International symposium on the vegetative and minimally conscious state

Wednesday 26th & Thursday 27th September 2007

Robinson College, Cambridge

Lecture Abstracts
Disorders of consciousness (DOC) include coma, the vegetative state (VS) and the minimally conscious state (MCS). Incidence and prevalence figures are difficult to obtain for these conditions as systematic surveillance is lacking. In the U.S. alone, it is estimated that at least 4,200 individuals are newly diagnosed with VS each year. The number of patients in MCS has been projected to be approximately seven times higher. The enormity of the problem is compounded by the fact that these disorders are among the most misunderstood conditions in medicine. Because there are no universally recognized standards to guide the nature or schedule of assessment, patient evaluations are often inadequate and formal monitoring procedures may be discontinued prematurely. These shortcomings have conspired to produce diagnostic error rates ranging from 15-43%. Of perhaps greater concern, limited funding resources and the lack of evidence-based rehabilitation research have prevented development of standards of care for treatment. Treatment decisions are often based on personal experience and trial and error with little attention directed to investigating cause-effect relationships.

The primary aims of this presentation are 1) to outline the commonalities and differences among previously-published international guidelines for assessment and diagnosis of DOC and 2) to briefly review the state of the science relative to treatment interventions and their effectiveness. The discussion is intended to lay the framework for subsequent presentations by identifying common ground, highlighting areas of disagreement and defining knowledge gaps.

Recent Publications


In recent years, we have shown that functional neuroimaging can identify residual cognitive function, and even conscious awareness, in some patients who are assumed to be vegetative, but retain abilities that have evaded detection using standard methods of examination. I will describe a series of functional neuroimaging paradigms that systematically increase in complexity with respect to the cognitive processes required, and therefore allow us to infer how much cognition remains based on ‘normal’ patterns of activation. We start with responses to various types of speech stimuli. A significant minority of vegetative patients produce speech-related responses in the superior temporal-lobe region that are indistinguishable from those observed in healthy volunteers performing the same task. More complex linguistic stimuli, which produce distinct patterns of activation associated with comprehension, also elicit normal responses in some, but fewer, patients. Importantly however, an appropriate neural response to the meaning of spoken sentences is not unequivocal evidence of conscious awareness. We have therefore developed a new approach in which patients assumed to be vegetative are instructed to perform mental imagery tasks at specific points during a scan. Results from a small group confirm that some patients retain the ability to understand spoken commands and to respond via their brain activity rather than speech or movement. Reproducible and robust task-dependent responses to commands without the need for practice or training could be a novel way for some vegetative, minimally conscious, or locked in patients to use their residual cognitive capacities to communicate thoughts by modulating their own neural activity.

Recent Publications


Estimating the capacity for recovery of brain function following severe injuries presents significant challenges. Standard clinical imaging modalities and behavioral assessments provide very limited guides for prognosis if negative predictive factors have been excluded. Moreover, current clinical practice in this context relies on probability estimates derived from these measures without consideration of a variety of possible underlying mechanisms producing impaired brain function. The discussion will focus on the use of multi-modal neuroimaging methods to evaluate residual functional capacity and structural connectivity in patients remaining in the minimally conscious state for prolonged time periods. Rare patients within this subgroup demonstrate spontaneous recoveries of consistent communication. We develop hypotheses for possible common mechanisms of brain dysfunction using measurements obtained from functional magnetic resonance imaging, quantitative electroencephalography, positron emission tomography, and diffusion tensor imaging techniques. The long-range goal of these studies is to establish methods to track and predict recovery across a heterogeneous pool of brain-injured patients. It is proposed that an approach based on using aggregate metrics that consider the brain from a physical systems point of view is essential for further diagnostic refinements in the evaluation of severe brain injuries.

Recent Publications


Background
Neurointensivist conducting neuroimaging work with severely brain damaged patients at the Pitié-Salpêtrière Hospital, Paris.

Title of Talk
A combined magnetic resonance spectroscopy and DTI approach to predict prognosis.

Outcome prediction following traumatic brain injury (TBI) is vitally important. In this presentation I will describe a study, which evaluated whether diffusion tensor imaging and $^1$H MR spectroscopy could be used as an early quantitative prognostic tool. Methodology: Thirty-three patients in a coma after severe traumatic brain injury were investigated at 24 ± 11 days after trauma with diffusion tensor imaging and 1H MR spectroscopy and compared with 15 healthy controls. Fractional anisotropy was measured as a mean of different discrete brain regions in infra and supratentorial areas. NAA/Cr ratio was measured in the thalamus, lenticular nucleus, the insula grey matter, the occipital periventricular white matter and the pons. Patients were dichotomized into two groups according to outcome at one year: poor outcome (GOS 1-3, n=19) and good outcome (GOS 4-5, n=24). ANOVA was used to compare FA and metabolites values in the two outcome groups and in controls. Linear discriminate analysis was used to evaluate if these values could be predictive markers of outcome. Results: MRI delay and major clinical criteria were not different between poor and good outcome populations. FA analysis and spectroscopic data showed highly significant differences between outcome groups. Linear discriminant analysis of combined MRI and MRS data enabled a clear-cut separation between GOS 1-3, GOS 4-5 and controls with no overlap between groups. 74% of the patients were classified with a probability of error below 5% in the correct outcome category. Conclusion: This study shows the major interest of early MRI combining DTI and spectroscopy to obtain a valuable cut off between patients with poor or good clinical outcome after TBI induced coma. Fractional anisotropy and NAA/Cr ratio might become major quantitative prognostic tools for predicting outcome from TBI at the subacute phase.

Recent Publications


11:30 – 12:00  **Steven Laureys**  
Head of Coma Science Group at the Cyclotron Research Centre, University of Liege and Neurology Clinics at Sart Tilman, University Hospital of Leige, Belgium.

**Background**  
Conducts neuroimaging investigations of residual brain function in coma, vegetative and minimally conscious and locked-in states supported by the Belgian National Fund for Scientific Research.

**Title of Talk**  
Achievements and the future direction of imaging research?

How can we contribute to a better understanding of the residual brain function of patients who survive acute brain damage, but remain in a coma, vegetative state (VS), minimally conscious state (MCS) or locked-in syndrome (LIS)? The evaluation of consciousness in severely brain damaged patients is of major medical importance. We here review functional neuroimaging studies of disorders of consciousness (DOC).

Studies have shown that the relationship between global levels of brain function and the presence or absence of awareness is not absolute, rather, some areas in the brain seem more important than others for the emergence of awareness. Using voxel-based analyses (SPM – statistical parametric mapping), it has been shown that regional changes in the frontoparietal network of associative cortices, more so than global changes in cerebral metabolism, are a better correlate of awareness in severely brain damaged non-communicative patients. Another hallmark of VS is the relative metabolic sparing of the pedunculopontine reticular formation, hypothalamus and basal forebrain - allowing for the maintenance of patients’ vegetative functions. Awareness is not exclusively related to activity in the frontoparietal ‘global workspace’ but, as importantly, to the functional connectivity within this network and the thalami. Long-range cortico-cortical (between latero-frontal and midline-posterior areas) and cortico-thalamo-cortical (between non-specific thalamic nuclei and midline-posterior cortices) ‘functional disconnections’ have been identified in the vegetative state. Moreover, recovery from VS is paralleled by a functional restoration of the frontoparietal network and part of its cortico-thalamo-cortical connections.

A critical node in the ‘frontoparietal network’ is the posterior cingulate and adjacent precuneal cortex. These areas best differentiate MCS from VS, are the most impaired in VS and resume near normal activity after recovery from VS. Functional neuroimaging studies have studied pain, auditory, language, emotional and visual processing in DOC. Classically, VS patients show no evidence of noxious stimulation-related downstream activation beyond primary somatosensory cortex. More importantly, functional connectivity assessment has shown that such activation exists as an island, dissociated from higher-order cortices that are regarded necessary for awareness. Auditory stimuli frequently activate primary auditory cortices in VS, despite substantial metabolic impairment. Compared to VS, MCS patients show a stronger functional connectivity between auditory and frontoparietal areas. Moreover, in MCS, auditory stimuli with emotional valence (verbal or non-verbal) induce a more widespread activation than does meaningless noise. Such context-dependent higher-order auditory processing in MCS, not assessable at the patient’s bedside, indicates that content does matter when talking to MCS patients. Recent fMRI paradigms asked non-communicative patients to perform mental imagery tasks at specific points during scanning. Task-specific activation permits us to unequivocally demonstrate consciousness in the absence of reliable behavioral motor command following.

**Recent Publications**


Background  Consultant Clinical Neuropsychologist with specialist interest in disorders of consciousness.

Title of Talk  A review of behavioural assessment techniques

The use of sensitive tailored approaches involving experienced multidisciplinary teams has been strongly advocated in VS/MCS assessment (Royal College of Physicians and British Society of Rehabilitation Medicine, 2003). Nonetheless, even experienced clinicians with access to functional imaging are presented with inherent difficulties in assessing possible responsiveness and preserved awareness in patients diagnosed as being in vegetative or minimally conscious state(s). On the basis of current diagnostic criteria, reliable detection of potential signs of awareness is based on observed behaviour. Possible threats to accurate diagnosis including confounding variables, observer bias and lack of professional awareness of VS/MCS and inadequate training will be outlined.

Recently developed measures such as the SMART (Gill-Thwaites & Munday, 1999) and WHIM (Shiel, Wilson, McLellan, Horn, & Watson, 2000), which employ operational defined behavioural observations facilitating the serial assessment of patient responsiveness and possible awareness will be reviewed. Examples of significant changes in WHIM profiles outside the acute recovery phase will be presented in patients following TBI and Hypoxic Brain Injury.

The benefits of tailored binomial assessment procedures (McMillan, 1996) in the assessment of access to autobiographical recall, new learning & memory, mood and decision making among patients who may be emerging beyond MCS will also be outlined using several case examples.

Finally, recommendations for the use and refinement of behavioural assessment techniques with VS and MCS patients will be discussed.


Recent Publications

Predicting the outcomes from severe traumatic brain injury, specifically vegetative and minimally conscious state, has implications for clinical care, resource allocation, research outcome, and family counseling. Over the years we have found several apparent markers of recovery, at least when applied in the general sense. However, translating research in this area into the practice of outcome prediction has significant challenges. When applied on an individual level one must consider the inherent inaccuracies and any potential harm of such “guesses”. In some treatment centers there has been an emergence of palliative care into the care of individuals with brain injury. Given the inaccuracies in individual outcome predictions the clinician should use caution in applying the current knowledge towards withdrawal of care. It is recommended that a clinician who is involved with seeing the full spectrum of brain injury outcomes is involved with such decisions. Outcome predictions are powerful in that they have the potential to guide expectations and consequently impact resource allocation. It is also important to consider that the literature on outcome is only as meaningful as the outcome measures utilized. Most studies on traumatic brain injury have categorized outcome in to good and bad recovery. In many cases, the broad category of “bad recovery” includes “severe disability”, thus combining outcomes ranging from dead, to vegetative, to not being able to pay your own bills. Many people with brain injury, their families, and clinicians would consider the later outcome quite meaningfully different from dead or vegetative. Outcome predictions also depend on the time and setting of the prognostication. For example, many of the variables that have been shown to be strong predictors in the acute care setting have not been found to be predictive of the outcomes of those who come to receive inpatient rehabilitation. And, predictors of changes later post-injury are different as well, and depend on the outcome in question. Markers for recovery might have a potential role in monitoring one’s recovery to identify when some one is not progressing as anticipated. Additionally, predicted outcomes may have a role as a standard by which intervention outcomes are compared, and have been postulated as a tool for stratifying randomization in clinical trials. Other challenges confronting the clinician are how to best approach families with this prognostic information, and how the information should be used clinically (if at all). Considering threshold values for the likelihood of a particular outcome is a recently proposed approach. What is the sensitivity and specificity of these factors? What is the utility of combining information from several available predictive factors? Another important question is the role of existing and emerging technologies in outcome prediction. The role of these factors and other patient and injury variables in prognostication will be reviewed. Published guidelines and approaches to prognostication, as well as limitations and challenges will be discussed.

Recent Publications


It is important to note that research has shown that cognitive recovery progresses more slowly than physical recovery. Giacino and Kalmar (1997) discuss the likelihood of recovery of consciousness after traumatic brain injury and Shiel (1999) suggested there were at least five different patterns of recovery following severe traumatic brain injury. These patterns are described briefly. Evidence for cognitive recovery is then reviewed with the main focus on two group studies and three single case studies. The first group study is a four year follow-up study of 41 patients (Shiel, 2005). Eight of these remained in a minimally conscious state with thirty showing moderate to good recovery. This paper also considered which early behaviours predicted outcome at the four year follow-up. The tentative conclusions were that time taken to achieve five behaviours may be predictive of later outcome. The second group study is of 13 patients in the Cambridge group. The three single case studies are all of young women. Each showed different degrees of cognitive recovery from minimal recovery (McMillan and Herbert 2004) to moderate recovery (Bekinschtein et al 2005) to good cognitive recovery despite severe physical limitations (Wilson et al 2001). In certain cases substantial improvement in cognitive functioning is possible even in patients with relatively long periods of reduced consciousness.

Recent Publications


The behavioural assessment is the standard method of detecting signs of awareness in severely brain injured patients. However, a high percentage of minimally conscious patients can be missed. Additional objective techniques are needed to facilitate accurate diagnosis. The electroencephalogram (EEG) is an objective tool that permits continuous and online monitoring of brain functions. However, EEG interpretation requires considerable expertise.

The bispectral index (BIS) reduces the information contained in EEG to a value ranging from 0 (isoelectric) to 100 (fully conscious). Therefore we investigated the utility of the BIS, as compared to other EEG parameters, to distinguish different levels of consciousness in brain damaged patients (i.e. coma, vegetative state [VS], minimally conscious state [MCS], and exit from MCS [EMCS]). The strongest correlation with behavioural measures of consciousness (the Glasgow Coma Scale, the Glasgow Liege Scale, the Wessex Head Injury Matrix and the Coma Recovery Scale-Revised) was observed with BIS recordings. An empirically defined BIS cut-off value of 50 differentiated unconscious patients (coma and VS) from conscious patients (MCS and EMCS) with a sensitivity of 75% and specificity of 75%. More precisely, BIS values significantly disentangled VS from MCS while other EEG parameters did not.

Recent Publications


**Background**
Investigates the neurophysiological foundations of consciousness and altered consciousness (particularly the minimally conscious state) using behavioural and electrophysiological methods.

**Title of Talk**
Residual cognitive functions revealed by ERPs

Event-related potentials (ERPs) reflect real-time cortical processing of stimuli. Their advantages are perfect temporal resolution, the availability of techniques to avoid or correct movement artifacts, mobility (they can be recorded at a patient’s bedside), and low cost. The main disadvantage is a low spatial resolution which, additionally, gets worse with increasing distance between the source of activity and the cortical surface. Examinations of patients with severe brain damage usually employ auditory stimuli. According to the stage of auditory processing the following ERP components are of interest: N1, signifying the arrival of the signal in the auditory cortex; mismatch negativity (MMN), indicating an automatic comparison between the incoming stimulus and its cognitive model; P3, indicating a complex memory-related process of linking the stimulus to behavioral goals and targets, and the N400 to verbal stimuli as a sign of analysis of their semantics (meaning). N1 has its main source in the primary auditory cortex. The same holds true for the MMN, though the activity of some other sources (e.g., in the frontal cortex) may also be important. The P3 emerges in a broadly distributed fronto-parietal network; and the N400 can largely be regarded as a product of the activity of speech-related left temporal areas. The N1 component can be found in many VS patients thus demonstrating that their cortex is not silent. In this respect, there are big differences between VS patients with the predominant 4-8 Hz (“benign EEG”), and those with diffuse delta-activity, or low voltage EEG, or a combination of slow waves and epileptic spikes (“malign EEG”). Among the former group virtually all patients have N1, whereas among the latter its frequency can be estimated between 20 and 30%. ERP components later than N1 virtually never occur in VS patients with a malign EEG pattern (in larger patient samples a certain rate of false positives is possible, thus the question is not whether a component can be found at least once, but rather, whether its occurrence exceeds the chance level). However, all these components can be present in VS patients with a benign EEG pattern. Their occurrence frequency does not differ from that in patients with the diagnosis of minimally conscious state (MCS), probably indicating the difficulty of the differential diagnostics. In both groups, these frequencies are significantly lower than in those patients with severe brain damage who are conscious and able to communicate. Furthermore, in benign VS patients N1 habituates with stimulus repetition, indicating a simple learning process (learning to not respond to insignificant stimuli) in the auditory cortex. In acute coma, the occurrence of the components N1, MMN and P3 is about the same as in VS and MCS. However, the N400 as the index of the processing of word meaning is rather exceptional in coma. The MMN is one of the most reliable predictors of awakening from coma. There are also data indicating that the presence of the MMN predicts emergence from VS.

**Recent Publications**


Assistant Professor, Institute of Medical Psychology and Behavioural Neurobiology, University of Tubingen, Germany.

Background
Has developed a flexible general purpose brain-computer interface system that uses either cortical slow potentials or mu-rhythm neurofeedback (visual, auditory) as a communication tool for locked-in patients.

Title of Talk
Brain-Computer Interfaces in the continuum of consciousness

In the past ten years brain-computer interface (BCI) research has increased rapidly. BCIs link the brain to an application which is controlled exclusively by the brain’s neural activity thereby circumventing the motor system. Patients in the locked-in state (LIS) are able to control a BCI and to use it for selection of letters, words or items on a computer screen, for neuroprosthesis control or for surfing the internet. The LIS is referred to as a state in which, as a consequence of total motor paralysis due to disease or injury, only yes/no communication via a single muscle twitch is possible. In some diseases the LIS may progress to the complete locked-in state which leaves the patients totally non-responsive. The LIS due to motor paralysis in which cognition and consciousness are supposed to be unaffected is traditionally opposed to non-responsiveness due to disorders of consciousness resulting from traumatic or non-traumatic brain injury, albeit the patients may appear very alike. However, recent studies indicate numerous transition states between these two extremes. Thus, we consider all non-responsive patients on a continuum of consciousness which may vary even within short time periods. As overt behaviour is lacking, cognitive function in such patients can only be investigated with neurophysiological methods. Typically, passive stimulation paradigms are used and the neural activity of the brain is recorded. We suggest that BCIs may provide a new tool to investigate cognitive function in disorders of consciousness, and propose a hierarchical procedure from passive stimulation, via volitional paradigms to the point of decision making and communication with BCI. It is completely unclear how much connectivity and integrity of the brain is necessary to control a BCI to achieve even the most basic yes/no communication or the communication of emotional states. Little is known about learning in the state of non-responsiveness and about the effectiveness of reinforcers in such a state. We consider the time ripe for merging BCI research and research on disorders of consciousness to the benefit of the patients, to improve diagnosis and to gain more insight into how much brain needs the mind.

Recent Publications


Background
Conducts empirical and theoretical work on the topic of access to consciousness. Has performed a variety of behavioral and neuroimaging experiments to study the contrast between subliminal versus conscious processing of masked words and digits.

Title of Talk
Looking for consciousness in patients who are not overtly conscious

Confronted with patients who are not able to communicate their inner mental reports ("I see X, I feel Y..."), we are left with two possibilities: either these patients are still covertly conscious, or they are simply not conscious. We can address this crucial issue by adopting a strategy of research with three goals: (1) enrich and develop our ability to read covert mental reports using behavioral and neurophysiological techniques; (2) use a "psychology-driven" approach to probe exclusive properties of conscious processing; and (3) use a neural correlates of consciousness (NCC) approach to probe neural signatures of conscious processing. I will discuss this general strategy and illustrate its application using several case studies.

Recent Publications


Investigates the neurophysiological foundations of consciousness and altered consciousness (particularly the minimally conscious state) using behavioural and electrophysiological methods.

**Title of Talk**

Neural correlates of consciousness (NCC): Should we look for structures or for functions?

The terms “consciousness” and “awareness” (which are used here as synonyms, as the distinction between the two does not exist in other European languages except English) are employed to describe at least three kinds of phenomena: (i) wakefulness (non-transitive consciousness; consciousness as the antonym of sleep and coma); (ii) subjective awareness (sensations, qualia, e.g., pain and pleasure); (iii) clear self-awareness (transitive consciousness, intentional states). Several approaches to the problem of the neural correlates of consciousness (NCC) are compared. The morphological approach presumes that the activity of some critical brain structures is necessary and sufficient for the emergence of consciousness. Within this approach specific and non-specific models can further be distinguished. The former follow the hypothetical flow of information processing in sensory systems, looking for the point at which that processing becomes conscious. The latter includes several further varieties, all of which assume the existence of modality-independent neuromorphological systems responsible for subjective awareness. In contrast, the functional approach is based on the assumption that the morphological basis of consciousness can be the activity of broadly distributed networks, only loosely related to what is known from brain anatomy. Therefore, the main question from this point of view is not which structures are involved, but how they are connected. This approach emphasizes temporal, rather than spatial, relationships between neurons and neuronal assemblies. An extreme version of the functional approach was suggested by the philosopher Daniel Dennett as the “multiple draft” model. According to it, consciousness is not a unitary phenomenon, nor even a set of different but closely related phenomena. Rather, we have a flexible array of criteria we rely upon in various situations to distinguish between conscious and unconscious behavior or to judge whether, e.g., a patient is conscious. Such criteria can be short- or long-term memory, verbal reports, particular selectivity in behavioral responses, and many others. Although each of these multiple functions should have its neurological correlates, there is no such thing as the NCC “as such”. These approaches are applied to the problem of altered states of consciousness, particularly in the vegetative state and the minimally conscious state. These considerations allow us to understand what is meant by the question, whether there can be consciousness in one of those states.

**Recent Publications**


Associate Professor of Neurology and Neuroscience at the Weill Medical College of Cornell University and Associate Attending Neurologist at the New York Presbyterian Hospital, USA.

**Nicholas Schiff**

**Background**
Conducts NIH supported research examining neurophysiological mechanisms of arousal and forebrain integration as well as clinical studies of the pathophysiology of impaired consciousness

**Title**
Should we amend the diagnostic criteria for the vegetative and minimally conscious state?

Although there is general agreement about the fundamental nature of the diagnostic categories of vegetative state and minimally conscious state, existing criteria have some differences. Modest amendments to existing criteria could aid uniformisation of data collection and reporting in the scientific literature. During this discussion session I will outline some of the amendments I believe are now required on the basis of emerging research. It is my opinion that any reforms should be based upon underlying biological mechanisms. The discussion will be opened to everyone to contribute. It is hoped we will create a list of the difficulties delegates experience distinguishing between these conditions based on the existing criteria and perhaps we can draw up a plan for further empirical work to address these difficulties.

**Relevant Publications**


The Long-term (Neurological) Conditions National Service Framework (NSF) was launched in March 2005. The NSF aims to transform the way health and social care services support people to live with long-term neurological conditions. Key themes are independent living, care planned around the needs and choices of the individual, easier, timely access to services and joint working across all agencies and disciplines involved. There is much common ground between the Long Term Conditions strategy and the Long term (Neurological) Conditions NSF, for example, around person-centred care planning, information and support, self-care and case management. The strategy will be able to use neurological examples and case studies to illustrate how case management and self-care can work. In turn it will rely on the NSF and all other NSF teams (e.g., renal, diabetes) to lead delivery of disease-specific issues under the broader long term conditions work. However, it is important to ensure that NSF for Long term (Neurological) conditions maintains its neurological focus and a discrete identity under this broader umbrella.

There are 11 targets in the NSF for Long Term Neurological Conditions:

1: A person-centred service
2: Early recognition, prompt diagnosis and treatment
3: Emergency and acute management
4: Early and specialist rehabilitation
5: Community rehabilitation and support
6: Vocational rehabilitation
7: Providing equipment and accommodation
8: Providing personal care and support
9: Palliative care
10: Supporting family and carers
11: Caring for people with neurological conditions in hospital or other health and social care settings

Only five of the targets relate to vegetative state: the need for the patient, sentient or not, to establish choice is problematic, the requirement for information, particularly for the carer is obvious. The early recognition of the possibility of vegetative state is likely, but the diagnosis may take months. Rehabilitation and the provision of emergency services is assured, but the provision of help to carers and access to information is more variable and should be audited.

Recent Publications


Session 5: Care management and rehabilitation

09:20 – 09:45  Keith Andrews  
Director of the Institute of Neuropalliative Rehabilitation, Royal Hospital for Neuro-disability, London.

Founder Director of the Institute of Neuropalliative Rehabilitation, at the Royal Hospital for Neuro-disability, London and responsible for setting up the first unit in the UK (at the Royal Hospital for Neuro-disability) specialising in the management of people in the vegetative state. Professor Andrews has a special interest in medical ethics, especially the ethics as it applies to profound neurological disabilities. He has published extensively on these topics and has been a key member of many national and international working parties.

Title of Talk  Dilemmas of VS and MCS

The understanding of Vegetative and Minimally Conscious States has come a long way since the original description by Jennett and Plum in 1972. Although there is still a nihilistic attitude to people in the vegetative state in many circles there has been a dramatic interest with the advent of better methods of neurophysiological diagnosis and possibility of new treatments. These all create new dilemmas:

1. What is the vegetative state – or more accurately what are the vegetative states?  
2. What are the legal and ethical implications of isolated clinical activity?  
3. How can the diagnosis be made more accurately?  
4. What are the implications of neurophysiological activity in the absence of any clinical evidence of awareness?  
5. Do vegetative patients feel pain and thirst?  
6. Should we try every new treatment that is claimed to be effective?  
7. In view of the Bland judgement should all people in the vegetative state have nutrition and hydration discontinued?  
8. Should all patients referred to the courts for withdrawal of nutrition and hydration have a fMRI scan?  
9. Should all patients referred to the courts for withdrawal of nutrition and hydration be given a trial of zolpidem?  
10. In view of uncertainties produced by new neurophysiological techniques should no patient be referred to court for withdrawal of nutrition and hydration?  
11. Should it be necessary to go through the high court for decisions on life sustaining treatment or are there better methods?

Some of these dilemmas will be resolved by research, some by clinical innovation, some by better clinical and managerial evaluation and some by legislation.

As we solve some of these dilemmas we will create new ones – such is the advancement in science, law and ethics.

Recent Publications


The Association for the Rehabilitation of the Brain Injured (ARBI) is a very unique, community-based program located in Calgary, Canada dedicated to delivering individualized, long-term rehabilitation to adults who have sustained severe acquired brain injury. ARBI’s team of therapists identified the need to develop an assessment scale, with highly sensitive indicators, to better detect the small changes observed on reassessment of program participants.

This presentation will:
- highlight key aspects of this dynamic rehabilitation model
- provide an overview of the CAMMRI scale
- describe the program illustrated through case examples

ARBI operates in the belief that every person deserves a chance to reach their maximum potential following brain injury and that therapists working closely with volunteers and rehab staff can play a key role in improving the quality of individuals’ lives through specialized, long-term rehabilitation. These individuals are often initially offered a poor prognosis due to the severity and extent of their injuries. At ARBI, positive and often unpredicted changes are witnessed in these individuals many years post-injury. ARBI’s client-centered program continually strives to improve the person’s quality of life.

Few agencies provide intensive and longer-term therapy for survivors of severe brain injury who remain minimally responsive. There are very limited measures sensitive enough to detect small incremental changes in this population. ARBI therapists (Physiotherapists, Occupational Therapists and Speech-Language Pathologists) developed the Comprehensive Assessment Measure for Minimally Responsive Individuals – CAMMRI, to document these changes following specialized rehabilitation.

The evaluation test is divided into three areas: motor control, communication skills and response to the environment. Each area has specific sub-tests designed to fit a seven point rating scale, generating objective information regarding the individual’s improvements. This information documents changes and assists therapists to develop a personalized and comprehensive rehabilitation plan that ultimately aims to improve the quality of life of these individuals.

**Recent Publications**

Helen Gill
Head of Occupational Therapy Department, Royal Hospital for Neurodisability, London and International Fellow in Low Awareness States, Institute of Neuropalliative Rehabilitation, Royal Hospital for Neurodisability, London.

Co-developer of the Sensory Modality Assessment and Rehabilitation Technique (SMART), advanced specialist in profound brain injury assessment and rehabilitation and International Fellow in Low Awareness States undertaking a wide range of research in to the neuropalliative rehabilitation of patients with impaired consciousness.

**Background**

Two forms of sensory stimulation, namely environmental and structured, have been proposed as effective interventions promoting recovery in vegetative patients. Environmental stimulation was introduced by LeWinn and Dianescu (1978) who referred to earlier work with rats that had suggested an enriched environment had a positive influence on synaptic reinnervation. This form of stimulation has been widely practiced, but reports are mixed regarding its effectiveness (Wilson et al, 1996). A Cochrane systematic review published in 2002 described three studies, which had used environmental stimulation in patients considered to be comatose (Lombardi et al, 2002). Although all three studies reported an improvement in responsiveness, Lombardi and colleagues criticised the methodology of these investigations and concluded that none provided useful and valid results on outcome. In contrast, structured stimulation, as the name suggests, is an attempt to apply stimulation in a systematic manner. This approach largely grew from Wood’s criticism of environmental or intensive stimulation programs (Wood, 1991). To counter the effect of over stimulation, Wood argued that the patient’s sensory environment should be structured and controlled in terms of intensity and frequency - the presentation of stimuli should occur in intervals in order to structure the patient’s sensory environment. To demonstrate the effect of this approach Wood et al (1992) published the results of a small pilot study conducted with four vegetative patients. Wood et al reported that the patients treated with structured stimulation were discharged earlier than a retrospective control group. Furthermore the treated patient group scored higher Glasgow coma scale scores than the untreated control group. More recent trials have also suggested a positive effect of controlled sensory stimulation. Oh and Seo (2003) performed an interrupted time series design experiment with seven patients. Over a period of 16 weeks they performed sensory stimulation for a period of four weeks followed by a recession period for four weeks and then a second sensory stimulation period for 4 weeks followed by a second recession period. There results showed significant alterations in consciousness level, as measured by the Glasgow coma scale score, 2 weeks after the first sensory stimulation period. This effect increased gradually and was maintained for 3-4 weeks. However, consciousness levels began to decline 2 weeks after terminating the first sensory stimulation intervention and this detriment continued until starting the second sensory stimulation intervention. During the second intervention period, consciousness levels began to increase again and in contrast to the first sensory stimulation intervention this improvement continued even after terminating sensory stimulation. Although Oh and Seo’s work is to date the most compelling advocate of sensory stimulation, it, like Wood’s (1991) work, was only conducted in a relatively small group of patients. Similarly, Oh and Seo’s use of the Glasgow coma scale, which is generally insensitive to subtle changes in behaviour, may have missed important improvements in arousal and awareness over longer periods of time (Gelling et al, 2003). Two recently developed tools; WHIM and SMART, provide a more effective measurement of response to sensory stimulation, thus enabling the assessor to accurately measure change over time. This presentation will focus upon the use of these scales to measure change.

**Recent Publications**


**Session 5: Care management and rehabilitation**

10:35 – 11:00  Ceri Bowen  
**International Fellow in Working with Families, Institute of Neuropalliative Rehabilitation, Royal Hospital for Neurodisability, London.**

**Background**  
Clinical Psychologist specializing in working with families within neurorehabilitation.

**Title of Talk**  
Psychological needs

Relatives of people in VS and MCS go through at least three patterns of complex emotions; they do not go through a bereavement process per se. The first relates to anxiety and guilt about the accident or injury and what they might have done to prevent it. Second, mistrust of rehabilitation staff can arise due to misunderstandings about the nature of brain injury and prognosis – often associated with high expectations. Third, difficulties coming to terms with the extent of the injuries can lead to blaming others for a lack of improvement. On occasions, an unresolved issue in this domain can lead to overt conflict and aggression, which can be very destructive to staff morale. This can result in constant striving for more treatment, new treatments or facilities. These reactions are due, in part, to the fact that families may have been given misleading information in the acute hospital setting, e.g. to the effect that their relative will die. This is often due to the difficulty of making a long-term prognosis in the early stages of brain injury. Furthermore, having fought for the chance for specialist rehabilitation relatives are not going to take professional opinion at face value. The process of family adaptation to neuro-degenerative life-threatening illness has been likened to “negotiating uncharted territory” (Steele, 2005). In conversations, relatives speak of ‘needing to find a home’ for their loved one, with staff that can cope with his or her complex needs, but who also show concern for them as a care-giver. Additionally, family members need to come to some resolution of dilemmas surrounding the decision to maintain life, when a decision to terminate life is warranted, and how they feel in relation to degrees of ‘brain injury’ (Andrews, 2004). Given the potential for relatives to be all consumed by VS and MCS, there is a need to perceive choices, for the patient and for themselves. While many relatives are ‘living in hope’, awaiting new treatments to bring about a miraculous cure, this can be damaging if this pursuit takes them away from previously enjoyed activities. More than anything, relatives need to be able to permit themselves time away from their injured relative, and potentially a new and independent life. Psychosocial interventions following on from the above aim to bring about a change in cognition and attachment, from old patterns to new longer-term possibilities. A comprehensive intervention has been described by Kreutzer et al (2002), and developed in Virginia, United States. The authors propose five levels of intervention: family therapy, marital therapy, individual therapy, group therapy, and bibliotherapy. These interventions are all underpinned and informed by what Kreutzer et al (2002) call the ‘Brain Injury Family Intervention Curriculum’. In many ways, the Kreutzer’s programme is an extension of earlier holistic models of family intervention proposed by Muir et al., (1990) who delineated six categories of intervention: patient-family education, family counselling, family therapy, behavioural family training (or CBT), respite care, and family support groups. Taken together, there could be up to ten or so levels of intervention to consider. A number of interventions trialed in RHN will be described, from providing an information service, to involving families in case conferences, to running support groups, also advice about when to refer on to outside family therapy services. First and foremost, clinicians must remember that each family is unique in its functioning and adaptation in the face of adversity.


**Recent Publications**

Background

Post doctoral scientist with a particular interest in consciousness and disorders of consciousness. Completed his PhD at the University of Buenos Aires and is currently undertaking a post-doctoral fellowship at INSERM.

Title of Talk

Classical conditioning in the vegetative and minimally conscious state

Awareness is a fundamental property of human cognition, but its determination in unresponsive subjects still relies almost exclusively on behavioural observations. There is no objective manner to prove conscious processing when verbal or voluntary responses are unavailable. In disorders of consciousness, patients’ behavioural portfolios are limited to reflexive responses in the vegetative state and inconsistent, but purposeful voluntary movements in the minimally conscious state. Eye blink trace conditioning –where a tone and a silent interval precede an airpuff to the eye- is considered a plausible objective test to assess awareness without relying on voluntary behavioural markers. However, whether this learning paradigm can probe awareness in these patients is unknown. Here we demonstrate that patients with disorders of consciousness, unable to report awareness explicitly, can learn the association between tone and airpuff. Learning was highly specific; it showed an anticipatory electromyographic response to the aversive stimulus (airpuff) triggered by the tone, but not to the unpaired stimulus (a white noise). This effect augmented in amplitude as the aversive stimulus approached. Our results suggest that patients with disorders of consciousness might exhibit partially preserved conscious processing, which cannot be detected by behavioural observations. We conclude that this approach forms a valuable objective assessment to inform clinical decision making in patients with disorders of consciousness.

Recent Publications


Background
A medical doctor currently undertaking her PhD in the Coma Science Group, University of Leige and Neurology training at the Sart Tilman University Hospital of Leige, Belgium. Uses behavioural, electrophysiological and neuroimaging methods to investigate sensory and cognitive function in patients with impaired consciousness.

Title of Talk
Integrity of sensory networks revealed by functional imaging

During this presentation I will review functional imaging (fMRI) work to reveal the integrity of sensory processing in minimally conscious (MCS) and vegetative (VS) patients. In contrast to the limited “lower-level” primary cortical activation classically found in VS, MCS patients show activation of “higher-level” association cortex, similar to controls, in response to auditory, emotional and noxious stimuli. Despite an apparent anatomical similarity between MCS and VS patients, functional imaging data show striking differences in cortical segregation and integration. Preliminary data show that cerebral responses to the patient’s own name as measured by fMRI are a potentially useful tool to preclinically distinguish “MCS–like” cognitive processing in some patients behaviourally classified as VS. The study of brain responses to complex and emotionally meaningful sensory stimuli in non-communicative brain injured patients could thus be a promising tool to detect patients who are evolving from VS to MCS.

Recent Publications


Background  A senior neuro-physiotherapist with a special interest in the assessment and rehabilitation of profoundly brain injured patients.

Title of Talk  The effect of standing patients on behavioural repertoire

The importance of good posture and position when assessing the behavioural presentation of patients with impaired consciousness has been widely stressed. Patient’s supine in bed, with limited ability to move or view their environment may be unable to demonstrate critical behavioural diagnostic markers and thus inadvertently distort any interpretation regarding their awareness of self or environment and ability to respond to command. Indeed, sub-optimal positioning and environment have been highlighted as possible causes for misdiagnosis. The importance of a multidisciplinary approach to ensure appropriate environment, method of application, positioning and support is now widely implemented. Allied health professionals, including Physiotherapist’s have a central role in ensuring the optimal conditions are available in which to assess the patient with impaired consciousness. Amongst the many interventions offered by physiotherapy the use of tilt-tables and standing frames has recently been highlighted as a technique to facilitate the observation of a patient’s behavioural portfolio. In this presentation I describe the effect of standing patients with impaired conscious on the highest ranked and total number of behaviours on the Wessex Head Injury Matrix (WHIM). In a group of 11 patients meeting the diagnostic criteria defining the vegetative state, 3 patients demonstrated significant increases in the highest ranked and total number of behaviours on the WHIM between supine and elevated position. A significant increase in the highest ranked and total number of behaviours was also observed in 8 out of 13 patients meeting the diagnostic criteria defining the minimally conscious state. Although the highest and total number of behaviours increased, the behaviours observed did not alter the patient’s diagnosis. No change in blood pressure was observed between supine and elevated positions. These findings corroborate earlier pilot studies demonstrating the positive effects of standing patients. In addition to the facilitation of the behavioural portfolio, standing using a tilt table is well known to increase uptake of nutrition in the cartilage and facilitate stretches (especially soleus, gastrocnemius, ilopsoas and hamstrings. Standing also facilitates changes in pressure areas for skin and trunk care; aids lung expansion; and provides vestibular and proprioceptive input to help re-establish head and trunk reflexes.

Recent Publications


Session 7: The neural basis of consciousness 2

13:30 – 14:00  David Menon  Professor and head of the University Division of Anaesthesia, Addenbrookes Hospital, University of Cambridge, UK.

Background  Leads an extensive research programme focusing upon the mechanisms of pathology, novel treatment interventions and recovery from acute brain injury, including emergence from coma.

Title of Talk  What can functional imaging studies of anaesthesia tell us about consciousness and its impairments?

Several studies over the last few years have highlighted the role of functional imaging in detecting both resting and task-activated neural processing in patients who show no behavioral evidence of such processing: a phenomenon which we have termed “covert cognition”. These studies have informed the discussion regarding cognition in coma and the vegetative state, and innovative paradigm design has allowed us to answer relatively sophisticated questions regarding cognitive capacity. However, any inferences that we make from such studies are necessarily constrained by the need to compare activation patterns in normal subjects with patients in whom neural processing of stimuli is variably and unpredictably compromised. Validation of such studies, and the use of their data to inform integrated models of consciousness, would be enormously facilitated by the ability to modulate neural processing in healthy volunteers in a reproducible, reversible, and safe way.

The use of functional imaging in the study of anaesthetic drug action offers this opportunity. Modern inhaled and intravenous anaesthetics have rapid onset and offset of action, their dose-effects can be precisely varied, and the pharmacokinetic models that underpin blood levels of these drugs are well understood. We have used this approach to understand the hierarchy of language processing in healthy volunteers, and to develop testable hypotheses regarding the relationship between semantic comprehension and memory encoding. Such studies allow unique insights into human conscious experience. They also provide an infrastructure for the development of paradigms for, and the interpretation of data from, functional imaging studies of covert cognition in disease states which impair consciousness.

Relevant Publications


Accurate prediction of an individual’s conscious experience based only on measurements of their brain activity would provide strong evidence for a close link between brain and mind. Recent empirical and methodological advances in such ‘brain reading’ have yielded promising findings. Conscious perception of both simple features and complex object categories can be predicted from characteristic, distributed activity patterns in human visual cortex. Furthermore, feature-selective processing can also be demonstrated for stimuli of which the subject is completely unaware. This talk will review recent empirical work from our laboratory and consider how it contributes to revealing the way in which individual perceptual experiences are encoded in the human brain.

**Recent Publications**


14:30 – 15:00  Ralf Claus  Department of Nuclear Medicine, Royal Surrey County Hospital, UK.

**Background**
With Dr Nel (South Africa) published the first reports of zolpidem use with vegetative and minimally conscious patients.

**Title of Talk**  Zolpidem

Zolpidem is a drug that is routinely prescribed for insomnia. It induces sleep by activating the GABA(A) receptor chloride channel macromolecular complex, which is implicated in sedative, anticonvulsant, anxiolytic and myo-relaxant drug properties. It is a chemically distinct imidazopiridine that works at the alpha sub-unit, referred to as the benzodiazepine (omega) receptor. There are at least three omega receptor subtypes. Benzodiazepines bind non-selectively to these while zolpidem binds preferentially to omega-1 receptors.

**Current literature on zolpidem efficacy in brain pathology**
A report by Clauss et al., (2000) of unexpected improvements after zolpidem administration in a patient with impaired consciousness, was the first of several similar cases that are listed in the table below. Zolpidem can achieve this effect years or even decades after the injury.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Patients</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td><strong>Anoxic Brain Damage</strong></td>
<td></td>
<td></td>
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<tr>
<td>Stroke</td>
<td>4</td>
<td>Clauss &amp; Nel, 2004, 2005; Cohen et al, 2004</td>
</tr>
<tr>
<td>Near drowning</td>
<td>2</td>
<td>Clauss &amp; Nel, 2004, 2006</td>
</tr>
<tr>
<td>Hypoxia cardiac arrest</td>
<td>1</td>
<td>Shadan et al, 2004</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>4</td>
<td>Jarry et al 2002, Clauss et al 2005</td>
</tr>
<tr>
<td>Bell’s Palsy</td>
<td>1</td>
<td>Clauss &amp; Nel, 2005</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>5</td>
<td>Clauss, Sathekge, Nel, 2004</td>
</tr>
<tr>
<td>Auditory impairment</td>
<td>2</td>
<td>Clauss et al, 2005</td>
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</tbody>
</table>

**Further experience and response rates (unpublished)**
Newspaper articles in early 2006 generated widespread requests for further information by patients, caregivers and doctors of neurologically disabled patients. By December 2006 the authors had responded to 300-400 individual requests and Dr Nel had treated over 200 patients in South Africa. The first dose response rate was around 10-15% in patients with marked neuro-disability, including VS and MCS, while it reached 30-60% in lesser disabilities. Further studies on response rate are required however, especially in view of a recent patient who took 8 days’ treatment to respond.

**Adverse Effects**
Side effects of zolpidem as a sedative in normal subjects include antegrade amnesia, hallucinations and sleepwalking. In patients with brain damage, sedation occurs commonly.

**Imaging and animal studies**
SPECT and PET brain imaging studies have shown activation of unresponsive tissues that were previously considered to be dead. They are now regarded as dormant instead. They show no typical location or distribution pattern and vary from patient to patient. Activation could be reproduced in animal studies and the effects blocked by flumazenil, a benzodiazepine antagonist.
Neurodormancy
The above research led to the proposal of the neuro-dormancy mechanism in 2004\(^2\). Neuro-dormancy has some features similar to the established diaschisis phenomenon but there are important differences, such as permanence, intralesional location and late onset. Neuro-dormancy appears to be a common denominator in brain pathology and explains the efficacy of zolpidem across a wide range of unrelated brain pathology.

Identification of patients
Responders may be identified by a simple clinical test of daily zolpidem for up to two weeks with close clinical observation, or SPECT or PET brain imaging studies before and after a dose of zolpidem. These scans can be combined with CT or MRI.

Initial Dosing
The UK recommended dose of zolpidem is 10mg at night. In brain damage a morning dose 1 hour after breakfast seems optimal. 5 mg may be given to minimise sedation followed by the same dose hourly until a response is detected. Response to the drug may start within 30 minutes, peak by 1 hour and last 3-4 hours. The response may be subtle, such as stringing sentences together for the first time and may be more difficult to detect if masked by sedation. One patient responded only after 8 days so it appears wise to continue for two weeks before pronouncing a patient unresponsive.

Longer term dosing
Patients may need several dose adjustments to achieve optimal balances between effect and sedation. Dose requirements may increase periodically or reduce when a response has become established. Our longest therapy has lasted for 8 years. The patient is fully conscious now and his IQ improves from 70 – 90 on zolpidem. Full blood count, liver and renal functions remain within normal limits. We recommend repeating such tests 6 monthly because the safety of continuous, long term dosing has not been fully established, despite the well-known safety of zolpidem in its traditional use, or in acute overdose.

Age of patients
Responses occur at any age. Our youngest patient was 2 years of age and the eldest are over 80 years\(^2\). Some patients injured at birth have responded when in their twenties or thirties.

Clinical trials
In spring 2007 ReGen Therapeutics began conducting a trial in 20 known zolpidem responders to compare a sublingual spray formulation with tablets for sedation vs. clinical benefit and time to onset of effect. Measurements include disability level, cognitive response and sedation. Results are awaited at the time of writing. A project to help patients and physicians in the UK to conduct trials of zolpidem to proper standards has been submitted to regulatory authorities.

Conclusion
The evidence for an important role of zolpidem in the treatment of brain damage becomes more compelling as more centres report their findings. A wide range of brain pathology has responded to zolpidem including PVS/MCS. SPECT and PET scans show that the mechanism includes reversal of dormant brain areas that were hitherto considered beyond repair.


Recent Publications

Background  Principal proponent of repetitive median nerve stimulation as a treatment for reduced consciousness and lead clinician in International trials evaluating this technique.

Title of Talk  Median nerve stimulation

Right median nerve electrical stimulation is a safe and convenient portal for resuscitation of the severely injured brain. In the last three decades, pulsed electrical stimulation has been shown to have both peripheral and central nervous system effects in paraplegia, quadriplegia, and post-traumatic coma. All of these conditions are amenable to electrical treatment with varying degrees of clinical success. In the 1990s, American pilot studies commenced at the University of Virginia, Duke University, and East Carolina University, and in 2005 at Renji Hospital in Shanghai, China. Subgroups of coma patients stimulated at the decerebrate/decorticate level experienced more rapid, and better awakening than control or historical similar level patients.

Injured central neural circuitry can be enhanced and reprogrammed from below by peripheral nerve surface electrical stimulation for a period of weeks or months. Two case studies from 12 and 2 years ago illustrated the very functional recovery of two young traumatic brain injury coma patients who were near death when stimulation began 2 to 3 weeks post injury. Video clips will show their progress over a period of months and years.

Recent studies in Shanghai of fluid percussion brain injured rats demonstrate the brainstem changes following electrical stimulation of the right upper limb. Microarray of mRNA is the efficient method for analysis of the molecular biology changes after brain trauma. Further investigation is needed to determine if the microarray results in the stimulated rats’ midbrains (contrasted to non-stimulated rats) will help to explain the neuroprotective effects observed clinically in electrically treated comatose humans.

Future applications of RMNS will cover the chronological spectrum of unconscious injured patients. A multi-centre investigation at eastern United States medical centers will be accomplished through the International Brain Research Foundation.

When electrical treatment is started in the early stage of coma, or the early phase of the vegetative state, RMNS can accelerate the upward progress toward re-awakening. Sometimes a more functional outcome will be the result. Median nerve stimulation can communicate with the profoundly injured idling brain. When electrical treatment is applied early as an adjunct to aggressive ICU and neurosurgical neuroresuscitation, a more functional outcome may result for many coma patients.

Recent Publications


Cooper EB, Cooper JB. Electrical treatment of coma via the median nerve. Acta Neurochirurgica Supplementum, 2003; 87:7-10.

Historically, deep brain stimulation (DBS) in the thalamus, upper brainstem and allied targets has been advanced as a method to restore consciousness to chronically unresponsive patients (brain dead or in chronic vegetative states) following severe brain injuries with limited evidence of effects. Although DBS is an increasingly used mode of treatment for neuropsychiatric disorders its underlying mechanisms of action in these applications are not well characterized. Recent proposals have considered the application of central thalamic DBS to improve cognitive function in conscious patients with severe cognitive disabilities. These efforts link closely to the basic neurophysiological functions of the DBS targets in forebrain arousal regulation mechanisms and the underlying pathology of chronically impaired cognitive function following severe brain injury.

In this presentation we will review the clinical background and scientific foundations underpinning a clinical study demonstrating behavioral improvements with central thalamic stimulation in a single human subject remaining in the minimally conscious state (MCS) for 6 years following a severe traumatic brain injury. These experimental and clinical data support further research to develop central thalamic DBS as an investigational therapeutic method. However, such development will require stringent efforts to develop patient selection criteria, study design and ethical frameworks to ensure that this line of enquiry remains aimed at achievable and desirable clinical goals.

Recent Publications


Structural problems such as hydrocephalus should be excluded before the diagnosis of vegetative state (VS) can be made\(^1\). 44\% of survivors of severe head injury (Glasgow Coma Scale score \(<\) or \(=\) 8) may develop posttraumatic ventriculomegaly\(^2\). However, the distinction between atrophy and potentially treatable hydrocephalus cannot be made on the basis of conventional computerised tomographic (CT) or magnetic resonance (MR) scanning alone - physiological measurements of intracranial pressure (ICP) and cerebrospinal fluid (CSF) outflow resistance may be helpful. Posttraumatic hydrocephalus, as identified by abnormal CSF dynamics, was diagnosed in 20\% of survivors of severe head injury and their outcome was significantly worse\(^2\).

Tests of CSF dynamics (intracranial pressure monitoring and computerized CSF infusion studies) will be reviewed particularly in the context of skull defects\(^3,4,5\). There is a limited literature available, based largely on case reports, that documents the effect of CSF diversion on outcome in "vegetative" patients\(^6\). It is important that families are counselled early on that, despite the poor prognosis, further investigations may be appropriate in the post-acute phase to exclude processes that may be impeding recovery. Without such counselling, families may find it difficult to come to terms with the possibility that a remediable component to their loved-one’s condition may have been missed. Multi site infections may make investigation and treatment difficult.

The use of cells to repair the damaged brain is not a new concept and has come to clinical fruition in a number of disorders. The best example of this approach is the use of fetal ventral mesencephalic tissue, which contains the developing dopamine cells of the substantia nigra, in the treatment of Parkinson’s disease – a disorder that is characterized by the loss of the dopaminergic nigrostriatal tract. These clinical studies have involved implanting dissociated fetal ventral mesencephalic tissue into the striatum of patients with moderately advanced Parkinson’s disease to see whether clinical improvement can be obtained and sustained. To date the data has been encouraging in that some patients have done extremely well with this procedure with benefits lasting over ten years. In other cases, however, troublesome side effects have been noted such as the development of involuntary graft induced dyskinesias – which in part relates to the selection of patients as much as to the procedure itself. Other disorders similarly have also been the targets of cell therapies including a UK study in Huntington’s disease using fetal striatal tissue with Cambridge as the surgical centre and studies in the US using stem cells for stroke. In Huntington’s disease the data to date suggests that there may be improvement in some patients whilst in stroke the evidence is less convincing.

Nevertheless these studies have shown that cell therapies to repair the damaged CNS is possible, if patients are carefully selected and appropriate tissue implanted at sites of primary pathology. It would therefore not be unreasonable to consider using such cell therapies for a range of other neurological disorders assuming a clear pathology can be defined.

In this talk I will concentrate on the use of cell therapies in Parkinson’s disease as an example of how this approach has been developed in a disorder with relatively focal pathology. The concepts and principles upon which this work is based can then be applied to other disorders, which may include more global insults to the central nervous system such as occurs in patients who develop vegetative state.

Recent Publications


Title
How can we improve the management and rehabilitation of patients with impaired consciousness?

Progress toward more effective rehabilitation of patients with disorders of consciousness is contingent upon establishing a systematic approach to clinical care and research. This discussion will propose a model of care that was designed to bridge clinical and research needs en route to accomplishing this goal. Participants will be invited to extend, critique and refute the model proposed.

Approach to Assessment:

- Patient characterization → behaviorally-based (v. diagnostically-based)
- Assessment measures → standardized, psychometrically-sound, functionally-relevant → individualized, qualitative
- Assessment schedule → fixed, tied to length of time post-injury
- Neuroimaging → explicit indications
- Outcome monitoring → core dataset

Approach to Treatment:

- Interventions → operationally-defined (what, when, how long) → linked to injury mechanism, pathophysiology
- Patients → explicit stratification parameters (inclusion/exclusion criteria, covariates)
- Trial design → pre-defined method to control for extraneous variables (spontaneous recovery)
- Efficacy monitoring → see Approach to Assessment
- Discontinuation criteria → algorithmic
- Role of caretakers/paraprofessionals → data on caretaker preferences, effectiveness??

Recent Publications

