior cingulate cortex (32)	9	20	43	7.01	<.001
Salience network					
R Insula/Middle frontal gyrus (10)	39	23	-11	inf	<.001
L Insula/Middle frontal gyrus (10)	-33	26	-14	inf	<.001
Anterior cingulate cortex (24/32)	6	20	40	6.43	<.001
L Inferior parietal lobe (40)	-66	-43	22	5.19	.005
R Inferior parietal lobe (40)	51	-43	31	5.36	.002
L Putamen	-15	5	-2	5.20	.005
R Putamen	15	8	1	5.67	<.001
R Middle temporal gyrus (21)	51	-25	-8	5.49	.001
Sensorimotor network					
Supplementary motor area/Midcingulate cortex (6/24)	-3	-13	43	inf	<.001
L Primary motor cortex (4)	-27	-22	64	7.58	<.001
L Premotor cortex (6)	-27	-13	52	7.35	<.001
R Premotor cortex (6)	39	-13	40	7.45	<.001
R Somatosensory cortex (3)	27	-28	67	6.77	<.001
L Insula	-39	-19	22	6.43	<.001

R Insula	36	-16	13	6.89	<.001
L Claustrum	-36	-1	7	6.38	<.001
R Claustrum	33	5	7	5.93	<.001
Auditory network					
Superior temporal gyrus (41)/ Insula	-39	-22	7	inf	<.001
Superior temporal gyrus (41)/ Insula	39	-16	4	inf	<.001
Midcingulate cortex (24)	-3	5	37	6.32	<.001
L Primary motor cortex/Somatosensory cortex (4/5)	-18	-22	70	6.37	<.001
R Primary motor cortex/Somatosensory cortex (4/5)	24	-31	67	5.83	<.001
L Thalamus	-15	-22	1	6.02	<.001
R Thalamus	15	-19	-2	5.81	<.001
Midbrain	15	-19	-2	5.81	<.001
Brainstem	6	-25	-20	5.59	.001
Visual network					
Primary visual cortex (17)	0	-85	7	inf	<.001
L Extrastriate cortex (19)	-24	-91	25	5.08	.008
R Extrastriate cortex (19)	6	-79	40	5.13	.005

Supplemental Table e-2. Patients’ demographic characteristics.

					Coma Recovery Scale- Revised								
Patient	**Gender (age)**	**Cause**	**Time of fMRI (days since insult)**	**Diagnosis**	**Auditory function**	**Visual function**	**Motor function**	**Oromotor/ Verbal function**	**Commu-nication**	**Arousal**	**Total score**	**MRI/CT**	**EEG**
Pat 1	Female (61)	CVA	38	Coma	None	None	Flexion withdrawal	Oral reflex	None	None	3	R anteromedial ponto-mesencephalic, bilateral frontal and middle corpus callosum lesions; peri-cerebellar subdural collections; hydrocephalus (Evans index 0.37)	BR 6.5 Hz theta
Pat 2	Male (73)	CVA	7	Coma	None	None	Flexion withdrawal	None	None	None	2	L frontoparietal hemorrhage with subfalcine herniation	BR 6 Hz irregular non-reactive, R lateralized theta
Pat 3	Male (70)	CVA	5	Coma	None	None	Abnormal posturing	None	None	None	1	Hemorrhagic lesion R lentiform nucleus and thalamus, R cerebral and cerebellar peduncle	BR irregular delta
Pat 4	Male (79)	Trauma	379	Coma	None	None	None	None	None	None	0	L subdural hematoma, contusions in corpus callosum, cingulate gyrus and L external capsule	BR 4Hz (badly structured on the L, R slower electrogenesis
Pat5	Female (64)	CVA	7	Coma	None	None	None	None	None	None	0	Bilateral brainstem, midbrain and cerebellar non-hemorrhagic ischemia	BR 8Hz, irregular, symmetrical
Pat6	Male (20)	Trauma	1475	LIS	Consistent movement to command	Object recognition	Functional object use	Vocalization/ oral movement	Functional	Attention	22	Hemorrhagic lesions in R cerebellum, L lenticular and R anterior frontal, cingulate gyrus. Multiple axonopathy lesions in frontal and parietal lobes. Quadriventricular hydrocephalus with vermian and midbrain atrophy. (Evans index 0.34)	NA
Pat7	Female (28)	CVA	2130	LIS	Consistent movement to command	Object recognition	Functional object use	Vocalization/ oral movement	Functional	Attention	21	Ischemic lesions in L cerebellar and pontine peduncles. Occlusion of distal vertebral arteries	NA
Pat8	Female (43)	Subarachnoid hemorrhage	31	MCS	Auditory startle	Visual pursuit	Flexion withdrawal	Oral reflex	None	Without stimulation	7	Anterior interhemispheric sub-arachnoid hemorrhage, saccular aneurysm on R internal carotid artery	BR theta range
Pat9	Male (38)	CVA	1854	MCS	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Vocalization/ oral movement	None	With stimulation	9	Lesions in L thalamus and posterior limb of L internal capsule, extending to the cerebral peduncle and corpus callosum	BR 5-6 Hz irregular reactive

Pat10	Female (34)	Trauma	3034	MCS	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Vocalization/ oral movement	None	Without stimulation	12	L thalamic contusional lesion. Juxta-cortical lesions in frontal and temporal lobes. Atrophy of the L cerebral peduncle and cerebellar vermis	BR 6-7 Hz irregular reactive
Pat11	Female (74)	Subarachnoid Hemorrhage	18	MCS	Auditory startle	None	Abnormal posturing	Oral reflex	Intentional	With stimulation	5	L parieto-occipital subarachnoid hemorrhage. Leucoencephalopathy in frontal and parietal lobes. Supratentorial hematoma including R thalamus and internal capsule extending to pons	BR 4-5 Hz irregular non-reactive delta.
Pat12	Male (52)	Seizure	20	MCS	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Vocalization/ oral movement	Intentional	Without stimulation	13	R cortico-subcortical fronto-insulo-temporal lesions	BR theta, non-reactive symmetrical
Pat13	Male (47)	Trauma	533	MCS	Reproducible movement to command	Object recognition	Flexion withdrawal	Oral reflex	None	Without stimulation	13	Bilateral leucoencephalopathy. Lesions in anterior pons, midbrain and frontal lobe. Hydrocephalus and atrophy in bilateral hippocampus and cerebellum (Evans index 0.35)	BR diffuse theta
Pat14	Male (29)	Trauma and anoxia	64	MCS	Auditory startle	Visual pursuit	Flexion withdrawal	Oral reflex	None	Without stimulation	9	No lesion on CT	BR 7 Hz, irregular non-reactive, symmetrical
Pat15	Male (41)	Anoxia	9900	MCS	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Vocalization/ oral movement	None	Without stimulation	12	Periventricular leuco-encephalopathy. Lesions in bilateral frontoparietal convexity and external capsule. Atrophy of frontal and temporal lobes hippocampi and thalami. Hydrocephalus (Evans index 0.37)	BR 6-7 Hz, symmetrical
Pat16	Male (37)	Trauma	342	MCS	Reproducible movement to command	Object recognition	Localization to noxious stimulation	Oral reflex	None	Without stimulation	14	Lesions in R posterolateral pons, R cerebral peduncles and corpus callosum	NA
Pat17	Male (60)	Trauma	12	MCS	Reproducible movement to command	Object recognition	Automatic motor reaction	Intelligible verbalization	Intentional	With stimulation	18	Diffuse axonal injury more important on R side. Lesions in R cerebral peduncle, pons and splenium of corpus callosum	BR theta-delta, irregular
Pat18	Female (36)	Anoxia	460	MCS	Reproducible movement to command	Visual pursuit	Flexion withdrawal	Vocalization/ oral movement	Intentional	Without stimulation	13	Hippocampal atrophy	BR 8 Hz, symmetrical
Pat19	Male (74)	Anoxia	92	VS/UWS	Auditory startle	None	Abnormal posturing	Oral reflex	None	With stimulation	4	Diffuse leucoencephalopathy most pronounced in occipital lobes. Diffuse atrophy in bilateral frontal and parietal lobes, hippocampus	Unstructured non-reactive theta

												and cerebellum. Anoxic lesions in bilateral basal ganglia. Hydrocephalus (Evans index 0.38)	
Pat20	Female (44)	Anoxia	8	VS/UWS	None	None	Abnormal posturing	None	None	With stimulation	2	Lesions in occipital lobes and parieto-temporo-occipital junction. Diffuse cortico-subcortical ischemic lesions	Diffuse non-reactive low-voltage delta
Pat21	Male (67)	CVA	43	VS/UWS	Auditory startle	None	Flexion withdrawal	Oral reflex	None	With stimulation	5	L medial temporal hematoma extending to L thalamus, posterior internal capsule, lenticular nucleus, insula and Wernicke's area. Diffuse leucoencephalopathy most pronounced in front al lobes	BR 6 Hz, non-reactive, symmetric
Pat22	Male (63)	CVA	30	VS/UWS	Auditory startle	Visual startle	Flexion withdrawal	Vocalization/ oral movement	None	Without stimulation	8	Bihemispheric ischemic lesions predominantly in posterior parietal and occipital lobes	BR unstructured delta
Pat23	Female (63)	Anoxia	1210	VS/UWS	Auditory startle	None	Abnormal posturing	Oral reflex	None	With stimulation	4	Multiple subcortical lesions in frontoparietal and temporal lobes. Diffuse atrophy in pons, midbrain and thalamus. Quadriventricular hydrocephalus (Evans index 0.42)	Hypovoltage unstructured non-reactive
Pat24	Male (87)	Subarachnoid hemorrhage	7	VS/UWS	None	None	Flexion withdrawal	Oral reflex	None	With stimulation	4	Subarachnoid hemorrhage and bifrontal lesions	Diffuse non-reactive theta
Pat25	Female (41)	Anoxia	1572	VS/UWS	Auditory startle	None	Abnormal posturing	Oral reflex	None	Without stimulation	5	Atrophy of corpus callosum, thalami, lenticular nuclei, midbrain, pons and cerebellum. Hydrocephalus (Evans index 0.44)	BR unstructured theta
Pat26	Male (44)	CVA	27	VS/UWS	Auditory startle	None	Abnormal posturing	None	None	Without stimulation	4	Lesions in frontal and temporal lobes, caudate nucleus, thalamus, bilateral insula and hippocampi	BR 6 Hz, irregular, non-reactive, symmetrical
Pat27	Female (69)	Anoxia	50	VS/UWS	Auditory startle	None	Flexion withdrawal	Oral reflex	None	With stimulation	5	Bilateral fronto-parieto-temporal leucoencephalopathy including external capsule, caudate nucleus, R thalamus and L insula. Bilateral hippocampal atrophy and hydrocephalus (Evans index 0.36)	Diffuse theta with L lateralized delta
Pat28	Female (49)	CVA	129	VS/UWS	Auditory startle	None	None	Oral reflex	None	Without stimulation	4	Lesions in pons and external capsule. Diffuse leuco-encephalopathy	Diffuse unstructured non-reactive delta
Pat29	Male (36)	Anoxia	2031	VS/UWS	Auditory startle	None	Abnormal posturing	Vocalization	None	Without stimulation	6	Bilateral periventricular leuco-encephalopathy. Supratentorial cortical and subcortical atrophy including basal ganglia and cerebellum. Hydrocephalus (Evans	BR 7 Hz, symmetrical

												index 0.41)	
Pat30	Male (34)	Anoxia	7814	VS/UWS	Auditory startle	Visual startle	Abnormal posturing	Oral reflex	None	With stimulation	6	Diffuse cortical and cerebellar atrophy. Hydrocephalus (Evans index 0.42)	BR 6 Hz, irregular non-reactive, symmtrical

CVA: cerebrovascular accident, LIS: locked-in syndrome, VS/UWS: vegetative state/unresponsive wakefulness syndrome, MCS: minimally conscious state, BR: basic rhythm, R: right, L: left.

Supplemental Table e-3. Areas (peak voxels) of the resting state networks identified in healthy controls.

Area		**x**	**y**	**z**	**z value**	**Corrected p value**
Default mode network						
	Precuneus/ Posterior cingulate cortex (7/31)[†]	6	-43	31	Inf	<.001
	Anterior cingulate cortex/ Mesiofrontal cortex (32/10)	3	56	4	7.66	<.001
L	Temporoparietal junction (39)	-51	-61	28	Inf	<.001
R	Temporoparietal junction (39)	45	-58	37	Inf	<.001
L	Middle frontal gyrus (8)	-21	26	37	5.99	<.001
R	Middle frontal gyrus (8)	24	29	40	5.09	.002
R	Thalamus	15	-28	7	4.58	.021
Anticorrelations default mode network						
L	Inferior frontal gyrus (46)	-45	38	7	5.87	<.001
R	Inferior frontal gyrus (46)	45	44	7	4.61	.018
L	Middle frontal gyrus (6)	-24	-1	61	5.65	<.001
R	Middle frontal gyrus (6)	48	2	46	5.81	<.001
L	Inferior parietal lobe (40)	-60	-28	31	4.50	.029
L	Superior temporal gyrus (22)	-54	8	-5	6.29	<.001
R	Superior temporal gyrus (22)	54	14	-5	5.92	<.001
	Supplementary motor area/Midcingulate cortex (6/24)	3	5	52	6.88	<.001
L	Extrastriate cortex (18/19)	-15	-73	-2	5.96	<.001
R	Extrastriate cortex (18/19)	12	-70	4	5.81	.005
L	Cerebellum	-9	-67	-23	4.92	.005
Left frontoparietal network						
L	Inferior frontal gyrus (46/9)[†]	-42	32	22	Inf	<.001
R	Inferior frontal gyrus (46/9)	48	38	10	Inf	<.001
L	Inferior parietal lobe (40)	-48	-43	46	6.58	<.001
R	Inferior parietal lobe (40)	48	-37	46	4.87	<.001

Right frontoparietal network						
R	Inferior frontal gyrus (46/9)†	45	35	19	Inf	<.001
L	Inferior frontal gyrus (46/9)	-45	32	22	Inf	<.001
R	Inferior parietal lobe (40)	48	-40	43	7.16	<.001
L	Inferior parietal lobe (40)	-45	-49	49	6.56	<.001
Salience network						
R	Insula/Middle frontal gyrus (10)†	39	26	-8	Inf	<.001
L	Insula/Middle frontal gyrus (10)	-35	14	-2	Inf	<.001
	Anterior cingulate cortex (24)	9	23	25	5.42	<.001
R	Putamen	24	2	1	4.78	.008
L	Putamen	-27	-13	4	4.33	.048
Sensorimotor network						
	Supplementary motor area/Midcingulate cortex (6/24)†	-3	-13	43	Inf	<.001
L	Primary motor cortex (4)	-12	-37	55	6.62	<.001
R	Primary motor cortex (4)	12	-37	52	7.08	<.001
L	Premotor cortex (6)	-36	-4	52	5.83	<.001
R	Premotor cortex (6)	36	-7	46	5.22	.001
L	Somatosensory cortex (3)	-39	-19	52	6.01	<.001
R	Somatosensory cortex (3)	24	-25	58	6.47	<.001
Auditory network						
L	Superior temporal gyrus (22)/ Insula†	-39	-22	7	Inf	<.001
R	Superior temporal gyrus (22)/ Insula	51	8	1	6.34	<.001
L	Pars opercularis (Broca’s area 44)	-57	5	7	7.45	<.001
L	Superior temporal gyrus (Wernicke’s area 22)	-57	-34	22	6.84	<.001
	Midcingulate cortex (24)	-9	-1	40	4.83	.008
R	Claustrum	39	8	-2	6.81	<.001
	Thalamus	15	-25	4	4.57	.022

Visual network						
	Primary visual cortex (17)†	-3	-82	7	Inf	<.001
R	Extrastriate cortex (19)	27	-76	-11	6.61	<.001
L	Extrastriate cortex (19)	-27	-76	-14	5.46	<.001

P values are corrected for multiple comparisons at family wise error rate $p<.05$ for the whole brain volume. † Seed area.

Supplemental Table e-4. Regression analysis of the Nociception Coma Scale total scores on the functional connectivity of the auditory network in 13 patients with disorders of consciousness. Areas show peak voxels at an uncorrected p<.001 for the whole-brain volume.

Area	**x**	**y**	**z**	**z value**	**p value**
R Caudate	24	-31	16	4.03	<.001
L Claustrum	-30	11	4	3.67	<.001
L Thalamus	-18	-22	10	3.50	<.001
R Postcentral gyrus (2)	66	-22	28	3.47	<.001
L Parahippocampal gyrus	-18	-43	7	3.33	<.001
R Inferior frontal gyrus (47)	36	14	-17	3.15	.001