Journal of

ISSN 1650-1977

REHABILITATION MEDICINE

Vol. 44. No. 6
May 2012

Official journal of the
– *International Society of Physical and Rehabilitation Medicine (ISPRM)*
– *UEMS European Board of Physical and Rehabilitation Medicine (EBPRM)*
– *European Academy of Rehabilitation Medicine (EARM)*
Published in association with the
– *European Society of Physical and Rehabilitation Medicine (ESPRM)*
– *Canadian Association of Physical Medicine and Rehabilitation (CAPM&R)*
– *Asia Oceania Society of Physical and Rehabilitation Medicine (AOSPRM)*
– *Baltic and North Sea Forum for Physical and Rehabilitation Medicine (BNFPRM)*

Special issue

CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY

Articles from the workshop held in July 6, 2010 in Salerno, Italy

The Non-profit Foundation for Rehabilitation Information

www.medicaljournals.se/jrm

Journal of Rehabilitation Medicine

Journal of Rehabilitation Medicine is an international peer-review journal published in English with ten regular issues per year. It is owned by a Swedish nonprofit organization: Foundation for Rehabilitation Information. Journal of Rehabilitation Medicine was former called Scandinavian Journal of Rehabilitation Medicine, which was founded by Olle Höök in 1968. The name was changed to Journal of Rehabilitation Medicine in 2001.

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Publication information: Journal of Rehabilitation Medicine (ISSN 1650-1977) volume 44 comprises ten regular issues published in January, February, March, April, May, June, July, September, October and November. Each issue comprises approximately 96 pages.

Subscr rates vol 44:	- for institutions:	paper incl. electronic access: EUR 430, electronic only: EUR 370
	- for individuals:	paper incl. electronic access: EUR 175, electronic only: EUR 145
	- for the organizations above:	paper incl. electronic access: EUR 75, electronic only: EUR 50

Indexing: Journal of Rehabilitation Medicine is indexed in Index Medicus/MEDLINE, Excerpta Medica/EMBASE, Biological Abstracts, Current Contents/Clinical Practice, Allied and Alternative Medicine Database (AMED), Applied Social Sciences Index & Abstracts, Ergonomic Abstracts, Psychological Abstracts PsycINFO, PSYCLIT DATABASE, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Developmental Medicine and Child Neurology, Exceptional Child Education Resources, Periodicals Scanned and Abstracted: Life Sciences Collection, Faxon Finder, Focus On Sports Science & Medicine, Research Alert, SCISEARCH, SportSearch.

J Rehabil Med 2012; 44: 481–516

CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY

Articles from the workshop held in July 6, 2010 in Salerno, Italy

Guest Editors

Giuliano Dolce, MD, Lucia F. Lucca, MD and Walter G. Sannita, MD

 doi: 10.2340/16501977-0992

 ISSN 1650-1977

Included in the special issue:
CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY
J Rehabil Med 2012; 44: 481–516

FOREWORD

Progress in intensive care has improved the outcome of patients with severe brain damage and increased their chances of surviving and developing a severe disorder of consciousness such as the vegetative or minimally conscious states. Recent data have documented early recovery from the vegetative state in a significant proportion of patients; late recovery is also possible years later. There is sound neuroimaging evidence that residual responsiveness is also detectable in subjects who have been unambiguously diagnosed as being in a vegetative state and, by definition, isolated from the environment. This evidence blurs further the diagnostic distinction between the vegetative and minimally conscious states, and brings into question the current diagnostic criteria, alters the perspective of health care and neurorehabilitation on this issue, and has led to increased interest amongst the scientific community in the mechanism sustaining consciousness. This issue is attracting the attention of scientists with diverse research backgrounds, due to progress in the investigation of higher brain function, advances in artificial intelligence, and diffuse perception of the inadequacy of traditional mind/body separation.

The workshop "*Consciousness and the vegetative state: today*" was held in Salerno, Italy, on 6 July 2010, in the framework of the *2nd Conference on Consciousness and Coma*, with the participation of leading scientists in neuroscience. The chairs were G. G. Celesia (Chicago) and W. G. Sannita (Genova/New York). The objectives of the workshop were to update the current characterization of consciousness and related terms (which remain to a significant extent ambiguously defined), focus attention on methodological and applicative problems, and promote multidisciplinary interaction and collaboration. It is hoped that the workshop and its proceedings will facilitate sharing of relevant information on this issue and promote further research.

Thanks are due to the Institute S. Anna – RAN for the successful organization, financial support and publication on this special issue as part of the program for advanced teaching and professional upgrading "Le giornate di Crotone, yrs. XIII and XIV".

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 doi: 10.2340/16501977-0967
 ISSN 1650-1977

J Rehabil Med 2012; 44: 484–486

Included in the special issue:
CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY
J Rehabil Med 2012; 44: 481–516

INTRODUCTION

CONSCIOUSNESS: TODAY

"*To demonstrate existential characters of neurons, any theoretically conceivable net embodying the possibility will serve.*" (Pitts, McCulloch, 1948)

Consciousness is a multifaceted concept combining awareness and wakefulness. In everyday neurology it is usually equated to the waking state, and fluctuations in the level of vigilance are thought to reflect changes in brain (cortical) activation. It is believed to imply (subjective) experience and awareness of self (self-consciousness, self-detection, awareness of awareness, self-knowledge) and of environment (1). Jackson (2) restricted consciousness to the momentary relationship between the subject and the object or (in his anatomical-physiological terms) to the organism adjustment to the environment. However, perception and behaviour are possible without formal awareness (3–8) and some sustained (self)consciousness also exists during sleep, as we remain ourselves in the most unrealistic dreams and are also aware of our dreaming (9).

Today, research on consciousness is expanding, with a major focus on its understanding in relation to cortical/brain activation or functional complexity, long-range connectivity, neuronal synchronization in selected frequency ranges, uni/multimodal perception, motor activation, focused attention, etc. The major current theories about consciousness involve large-scale information processing, social processes, or neurobiological mechanisms (1). Distinctions between consciousness and attention have been documented (10–12), with implication in the cognitive neuroscience that consciousness could be distinct from other higher brain functions (13). The brain structures and processes thought to mediate in sustaining consciousness nevertheless are identified by the impairment of varying severity that results from local damage. Consciousness thus appears to be the result of a complex functional arrangement in which sustained sensory input, activation of non-specific ascending systems and primitive motor systems, activation of cortical neurones at due frequency, sensory-motor interaction, and balanced metabolism and neurotransmitters modulation are crucial (14, 15). This complex functional set-up conceivably also accounts for some specificity of the neurological signs predicting the outcome from the vegetative state (also referred to as unresponsive wakefulness syndrome) (16) and its evolution into a minimally conscious state (17–23).

Further investigation is needed to define the extent to which the reported electrophysiological, functional magnetic resonance imaging, positron emission tomography scan or autonomic changes imply some specificity of response or have clinical or prognostic relevance. This caveat notwithstanding, neuroimaging has documented retained connectivity in segregated networks in response to stimulus conditions in both minimally conscious and vegetative state subjects, with indication of the capability of the severely damaged brain to express surviving modular functions in the absence of the integrative processes necessary to consciousness (24–28). Although restricted to a relatively small portion of patients (29), this evidence further promoted research on the neuronal correlates of (un)consciousness (30) and expanded the clinical scenario. As a result, the vegetative and minimally conscious states appear today neither static nor homogeneous, and a tacit revision of the anatomo-functional set-ups underlying these conditions is *de facto* underway, warranting a formal nosographic revision of the current descriptive categories or accuracy of diagnosis (16, 31).

Regionally-mediated micro-consciousness processes have been proposed based on evidence of local neuronal organization in visual perception (32). On the other hand, increased synchronization between large neuronal populations of distinct areas related to perceptual dominance has been documented during conscious visual perception (33). The observation is consistent with evidence suggesting that neuronal activity synchronizes across cortical areas at conscious perception and with the theories of neural integration and complexity accounting for the properties of conscious experience and consciousness itself (13, 34–37). Long-range synchronization (e.g. in the gamma range) is thought to mediate in conscious perception (33) as it does in binding visual features and in all conditions in which neurones are selectively assembled to respond to any momentary functional requirement (38–44). However, its role in sustaining consciousness remains undocumented (45). In this respect, the major unsolved problem of biology is how billions of nerve cells work together to create consciousness (46, 47).

Consciousness is topical and is increasingly attracting scientists in neuroscience, medicine, neurocomputing, artificial intelligence, and robotics. Interest is increasing with the rapid progress in the investigation of higher brain function, advances in artificial intelligence, and diffuse perception of the inadequacy of traditional mind/body separations. The issue is also crucial in methodological and bioethical controversies pertaining to medicine and public or private healthcare (16, 31, 48). However, consciousness and related terms remain to a significant extent ambiguously defined and inadequately characterized. Peculiar conditions, such as epilepsy or the vegetative and minimally conscious states, may question the correlation between wakefulness and awareness and the available computational models of brain activity (30, 49, 50). Research attempting to correlate the contents of conscious experience with representations in specific neural populations relies to a relevant extent on the linguistic neutrality of "correlates" when the experimental paradigms and explanatory canons of neuroscience are not neutral about the mechanical relations with the brain and are supposed to investigate causes

 doi: 10.2340/16501977-0939
 ISSN 1650-1977

(51). A taxonomy of conscious, preconscious, and subliminal processing is still needed (52).

Neuroscience has advanced to the point that it appears that we can now treat consciousness as a scientific problem like any other (53), disregarding objections that it is epiphenomenal, not evolutionary in function, unaccountable by brain processes, unsuitable to objective investigated, etc. (53). To this end, a proper definition of consciousness and an up-to-date scrutiny of its descriptors are needed in order to be able to think scientifically about consciousness and to design experimental studies.

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Key words: consciousness; descriptors; neuronal mechanisms; research.

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J Rehabil Med 2012; 44: 487–494

Included in the special issue:
CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY
J Rehabil Med 2012; 44: 481–516

ORIGINAL REPORT

METABOLIC ACTIVITY IN EXTERNAL AND INTERNAL AWARENESS NETWORKS IN SEVERELY BRAIN-DAMAGED PATIENTS

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Objective: **An extrinsic cerebral network (encompassing lateral frontoparietal cortices) related to external/sensory awareness and an intrinsic midline network related to internal/self-awareness have been identified recently. This study measured brain metabolism in both networks in patients with severe brain damage.**

Design: **Prospective [18F]-fluorodeoxyglucose-positron emission tomography and Coma Recovery Scale-Revised assessments in a university hospital setting.**

Subjects: **Healthy volunteers and patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS), emergence from MCS (EMCS), and locked-in syndrome (LIS).**

Results: **A total of 70 patients were included in the study: 24 VS/UWS, 28 MCS, 10 EMCS, 8 LIS and 39 age-matched controls. VS/UWS showed metabolic dysfunction in extrinsic and intrinsic networks and thalami. MCS showed dysfunction mostly in intrinsic network and thalami. EMCS showed impairment in posterior cingulate/retrosplenial cortices. LIS showed dysfunction only in infratentorial regions. Coma Recovery Scale-Revised total scores correlated with metabolic activity in both extrinsic and part of the intrinsic network and thalami.**

Conclusion: **Progressive recovery of extrinsic and intrinsic awareness network activity was observed in severely brain-damaged patients, ranging from VS/UWS, MCS, EMCS to LIS. The predominance of intrinsic network impairment in MCS could reflect altered internal/self-awareness in these patients, which is difficult to quantify at the bedside.**

Key words: vegetative state; minimally conscious state; positron emission tomography; consciousness; self-awareness; traumatic brain injury.

J Rehabil Med 2012; 44: 487–494

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Submitted September 29, 2011; accepted December 5, 2011

INTRODUCTION

The assessment of consciousness in severely brain-damaged patients remains a major challenge (1). For clinicians, consciousness has two main components: arousal (i.e. wakefulness or vigilance) and awareness (i.e. comprising all subjective perceptions, feelings and thoughts) (2). Awareness has recently been subdivided into "external or sensory awareness" (i.e. perceptual awareness of the environment) and "internal or self awareness" (i.e. stimulus-independent thoughts, mental imagery, inner speech, daydreaming or mind wandering) (3). At the bedside, arousal is typically measured by examining eye opening. External awareness is assessed by showing the presence of reproducible command following or "non-reflex"/voluntary movements (4). After severe brain damage and the acute setting of coma, 4 different clinical entities can be disentangled: (*i*) patients who "awaken" but remain without reproducible signs of command following (i.e. vegetative state (VS), now also called "unresponsive wakefulness syndrome" (UWS) (5); (*ii*) minimally conscious state (MCS) patients showing reproducible, albeit fluctuating, signs of consciousness, but without functional communication (6); (*iii*) patients who emerge from MCS (EMCS) recovering functional communication or object use (6); and (*iv*) locked-in syndrome (LIS) patients who are fully aware yet completely paralysed with the exception of small eye-movements permitting an eye-coded communication (7).

The behavioural assessment of consciousness in non-communicative brain-damaged patients is difficult because movements can be very small, inconsistent and easily exhausted (8, 9). This issue is further complicated when patients have underlying deficits in the domain of verbal or non-verbal communication functions, such as aphasia, agnosia or apraxia (4, 10, 11). Quantifying internal or self-awareness is even more difficult than the assessment of external awareness in these patients. Most, if not all, of the employed consciousness scales mainly assess command-following or the presence of non-reflex movements (i.e. orientation to pain or visual pursuit) (12, 13). Regarding the latter behaviour, some scales,

 doi: 10.2340/16501977-0940
 ISSN 1650-1977

such as the Coma Recovery Scale-Revised (CRS-R) (14) explicitly require the use of a mirror (15), hence possibly assessing some form of self-recognition/internal awareness. Similarly, presentation of the patient's own name, another auto-referential attention-grabbing stimulus, has been employed by some consciousness scales (e.g. the Wessex Head Injury Matrix (16)). Most behavioural scales, however, mainly, if not totally, assess external or sensory awareness and give little or no information about any possible form of internal or self-consciousness (17).

Recent studies have started to identify the neural correlates of internal and external awareness. An increasing body of evidence, mainly coming from functional neuroimaging (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies) and electrophysiology point to the critical role of a widespread fronto-parietal network in the emergence of conscious awareness, also called "global neuronal workspace" (18–20). Within this widespread fronto-parietal network, two separate systems can be identified: (*i*) an *extrinsic*/*lateral* network encompassing lateral parietal and dorsolateral prefrontal cortices, mainly related to external awareness (i.e. stimulus-dependent or perceptual awareness of the environment) and (*ii*) an *intrinsic*/*midline* network encompassing midline precuneus/posterior cingulate and mesiofrontal/anterior cingulate cortices, mainly related to internal awareness (i.e. stimulus-independent thoughts and self-related thoughts) (3). Given our clinical limitation to objectively measure internal awareness, we here employed objective brain metabolism data obtained from PET in patients with disorders of consciousness (i.e. VS/UWS, MCS, EMCS) and conscious LIS and controls, aiming to measure differences in activity in extrinsic and intrinsic network activity.

METHODS

Brain metabolism was studied by means of [18F]-fluorodeoxyglucose-PET (FDG-PET). The clinical diagnosis was based on the best response obtained by repeated CRS-R (14) assessments the day of the PET study and the two days before and after the PET acquisition. We applied the diagnostic criteria, as published by the Multi Society Task Force on PVS (21), the Aspen Neurobehavioral Conference Workgroup (22) and the American Congress of Rehabilitation Medicine (7). Exclusion criteria for the present study were: (*i*) the presence of pre-morbid neurological disease; (*ii*) the presence of ambiguous behavioural signs not permitting reliable clinical diagnosis; (*iii*) the presence of large structural brain damage exceeding 25% of the whole brain volume not permitting reliable spatial normalization to the standardized stereotaxic brain template; and (*iv*) the absence of good quality PET data not permitting reliable image reconstruction or correction for attenuation. The control population consisted of age-matched healthy volunteers ($n = 39$; mean age 45 years (median 45) (range 18–80); 18 men).

FDG-PET data were acquired after intravenous injection of 5–10 mCi of FDG on a Siemens CTI 951 R16/31 scanner (as described in 23) at the University Hospital of Liège, Belgium. Data were pre-processed and analysed using Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm) as described elsewhere (24–26). In brief, FDG-PET data from each subject were normalized to a standard stereotactic space (using a spatial template adapted to severe brain damage, as previously described in 27) and smoothed with a 14-mm full-width half-maximum isotropic kernel. The design matrix included the VS/UWS, MCS, EMCS and LIS patients' and control subjects' scans. Global normalization was performed by applying proportional scaling. The analyses identified brain regions where glucose metabolism was lower in each patient population compared with the control group. The resulting set of voxels values for each contrast, constituting a map of the *t* statistics (SPMt), was transformed to the unit normal distribution (SPMZ) and thresholded at $p < 0.001$. Results were considered significant at $p < 0.01$ family-wise correction for multiple comparisons. Next, we identified brain areas showing a linear correlation with CRS-R total scores. Here, results were thresholded for significance at $p < 0.001$ with small volume correction (8 mm radius) for multiple comparisons around the previously identified areas (24–26).

Informed consent was obtained from all control subjects and for LIS and EMCS patients, and from the legal representative of all non-communicative patients. The study was approved by the ethics committee of the University and University Hospital of Liège, Belgium.

RESULTS

A total of 132 patients were prospectively enrolled, of whom 62 were excluded because of: (*i*) pre-morbid neurological disease (8 patients); (*ii*) ambiguous behavioural signs not permitting reliable clinical diagnosis (12 patients); (*iii*) large structural brain damage (19 patients) and (*iv*) technical problems related to the FDG-PET acquisition (23 patients). Hence, 70 patients of the initial cohort were included for further analysis: 24 VS/UWS (mean age 51 years (median 50.5) (range 20–78); 10 men, 2 traumatic), 28 MCS (mean age 41 years (median 36.5) (range 17–81); 19 men, 16 traumatic), 10 EMCS (mean age 41 years (median 41) (range 14–76); 8 men, 4 traumatic) and 8 LIS (mean age 40 years (median 43) (range 22–53); 2 men, 1 traumatic). Patients were studied after a median of 26 months (interquartile range 24 months). Demographic and clinical data are summarized in Table I.

VS/UWS patients showed metabolic dysfunction in both thalami and in a widespread cortical network encompassing the extrinsic/lateral network (i.e. bilateral posterior parietal and prefrontal areas) and the intrinsic/medial network (i.e. the precuneus and adjacent posterior cingulate cortex and mesiofrontal and adjacent anterior cingulate cortex), compared with controls (Fig. 1). MCS patients showed metabolic dysfunction in both thalami and in the intrinsic/medial network. EMCS patients showed metabolic dysfunction in the posterior cingulate cortex and adjacent retrosplenial cortex. LIS patients showed metabolic dysfunction only in infratentorial regions (i.e. the cerebellum) (Table II).

At the group level, CRS-R total scores showed a positive correlation with a widespread cortical network encompassing both extrinsic/lateral network (i.e. bilateral posterior parietal and prefrontal areas) and part of the intrinsic/medial network (i.e. the precuneus and adjacent posterior cingulate cortex) (see Table III).

Table I. *Patient demographic, clinical and Coma Recovery Scale-Revised subscore data*

State	Age, sex	Aetiology	Time of PET	Audition	Visual	Motor	Verbal	Comm	Arousal
VS/UWS 1	30, M	ARCA	25 months	Startle reflex	None	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 2	44, M	ARCA	11 days	None	None	Abnormal posturing to pain	None	None	With stimulation
VS/UWS 3	69, M	ARCA	24 days	None	None	Abnormal posturing to pain	Oral reflexes	None	With stimulation
VS/UWS 4	62, M	Anoxia	9 months	Startle reflex	None	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 5	53, M	Basilar stroke	16 days	None	None	Flexion to pain	None	None	With stimulation
VS/UWS 6	34, F	ARCA	18 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 7	47, M	ARCA	55 days	Startle reflex	None	None	Oral reflexes	None	With stimulation
VS/UWS 8	63, F	ARCA	40 months	Startle reflex	None	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 9	65, F	Anoxia	12 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 10	54, M	ARCA	6 months	Startle reflex	None	Abnormal posturing to pain	Oral reflexes	None	With stimulation
VS/UWS 11	42, M	Anoxia	20 days	Startle reflex	None	Abnormal posturing to pain	Vocalization	None	Without stimulation
VS/UWS 12	43, M	ARCA	29 days	Startle reflex	None	Abnormal posturing to pain	None	None	Without stimulation
VS/UWS 13	73, F	Stroke	45 days	Startle reflex	None	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 14	41, M	ARCA	6 months	Startle reflex	Visual fixation	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 15	56, F	ARCA	43 days	Startle reflex	None	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 16	70, F	Anoxia	52 days	Startle reflex	None	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 17	49, F	ARCA	4 months	Startle reflex	None	None	Oral reflexes	None	Without stimulation
VS/UWS 18	52, M	Anoxia	10.5 months	Startle reflex	Blink to threat	Abnormal posturing to pain	Oral reflexes	None	Without stimulation
VS/UWS 19	78, F	Aneurysm	32 days	None	None	Flexion to pain	Oral reflexes	None	None
VS/UWS 20	48, M	Anoxia	30 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	With stimulation
VS/UWS 21	53, M	Stroke	66 days	Startle reflex	Blink to threat	Flexion to pain	None	None	Without stimulation
VS/UWS 22	46, F	Traumatism	37 days	Startle reflex	None	None	Oral reflexes	None	With stimulation
VS/UWS 23	34, F	Anoxia	260 months	Startle reflex	Blink to threat	Flexion to pain	Oral reflexes	None	Without stimulation
VS/UWS 24	20, M	Traumatism	15 days	None	None	Flexion to pain	Oral reflexes	None	None
MCS 1	35, F	Traumatism	101 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Vocalization	None	Without stimulation
MCS 2	28, F	Traumatism	80 months	Localization to sound	Visual pursuit	Automatic motor reaction	Vocalization	None	Without stimulation
MCS 3	81, F	Stroke	44 days	Reproducible movement to command	Object localization	Automatic motor reaction	Vocalization	Intentional	Without stimulation
MCS 4	37, M	Traumatism	87 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	Intentional	Without stimulation

Table I. *Condt.*

State	Age, sex	Etiology	Time of PET	Audition	Visual	Motor	Verbal	Comm	Arousal
MCS 5	33, M	ARCA	39.5 months	Startle reflex	Visual pursuit	Automatic motor reaction	Vocalization	None	Without stimulation
MCS 6	64, M	Aneurysm	6 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible verbalization	Intentional	With stimulation
MCS 7	50, F	Aneurysm	28 days	Startle reflex	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 8	38, M	Anoxia	4 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 9	81, M	meningitis encephalopathy	46 days	Localization ton sound	Visual pursuit	Localization to pain	Oral reflexes	None	Without stimulation
MCS 10	19, F	Traumatism	30 months	Startle reflex	Visual pursuit	Flexion to pain	Vocalization	None	Without stimulation
MCS 11	46, M	Traumatism	17 months	Startle reflex	Visual pursuit	Flexion to pain	None	None	Without stimulation
MCS 12	36, M	Traumatism	270 months	Reproducible movement to command	Visual pursuit	Automatic motor reaction	None	None	Without stimulation
MCS 13	29, M	Traumatism	46 days	Startle reflex	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 14	50, F	ARCA	65 days	Reproducible movement to command	Blink to threat	Flexion to pain	Vocalization	None	With stimulation
MCS 15	40, M	Traumatism	70 days	Reproducible movement to command	Visual fixation	Localization to pain	None	None	Without stimulation
MCS 16	50, M	ARCA	7 months	Reproducible movement to command	Object localization	Automatic motor reaction	Intelligible vocalization	Intentional	Without stimulation
MCS 17	56, F	Hydrocephaly	75 days	Startle reflex	Visual pursuit	None	Oral reflexes	None	Without stimulation
MCS 18	63, F	Stroke	17 days	Consistent movement to command	Visual fixation	None	None	None	With stimulation
MCS 19	17, M	Traumatism	4 months	Reproducible movement to command	Visual fixation	Localization to pain	Oral reflexes	None	Without stimulation
MCS 20	32, F	Anoxia	15 months	Startle reflex	Visual pursuit	Abnormal posturing to pain	Oral reflexes	None	With stimulation
MCS 21	50, M	Anoxia	85 months	Reproducible movement to command	Object localization	Automatic motor reaction	None	Intentional	With stimulation
MCS 22	23, M	Traumatism	11 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 23	22, M	Traumatism	99 months	Startle reflex	Visual fixation	Automatic motor reaction	None	None	Without stimulation
MCS 24	27, M	Traumatism	4 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 25	30, M	Traumatism	131 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	With stimulation
MCS 26	36, M	Traumatism	4 months	Reproducible movement to command	Visual pursuit	Flexion to pain	Oral reflexes	None	Without stimulation
MCS 27	65, M	Traumatism	21 months	Reproducible movement to command	None	Abnormal posturing to pain	Vocalization	None	With stimulation

Table I. *Condt.*

State	Age, sex	Etiology	Time of PET	Audition	Visual	Motor	Verbal	Comm	Arousal
MCS 28	23, M	Traumatism	73 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Intentional	Attention
EMCS 1	38, M	ARCA	45 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
EMCS 2	45, F	Traumatism	6 months	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
EMCS 3	32, M	Traumatism	26 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 4	37, M	ARCA	9 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 5	14, M	Traumatism	14 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 6	56, M	Stroke	64 days	Consistent movement to command	Object localization	Functional use of object	Intelligible vocalization	Intentional	Attention
EMCS 7	25, M	Traumatism	9 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 8	44, M	Stroke	7.5 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
EMCS 9	44, M	ARCA	88 days	Consistent movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
EMCS 10	76, F	Intoxication	81 days	Reproducible movement to command	Object recognition	Automatic motor reaction	Intelligible vocalization	Functional	Attention
LIS 1	53, M	Basilar stroke	81 days	Reproducible movement to command	Visual pursuit	Abnormal posturing to pain	Vocalization	Intentional	None
LIS 2	47, F	Basilar stroke	20 days	Reproducible movement to command	Object recognition	Flexion to pain	Oral reflexes	Intentional	Without stimulation
LIS 3	39, M	Traumatism	51 months	Reproducible movement to command	Object recognition	Flexion to pain	Oral reflexes	Intentional	Attention
LIS 4	44, F	Basilar stroke	52 months	Consistent movement to command	Object recognition	Functional use of object	None	Functional	Attention
LIS 5	44, F	Basilar stroke	19 days	Consistent movement to command	Object recognition	Flexion to pain	Oral reflexes	Functional	Attention
LIS 6	22, F	Basilar stroke	14 days	None	None	Flexion to pain	Oral reflexes	None	None
LIS 7	27, F	Basilar stroke	71 months	Consistent movement to command	Object recognition	Functional use of object	Intelligible vocalization	Functional	Attention
LIS 8	42, F	Brain stem haemorrhage	56 days	Reproducible movement to command	Visual pursuit	Flexion to pain	None	Intentional	With stimulation

PET: positron emission tomography; VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; EMCS: emergence from MCS: LIS: locked-in syndrome; M; male; F: female; Comm: communication; ARCA: cardiac arrest.

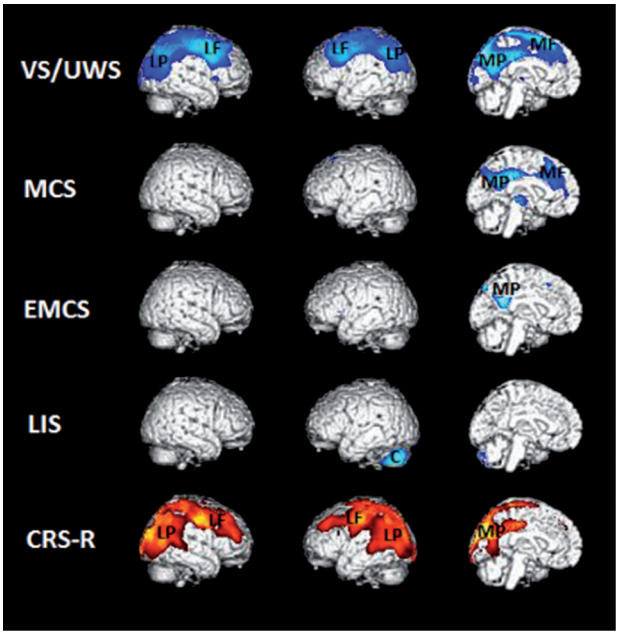

Fig. 1. Areas with significant metabolic impairment (*blue*) in vegetative state/unresponsive wakefulness syndrome (VS/UWS, $n=24$), minimally conscious state (MCS, $n=28$), emergence from MCS (EMCS, $n=10$) and locked-in syndrome (LIS, $n=8$) compared with age-matched controls ($n=39$) (thresholded at $p<0.01$ family-wise correction for multiple comparisons). The lower panel shows the areas where metabolic activity correlated with Coma Recovery Scale-Revised (CRS-R) scores (thresholded at uncorrected $p<0.001$; *red*). Note that in VS/UWS there is a metabolic dysfunction in the thalamus (T) external network encompassing left and right lateral parietal (LP) and lateral prefrontal (LF) cortices and in the internal network encompassing midline precuneus/posterior cingulate (MP) and mesiofrontal/anterior cingulate (MF) cortices. In MCS the thalamus (T) and intrinsic network is impaired (MP, MF). EMCS shows partly impaired intrinsic network activity (MP) and LIS fully preserved awareness networks, with only impairment in the cerebellum (C). The behavioural assessment scores correlate with activity in the extrinsic network (LP, LF) and part of the intrinsic network (MP).

Table II. *Coordinates of peak voxels of hypometabolic areas in vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS), emergence from MCS (EMCS) and locked-in syndrome (LIS)*

Areas	x (mm)	y (mm)	z (mm)	Z	*p*
VS/UWS					
Right thalamus	8	–18	4	5.21	<0.0001
Left thalamus	–2	16	2	4.94	<0.0001
Right lateral parietal	50	18	0	4.5	<0.0001
Left lateral parietal	–38	–72	42	7.29	<0.0001
Right lateral prefrontal	52	–4	52	Inf	<0.0001
Left lateral prefrontal	–34	4	54	7.56	<0.0001
Precuneus/posterior cingulate	2	–36	34	Inf	<0.0001
Mesiofrontal/anterior cingulate	2	–36	34	Inf	<0.0001
MCS					
Right thalamus	4	–18	2	7.37	<0.0001
Left thalamus	–4	–20	2	4.2	<0.0001
Precuneus/posterior cingulate	0	–36	32	Inf	<0.0001
Mesiofrontal/anterior cingulate	6	18	30	6.22	<0.0001
EMCS					
Posterior cingulate/ restrosplenial	–2	–48	22	5.49	<0.0001
LIS					
Cerebellum	–38	–68	–38	3.88	<0.0001

Inf: inferior than 0.0001.

Table III. *Coordinates of peak voxels from areas showing a linear positive correlation with Coma Recovery Scale-Revised total scores*

Regions	x (mm)	y (mm)	z (mm)	Z	*p*
Right lateral parietal	50	18	0	4.5	<0.0001
Left lateral parietal	–58	–50	38	4.85	<0.0001
Right lateral prefrontal	52	–4	52	Inf	<0.0001
Left lateral prefrontal	–34	4	54	7.56	<0.0001
Precuneus/posterior cingulate	2	–36	34	Inf	<0.0001

Inf: inferior than 0.0001.

DISCUSSION

Our results in VS/UWS of different aetiologies show a widespread fronto-parietal cortical dysfunction, in agreement with previous studies (9, 28–30). We observed a hypometabolism in the external network encompassing left and right lateral parietal and lateral prefrontal cortices and in the internal network encompassing midline precuneus/posterior cingulate and mesiofrontal/anterior cingulate cortices. In MCS patients it seems that the extrinsic/lateral network is less impaired than is the intrinsic/medial network. This result is consistent with the clinical finding that these patients show evidence of external/sensory awareness, known to depend upon the functional integrity of the extrinsic/lateral fronto-parietal system (3, 31–35). The predominance of intrinsic/midline network impairment in MCS could reflect an impaired internal/self-awareness in these patients, which is very difficult to quantify at the bedside. Indeed, CRS-R assessments only have one item possibly assessing some form of internal/self-awareness: visual pursuit in response to a moving mirror (36).

In our view, the current data could shed some light on impaired internal/self-awareness in MCS via the study of patients' residual brain function. An increasing body of evidence points to the critical role of the intrinsic network in the emergence of internal/self-awareness including stimulus-independent cognitive processes, such as daydreaming, mental imagery, inner speech and self-oriented thoughts (37–40). In fMRI studies, the latter network, recorded during the so-called "resting state" condition has also been coined "default mode network" (41–43). In both VS/UWS and MCS patients a significant thalamic metabolic impairment was identified, in line with previous PET (29, 30, 44) and diffusion tensor imaging (45) MRI studies, and post-mortem neuropathology (46). This finding can also be related to the clinical observation that both patient groups have fluctuating arousal levels. Indeed, in our cohort 10 out of 24 (42%) VS/UWS and 7 out of 28 (25%) MCS showed CRS-R

arousal subscores of 1, meaning that patients needed tactile or noxious stimulation at least once during the examination in order to obtain sustained eye opening (47).

EMCS patients showed a near-normal brain metabolism with preserved extrinsic network activity and only dysfunction of posterior cingulate cortex and adjacent retrosplenial cortex. This area, part of the intrinsic network, is known to be involved in autobiographical memory and self-reflexion (48, 49). Clinically, EMCS patients indeed classically experience confusion and amnesia syndromes (50, 51). Finally, our studied LIS patients failed to show metabolic dysfunction in any supratentorial brain area. Both the extrinsic and intrinsic network activity was preserved in LIS and only the cerebellum was shown to be impaired, in line with previous studies (52, 53). Previous neuropsychological studies have indeed shown that classical LIS patients have no deficit in cognitive functioning (54). Despite the fact that 6/8 LIS patients experienced basilar artery stroke and showed structural lesions on MRI in the ventral pontine region (encompassing the corticospinal and adjacent corticobulbar pathways) the resulting metabolic impairment was localized not in the brainstem, but in the cerebellum. This can be explained by the fact that PET-FDG functional imaging, in contrast to MRI structural imaging, does not show white matter structural damage (i.e. in brainstem), but rather the cortical metabolic consequences (i.e. in cerebellar hemispheres), reflecting de-afferentation.

The observed progressive recovery of intrinsic network metabolic activity, as measured by FDG-PET in severely brain-damaged patients, ranging from VS/UWS, MCS, EMCS to LIS, corroborates previous fMRI "resting state" studies showing a progressive recovery of functional connectivity in the "default mode network" in these patients (55). The latter study also identified a linear correlation between CRS-R total scores and functional connectivity in the default mode network. We expand these findings here, showing an additional correlation with the extrinsic/lateral network metabolic activity and CRS-R total scores.

In conclusion, the objective measurement of extrinsic/lateral and intrinsic/midline metabolic activity in severely brain-injured patients following coma, permits us to better understand the residual external/sensory and internal/self-awareness in disorders of consciousness. Our data show, for the first time, that patients with MCS, in contrast to those with VS/UWS, show cortical dysfunction of the intrinsic/internal awareness system more than of the extrinsic/external awareness networks. If confirmed, these findings indicate an impairment of a clinically barely measurable dysfunction of internal or self-awareness in MCS.

ACKNOWLEDGEMENTS

This study was supported by the Fonds de la Recherche Scientifique (FRS), Fonds pour la Recherche Industrielle et Agronomique (FRIA), French Speaking Community Concerted Research Action, University and University Hospital of Liège, James S. McDonnell Foundation, Mind Science Foundation and European Commission (Mindbridge, DISCOS, DECODER & COST).

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J Rehabil Med 2012; 44: 495–501

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J Rehabil Med 2012; 44: 481–516

REVIEW ARTICLE

HEART RATE VARIABILITY AND THE CENTRAL AUTONOMIC NETWORK IN SEVERE DISORDER OF CONSCIOUSNESS

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Objective: **To review the applicability of heart rate variability measures in research on severe disorder of consciousness.**
Methods: **The available evidence on the correlation between heart rate variability measures and the outcome or residual functional state/responsiveness of severely brain-injured patients (including those in vegetative or minimally conscious states) are reviewed and discussed with reference to the central autonomic network model.**
Results and conclusion: **Heart rate variability analyses appear to be applicable to assess residual or emerging (higher level) function in brain-injured patients with disordered consciousness and to predict outcome. In this regard, the central autonomic network model is heuristic in the understanding of heart rate variability descriptors of the central nervous system/autonomic systems relationship.**

Key words: disorder of consciousness; brain injury; heart rate variability; HRV; vegetative state; minimally conscious state; central autonomic network.

J Rehabil Med 2012; 44: 495–501

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Submitted September 29, 2011; accepted February 16, 2012

INTRODUCTION

Subjects in a vegetative state (VS; today also referred to as unresponsive wakefulness syndrome) after severe brain injury are, by definition, disconnected from the environment, with no indication of awareness, voluntary or otherwise, purposeful movement, or communication (1–5). Autonomic functions are thought to prevail on central nervous system activities. In contrast, research by advanced positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) techniques has documented stimulus- or condition-related regional brain activation that reflects retained connectivity in segregated networks. These observations are deemed indicative of surviving sensory, emotional and "cognitive" modular processing at varying levels of functional complexity in the absence of the integrative processes necessary to consciousness (5–14). The clinical scenario and perspective have expanded significantly, with far-reaching implications and requirements as to healthcare and neurorehabilitation of subjects in the VS. Emerging evidence suggests that the autonomic system can also mediate in patterns of brain activation at varying levels of complexity, and measures of heart rate variability (HRV) are applicable in the description of the brain functional organization in homeostasis and homeostatic response (15–18).

METHODS

The US National Library of Medicine Database and Google Scholar databases were used to trace published reports on HRV, VS, minimally conscious state (MCS), and autonomic system/function over the period 1993–2011, using appropriate keywords and their combinations. Cohort studies, case control studies, case reports and case series of adult or paediatric brain-injured patients were included in this review. Animal studies were not included.

HEART RATE VARIABILITY: MEASURES AND MEASUREMENTS

Measures of the HRV reportedly indicate or anticipate cardiac disorders (19–21) and reflect the action of physiological factors modulating the heart rhythm and its adaptation to changing conditions. The dynamic interplay between the autonomic subsystems enables efficient cardiovascular responses to endogenous/exogenous influences (22–24) and the efficiency of these responses can be quantified by appropriate data processing.

HRV recording techniques are non-invasive and HRV signals (the heart tachogram, i.e. the variation over time of the interval between consecutive heartbeats) have excellent signal-to-noise ratio compared with most brain signals in use in neuroscience or clinical neurophysiology, but are not periodic. Stimulus- or condition-related changes occur within the heart rate physiological range of variability in the absence of cardiac disorders and are seldom detectable without appropriate data treatment. To this purpose, the tachogram needs processing in the time or frequency domains or by geometrical or non-linear methods, as suggested by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (25, 26). HRV fluctuations are conventionally measured in the time domain by calculating indices based on statistical operations on RR intervals; fast Fourier transform (FFT) or autoregressive models (26) are of common use in analyses of frequency. The

 doi: 10.2340/16501977-0975
 ISSN 1650-1977

HRV spectral profile is characterized by 3 main components: the high-frequency interval (0.15–0.5 Hz; HF), mainly associated with activation of the parasympathetic nervous system; the low-frequency interval (0.04–0.15 Hz; LF), reflecting contributions from both the parasympathetic and sympathetic systems; and the very-low-frequency bandwidth (< 0.04 Hz; VLF), thought to reflect temperature, vasomotor, hormonal, and metabolic regulation. The LF/HF ratio is typically used as a measure of the sympathovagal balance.

HRV descriptors are also derived by non-linear methods, such as entropy analysis, in order to describe the complexity, irregularity or randomness of HRV and its changes (27–30). Developments in the non-linear analysis theories provide new instruments of the data analysis in the entropy domain, such as the approximate entropy (ApEn) and the simple entropy (SapEn), which are thought to provide global information on autonomic system functioning and complexity (Table I).

HRV measures are now being regarded with increasing interest as reliable descriptors of autonomic reaction to events with emotional resonance, and there is evidence that HRV can reflect the CNS/autonomic functional interaction under conditions involving motor, cognitive, emotional, behavioural or stressful tasks or adaptation to environmental change (16, 27, 31, 32). Clinical application is mainly in the investigation of subjects with psychiatric disorders, traumatic brain injury (TBI), impaired emotion-specific processing, and personality or communication disorders (33–41). The (partial) independence of HRV parameters from conscious experience also makes application possible when the requirements for active collaboration need to be limited (e.g. during monitoring) or continuous collaboration is questionable even in simple experimental paradigms (e.g. in subjects with severe brain damage). In this respect, the approach appears to be suitable for privileged application in the study of subjects with severe disorder of consciousness, such as those in a VS or MCS.

HEART RATE VARIABILITY AND BRAIN INJURY

Two patterns of autonomic hyperactivity have been described, namely a paroxysmal sympathetic hyperactivity in the absence of parasympathetic major contribution, and the combined sympathetic/parasympathetic hyperactivity ("mixed autonomic hyperactivity disorders") (42). Non-neurological organ dysfunction (with paroxysmal sympathetic hyperactivity resulting in respiratory/cardiovascular dysfunction) seems to be associated with brain injury (43, 44) and the risk of death increases in patients with severe cardiac uncoupling and depressed HRV (45, 46). Sympathetic hyperactivity and over-responsiveness to afferent stimuli have been observed in a HRV study on TBI patients with dysautonomia (42, 47–50). A parallel increase in the vagal activity and intracranial pressure (possibly due to compression of the vagal nuclei or brainstem) has been documented in patients changes in the LF power (51–53). A significant decrease in the LF/HF ratio was observed in TBI children at intracranial pressure above 30 mmHg (54). Lowensohn et al. (55) observed a HRV decrease with rising intracranial pressures in subjects with severe brain injury. Subacute studies have shown comparable changes in the LF/HF ratio compared with controls or a decrease in the HF power (56, 57) (Table II).

HEART RATE VARIABILITY AND PREDICTION OF OUTCOME

HRV has been proposed as a useful predictor of outcome in brain-injured patients (27, 58, 59). Reduced LF/HF ratios have been associated with low scores on the Glasgow Coma Scale and increased risk of brain death (54). A correlation between LF, severity of neurological dysfunction and outcome has been reported in TBI children (60, 61) and adults (62). The global HRV and parasympathetic tone were higher in TBI patients who later died than in those who survived; during the awak-

Table I. *Heart rate variability (HRV) measures*

HRV analyses	Description	Output variables
Time domain	Statistical processing of consecutive intervals	HR, SDHR, NN, SDNN, RMSDD SDNN, pNN50
	Frequency distribution	TINN (baseline width of the RR interval histogram), HRV triangular index (integral of the RR interval histogram divided by the height of the histogram)
Frequency domain	Frequency spectrum	FFT and AutoRegressive Analysis
		Power: Total, ULF (<0.003 Hz), VLF (0.003–0.04 Hz), LF (0.04–0.15 Hz), HF (0.15–0.4 Hz), Normalized Unit (LF, HF)
		Time spectrum analysis
Non-linear analyses	Detrended fluctuation analysis (measures the correlation within the signal)	Typically the correlations are divided into short-term (α_1) and long-term (α_2) fluctuations
	Poincare plot (graphical representation of the correlation between successive RR intervals)	SD1 (short-term variability)
		SD2 (long-term variability)
	Entropy	Measures of the complexity or irregularity of the signal (ApEn, SampEn)

ApEn: approximate entropy; SampEn: sample entropy; pNN50: proportion greater than 50 ms; RMSDD: root mean square of standard deviation; SD: standard deviation; SDNN: standard deviation of 5 min means; HF: high frequency; ULF: ultralow frequency; VLF: very low frequency; LF: low frequency; FFT: fast Fourier transform; HR: heart rate.

Table II. *Heart rate variability (HRV) and brain injury*

Author	Subjects	Results
Perkes et al., 2010 (42)	349	The core clinical features of PSH-heart rate were correlated with, blood pressure, respiratory rate, temperature, sweating, and motor hyperactivity.
Riordan et al., 2007 (46)	4,116	Reduced HRV was associated with an increase in mortality; beta B exposure appears associated with increased survival across all stratifications of cardiac uncoupling.
Riordan et al., 2009 (45)	2,178	Reduced HR multiscale entropy was significantly associated with increasing mortality and is a reliable predictor of mortality in TBI patients.
Baguley et al., 2009 (50)	27	HRV measures differentiate between (TBI) subjects with normal and elevated autonomic activity. HRV and event-related heart rate changes help in the diagnosis of dysautonomia. The comparison of HRV and heart rate parameters suggested an over-responsivity to nociceptive stimuli in dysautonomic subjects.
Kawahara et al., 2003 (51)	42	HRV analysis showed enhanced parasympathetic activity, probably associated with increased intracranial pressure in patients with acute subarachnoid haemorrhage.
Mowery et al., 2008 (51)	291	Cardiac uncoupling increases with ICP, cardiac uncoupling and ICH predict mortality.
Morris et al., 2006 (53)	1,425	Reduced heart rate variability is a new biomarker reflecting the loss of command and control of the heart (cardiac uncoupling).
Keren et al., 2005 (56)	20	Change towards HRV normalization predicts recovery of the autonomic nervous system in patients with TBI.

HR: heart rate; PSH: paroxysmal sympathetic hyperactivity; TBI: traumatic brain injury; ICP: intracranial pressure; ICH intracranial hypertension.

ing period, the global HRV and parasympathetic tone were lower in those patients whose neurological condition later worsened compared with patients with a good recovery (58, 62–64). Attenuated parasympathetic tonus and low HF were found to correlate with the severity of brainstem damage, while very low LF and HF power was associated with progression towards brain death in TBI patients (65). Amelioration of the HRV total power in the first 3 months after TBI was correlated with recovery of autonomic function in a prospective study (56). Changes in autonomic reactivity, namely decrease in parasympathetic activity (normalized unit of high-frequency (nuHF)) and increase in sympathetic activity (normalized unit of low-frequency (nuLF)), were found to parallel the recovery of consciousness in TBI patients (66) (Table III).

HEART RATE VARIABILITY AND RESPONSIVENESS

HRV measures are used to assess the contributions of the autonomic nervous system in sustaining consciousness and its functional re-organization during recovery in subjects with severe disorder of consciousness. The nuLF descriptor of sympathetic activity was found to increase in VS subjects interacting with relatives (the "mom effect") (Fig. 1) in the absence of any activation in control conditions (67). Higher HRV and HF values were recorded in a comparable study (68, 69), with minor differences conceivably depending on different stimulus paradigms and HRV data processing (70). Consistent patterns of variation in HRV (e.g. in the nuLF values) were observed in healthy controls and TBI patients

Table III. *Heart rate variability (HRV) and prediction of outcome*

Author	Subjects	Results
King et al., 2009 (58)	75	HRV triages and discriminates the severely brain injured patients during helicopter transport better than routine trauma criteria or en-route pre-hospital vital signs.
Cooke et al., 2006 (59)	84	Heart period variability analyses discriminate patients with poor prognosis (death) from those surviving TBI.
Biswas et al., 2000 (54)	15	HRV power spectral analysis (e.g. LF/HF ratio) as a useful ancillary test in determining the severity of brain insult and prognosis in children with traumatic brain injury.
Goldstein et al., 1993 (60)	11	Damaged sympathetic cardiovascular system in children with severe brain injury and complete interruption of the autonomic cardiovascular pathways in brain death.
Goldstein et al., 1996 (61)	36	Sequential changes in heart rate, respiratory rate, blood pressure, heart rate power spectra, and plasma catecholamine concentrations in patients with acute brain injury identify disruption of the autonomic nervous system control on heart rate proportionally to the degree of neurological insult in children with brain injury.
Rapenne et al., 2001 (62)	20	HRV provides useful information in the early prognosis of patients with severe brain trauma.
Norris et al., 2005 (64)	1,316	HRV independently predicts death in TBI patients and detects early differences in the mortality rate of groups of patients.

LF: low frequency; HF: high frequency; TBI: traumatic brain injury.

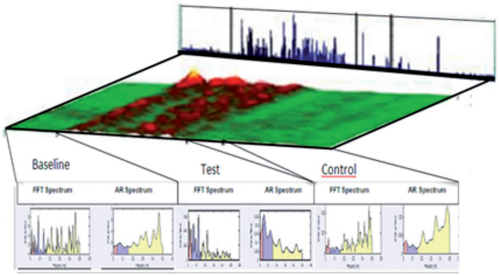

Fig. 1. The "mom's effect" in a subject in the vegetative state (VS): heart rate variability measures (fast Fourier transform (FFT) and auto regressive (AR)) in resting condition (baseline), while the subject's mother was trying a personal interaction (test condition) and with an unfamilial person repeating the mother's approach (control) (71).

listening to classical music of different authorship aimed at evoking distinct emotional responses. The responses were classified as "positive" or "negative" based on the controls' subjective reports; the nuLF patterns during listening differed from baseline and among musical samples, with a relationship with the music structure (71). Changes in the HRV patterns comparable to those observed in brain-injured subjects and in controls were detected in the same experimental conditions in subjects unambiguously diagnosed as being in a VS (72–74) and a relationship was observed between the HRV nuLF and LF peak and the occurrence of a visual pursuit response, a neurological marker of the subject's evolution from the VS to the MCS (75–77) (Table IV).

HEART RATE VARIABILITY AND THE CENTRAL AUTONOMIC NETWORK

The central control of autonomic function and the complex interplay between the CNS and the autonomic system and between the sympathetic and parasympathetic subsystems

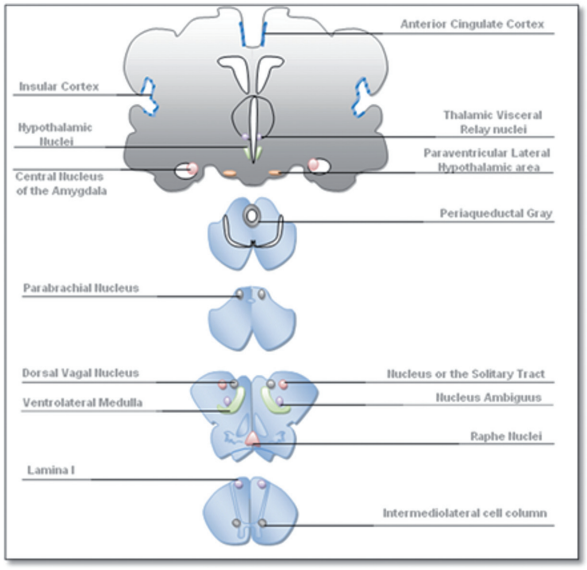

Fig. 2. Schematic outline of the central autonomic network (adapted from Benarroch (92)).

is modulated by direct/indirect descending, ascending and bidirectional connections among neural structures (24, 78, 79). A functional integrated model (usually referred to as the central autonomic network, or CAN) has been proposed and would include cortical components (medial prefrontal, anterior cingulate, and insular cortex), the paraventricular, amygdala central and lateral hypothalamic nuclei, and structures in the midbrain (the periacqueductal gray region) and pons (nucleus of the *tractus solitarius*, *nucleus ambiguus* and ventrolateral medulla), with primary outputs from stellate ganglia and vagus nerve to the sinoatrial node of the heart (24, 31) (Fig. 2). Telencephalic structures are connected with the hypothalamus and brainstem and contribute in the control of the autonomic or-

Table IV. *Heart rate variability (HRV) and responsiveness*

Author	Subjects	Results
Wijnen et al., 2006 (66)	16 TBI subjects	Autonomic reactivity provides useful information on the severely damaged brain responsiveness to environmental changes.
Dolce et al., 2008 (67)	12 VS subjects	HRV changes in response to a relative's presence or voice (the "mom effect") suggest residual rudimentary personal interaction in VS subjects.
Gutiérrez et al., 2010 (68)	Case report	Auditory stimulation induced recordable changes in HRV in VS subjects, suggesting residual preserved cognitive function detectable by cardiovascular descriptors.
Machado et al., 2011 (69)	Case report	Changes of HRV related to the emotional response to the mom's voice (the "mom effect").
Riganello et al., 2011 (70)	12 VS subjects	Modifications in the HRV (nuLF) in response to emotional stimuli (voice of relatives), but not to controls.
Riganello et al., 2008 (71)	16 TBI subjects 26 healthy controls	HRV described autonomic concomitants of emotional responses to complex sensory stimuli with emotional relevance (symphonic music).
Riganello et al., 2010 (72)	9 VS subjects 16 healthy controls	Comparable autonomic changes with emotional relevance were induced by complex stimuli (music) in VS subjects and controls.
Candelieri et al., 2011 (77)	7 VS subjects 8 MCS subjects	Two parameters obtained by HRV analysis (nuLF and peak of LF) proved highly correlated to eye-tracking.

TBI: tramatic brain injury; VS: vegetative state; nuLF: normalized unit of low-frequency.

ganization (24, 80). The insula (visceromotor area) is involved in the control of sympathetic and parasympathetic outputs (via a relay in the lateral hypothalamic area and through the amygdala) and in the autonomic and endocrine responses and motor activation needed to express the emotional response (78). The anterior cingulated cortex and its projections to the prefrontal cortex, amygdala, hypothalamus and brainstem are involved in the modulation of autonomic output in response to pain and emotional or behaviourally significant stimuli (81). The hypothalamus is thought to integrate autonomic and endocrine responses and to sustain vital homeostatic mechanisms, such as thermoregulation, osmoregulation, response to stress, etc. (82).

The CAN is essentially a dynamic system, with its activity depending on initial state (83). A functional relationship between HRV measures, the CAN operational status and the activity in the neural structures involved in affective and autonomic regulation has been first suggested by Thayler (84–86). Parasympathetic activation decreases the firing rate of pacemaker cells and HR, while sympathetic activity results in an increase of HR and firing rate of the pacemaker cells in the heart sinoatrial node (87). Autonomic, attentional, and affective systems can be integrated in a functional model with the cardiac vagal tone (23, 88, 89). The autonomic nervous system, in general, and the CAN, in particular, are thought to be indexed by HRV measures.

CONCLUSION

HRV is an output measure with potentially wide application, but its use in neuroscience and medicine is occasionally questioned (90–92). A number of autonomic functional tests, including plasma and urinary catecholamines, provide indirect information on the sympathetic or parasympathetic function (93), and direct measures of sympathetic activity have been obtained from the cardiac norepinephrine spillover and by microneurographic techniques or direct recording from skeletal muscle (94–95). However, these approaches are invasive and inapplicable on large subjects' samples, and only indirect methods are available today to obtain information on the parasympathetic system (96, 97). In this respect, HRV methodologies benefit from being non-invasive, with high benefit/cost ratio. HRV measures are obtained at limited costs, labour and accuracy of recording and information on the autonomic system functional condition or response, albeit indirect, is obtainable also when voluntary reports would be distracting, in the absence of the subject's collaboration (as in cases of the severe disorder of consciousness), whenever sophisticated experimental designs and data recording procedures are impracticable (e.g. in the intensive care unit), or when observation needs to be non-invasive and must cause no discomfort (e.g. in psychiatry or in sports medicine), or long-term observation is necessary.

HRV remains a suitable, although indirect, tool to assess residual or emerging sensory/cognitive function and to predict outcome of subjects with severe brain injury, including subjects in a VS or MCS. The CAN model provides an independent approach in the understanding of the HRV measures as descriptors of the integrated function of, and interaction between, the CNS and autonomic (parasympathetic and sympathetic) system. There is evidence of applicability in the study of severe disorder of consciousness.

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J Rehabil Med 2012; 44: 502–504

Included in the special issue:
CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY
J Rehabil Med 2012; 44: 481–516

ORIGINAL REPORT

DECREASING INCIDENCE OF PAROXYSMAL SYMPATHETIC HYPERACTIVITY SYNDROME IN THE VEGETATIVE STATE

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Objective: **To update knowledge of the incidence of paroxysmal sympathetic hyperactivity (PSH, also referred to as dysautonomia), an emergency condition tentatively attributed to sympathetic paroxysms or diencephalic-hypothalamic disarrangement associated with severe diffuse brain axonal damage or hypoxia. This condition is reportedly common in the vegetative state, threatens survival and affects outcome.**
Methods: **The results of a retrospective study on 333 subjects in a vegetative state admitted to a dedicated unit in 1998–2005 are compared with a survey on patients admitted to the same unit in 2006–2010.**
Results and comment: **In the 1998–2005 period, the incidence of PSH was 32% and 16% in post-traumatic and non-traumatic patients, respectively. It decreased to 18% and 7% in the 2006–2010 period. The PSH duration and the time spent in emergency units before admission and in the dedicated unit for the vegetative state after admission also decreased significantly. Incidence was greater among post-traumatic patients; its effect on outcome does not appear to have changed.**

Key words: paroxysmal sympathetic hyperactivity; dysautonomia; incidence; vegetative state; outcome.

J Rehabil Med 2012; 44: 502–504

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Submitted September 27, 2011; accepted March 23, 2012

INTRODUCTION

The critical association of signs such as tachycardia (> 120 beats/min), tachypnea (> 30/min), systolic hypertension (> 160 mmHg), hyper/hypothermia, excessive sweating, decerebration/decortication, increased muscle tone, horripilation and/or flushing is collectively referred to as "dysautonomia" or "paroxysmal sympathetic hyperactivity" syndrome (PSH) (1, 2). PSH is reportedly a common event in the vegetative state (VS, also referred to as "unresponsive wakefulness syndrome" or UWS) (3) and threatens these subjects' survival and recovery. It is tentatively attributed to sympathetic paroxysms or diencephalic-hypothalamic disarrangement associated with severe diffuse brain axonal damage or hypoxia, and, by all criteria, is classed as an emergency condition (1–9).

A total of 333 subjects with severe disorder of consciousness following massive traumatic ($n = 213$; 64%) or non-traumatic (vascular, anoxic-hypoxic, infective or others) acute brain damage were retrospectively surveyed in a previous study (8). All patients had been referred to the S. Anna Institute – RAN in the years 1998–2005 for being in a VS/UWS condition (8). PSH occurred in 26.1% of them, with greater incidence after traumatic than non-traumatic brain injury (31.9% vs 15.8%). Outcome was worse following non-traumatic brain damage irrespective of PSH and worst among non-traumatic subjects with PSH. Occurrence of PSH and outcome were accounted for by the variance explained by variables (such as aetiology, age and sex) that are already known to be predictors of outcome for patients with severe disorder of consciousness, such as the VS/UWS (10–14). However, the mathematical model correlating the occurrence of PSH with the subjects' clinical characteristics accounted for only 40% of the overall data variance (8). In this respect, the study was inconclusive and the natural history of the PSH remains poorly understood. Incidence is also unclear due to the lack of studies on large samples and over time (1, 4, 5). The purpose of this paper was to compare the incidence of PSH in 1998–2005 with a new group of subjects in VS/UWS admitted to and cared for in the same institute in the period 2006–2010.

PATIENTS AND METHODS

A new database of 169 patients admitted to the dedicated semi-intensive care unit of the S. Anna – RAN institute over a 4-year period (January 2006 to May 2010) was compared with the subjects' group of the first survey (8). Eighty-eight subjects (52%) were in a VS/UWS due to traumatic brain injury; non-traumatic aetiologies (major vascular insults, anoxia-hypoxia, etc.) were documented for 81 subjects (48%). Subjects were diagnosed at admission as being in a VS/UWS according to the current clinical criteria (11, 16–19) and established evaluation scales. The scores of subjects in VS/USW were lower than 25 on the Loewenstein Scale (20), lower than 2 on the Level of Cognitive Function scale (21), and higher than 21 on the Disability Rating Scale (22). The revised Coma Recovery Scale (CRS-r) (23) global score was assessed retrospectively and found to be lower than 8 in all subjects. In all cases, subjects with infection, metabolic disorder, lung diseases affecting the cardio-respiratory function, or drug side-effects were excluded from the study. Outcome was defined in full accordance with the Glasgow Outcome Scale (GOS) (23, 24). The ranking classes were: 1 = death; 2 = VS/UWS exceeding 1 year in duration; 3 = recovery, with severe disabilities; 4 = recovery, with mild disabilities; and 5 = full recovery or recovery with minimal disabilities not interfering with everyday life (24–27).

 doi: 10.2340/16501977-0981
 ISSN 1650-1977

With the exception of the revised Coma Recovery Scale (which was not in use in this country before 2007), the criteria by which patients have been diagnosed as being in a VS/UWS and by which PSH was identified were the same in the two studies, as were the monitoring, healthcare, pharmacological treatment (27) and rehabilitative procedures and protocols in the S. Anna – RAN unit; in addition, the attending physicians were the same. The data from the 1998–2005 and the 2006–2010 periods were compared using the exact Fisher's test.

The study is retrospective and was approved by the local public healthcare ethics committee. Regulations about subjects' privacy and the ethical principles of the Declaration of Helsinki (1964) of the World Medical Association concerning human experimentation were followed.

RESULTS

The incidence of PSH was found to have decreased from the 1998–2005 period to the 2006–2010 period, with a reduction from 32% to 18% and from 16% to 7% among subjects with post-traumatic and non-traumatic brain damage, respectively.

Both the time spent in the emergency or intensive care units before admission to the S. Anna – RAN dedicated unit for the VS/UWS and the permanence in this unit have decreased irrespective of aetiology; the PSH duration decreased among non-traumatic subjects (Table I). Outcome did not change significantly (χ^2, Pearson's = 0.332, $p = 0.56423$), although the percentage of subjects with outcome in the GOS rank 1 (death) appears to have increased (Fisher's exact test: $p = 0.8053633$) (Fig. 1).

DISCUSSION

Epileptogenic mechanisms cannot be excluded *a priori* in all cases (29), but the pathophysiological processes starting and sustaining PSH remain a matter of speculation. Two main underlying mechanism have been suggested, notably a functional disconnection or unbalanced activation of structures usually under the control of higher brain centres (30), and an excitatory/inhibitory ratio model of paroxysms resulting from the abnormal processing of and over-responsiveness to the afferent stimuli from the medulla (31). A residual neuroendocrine reactivity is suggested by the lower incidence among anoxic-hypoxic patients with diffuse brain damage (9); its remission following treatment with serotonin or GABA modulators (32, 33) suggests hypothalamic dysregulation (34, 35). A multifactorial origin appears conceivable and would be consistent with the variability of the PSH clinical picture as to number, relevance, variability or development over time, and spontaneous or drug-mediated remission of clinical signs.

Undetected (interactions among) factors possibly modifying the clinical picture or affecting its incidence may have accounted for the differences observed in the two subject groups and are not necessarily compensated for by the group sizes. This caveat notwithstanding, the comparison between two large patient groups monitored in the same unit for a short time interval suggests that the incidence of PSH may be decreasing, and that the condition has somehow become less severe and/or is better managed, at least in subjects with VS/UWS of non-traumatic aetiology. A more effective (although not necessarily intentional) prevention and better focused treatment in intensive care units appears possible; improved procedures to reduce brain oedema and control intracranial hypertension and early sedation in intensive care units are possible factors that may help reduce the incidence of dysautonomia (36).

Outcome does not seem to have improved in recent years, however. The differences between the two subject groups in a VS/UWS of non-traumatic aetiology suggests a higher percentage of subjects who died during the observation after PSH (i.e. with outcome to be rated as GOS 1), but in all cases death

Table I. *Incidence of paroxysmal sympathetic hyperactivity (PSH) syndrome in vegetative state (VS)/unresponsive wakefulness syndrome (UWS) following traumatic and non-traumatic brain injury. Comparison between the subjects admitted in the 2006–2010 period with those of the previous survey (1998–2005)*

	Traumatic brain injury		Non-traumatic brain injury	
	1998–2005	2006–2010	1998–2005	2006–2010
Subjects with PSH, %	32	18	16	7
Age, years, mean (SD)	25.0 (9)	25.5 (9)	31.0 (15)	50 (15)
Time in emergency/ intensive care units before admission to the dedicated unit for VS, days, mean (SD)	77.0 (71)	44.3 (26)*	74.0 (65)	58.6 (15)***
Time in the dedicated unit for VS, days, mean (SD)	186 (69)	164 (104.5)**	224.0 (88)	201 (125)**
Duration of PSH, days, mean (SD)	162 (90)	70 (34)	190.0 (50)	116 (146)***

Fisher's exact test vs 1998–2005. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. SD: standard deviation.

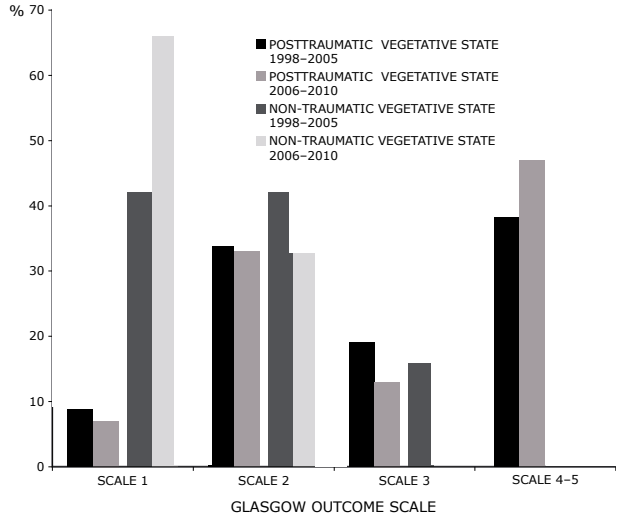

Fig. 1. Outcome of subjects in a vegetative state with paroxysmal sympathetic hyperactivity syndrome. Comparison between the 1998–2005 and 2006–2010 subject groups.

resulted from clinical events unrelated to the pathophysiology of the VS/UWS or PSH. The relevance of PSH as a negative prognostic indicator remains confirmed; patients should be monitored for its occurrence and *ad hoc* therapeutic procedures should be devised.

ACKNOWLEDGEMENTS

The study has been carried on at the S. Anna – RAN Institute with support from the institute; authors are all employees of the institute.

The authors report no conflicts of interest.

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J Rehabil Med 2012; 44: 505–511

Included in the special issue:
CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY
J Rehabil Med 2012; 44: 481–516

ORIGINAL REPORT

RECOVERY OF COGNITIVE FUNCTION DURING COMPREHENSIVE REHABILITATION AFTER SEVERE TRAUMATIC BRAIN INJURY

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Objective: **To explore the course and timing of functional recovery in patients who have emerged from coma after undergoing severe traumatic brain injury.**
Methods: **An observational study involving 19 patients with traumatic brain injury recovered from coma who underwent holistic, intensive and multidisciplinary neurorehabilitation. Daily performance in each cognitive function (long-term memory, short-term memory, orientation, calculation, attention, mental control, automation, and planning) was clinically scored and compared at admission and discharge.**
Results: **The course of cognitive recovery after post-traumatic coma is not uniform, offering a curve with many ups, downs and plateaus. To achieve a good response and outcome nearing normalcy, a patient needs over 300 h of intensive rehabilitation.**
Conclusion: **The consolidation of functional recovery in patients with traumatic brain injury requires time and adequate training, and discharge is not recommended until cognitive improvement is established.**

Key words: cognitive functions; neuropsychological rehabilitation; neurorehabilitation; traumatic brain injury.

J Rehabil Med 2012; 44: 505–511

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Submitted September 27, 2011; accepted March 15, 2012

INTRODUCTION

Functional disorders affecting daily living activities are frequent in patients who emerge from coma after sustaining severe traumatic brain injury (TBI). These disorders usually result in impairment to memory, attention, reasoning, mental imagery, language, problem-solving abilities or executive functioning, as noted by León-Carrión (1), and require treatment to achieve functionality. Recent studies have proven the efficacy of functional rehabilitation for patients who have emerged from deep coma. As shown by Cicerone et al. (2), there is substantial evidence supporting interventions for attention, memory, social communication skills, and executive functioning, and for comprehensive neuropsychological rehabilitation after TBI, designed to help the person recover maximum functionality nearing pre-injury level. However, the timing and duration of these interventions has not been established. Prigatano (3) reports that "cognitive rehabilitation is labor intensive. Patients must spend hours at cognitive remediation tasks before any notable change can be achieved. No matter how well-randomized or designed, studies that employ less than 100 hours of cognitive rehabilitation will most likely be associated with minuscule results. This reality exists because we do not know how to deliver re-training activities systematically in a cost-efficient manner".

In the search for TBI treatment, insurance companies, healthcare professionals, families, and patients are concerned with the duration of neurorehabilitation and whether it will be worthwhile. Different systematic reviews, most notably Rohling et al.'s (4), have demonstrated that in-hospital cognitive rehabilitation for patients with moderate-to-severe TBI is more effective than at-home rehabilitation or no rehabilitation post-injury. Studies by Cicerone et al. (5) and Yu (6) have also shown that a certain degree of spontaneous recovery occurs during the first few weeks, and even months, after injury. A previous study by Leon-Carrion & Machuca-Murga (7) analysed the course of post-TBI cognitive deficits in patients who did not receive neuropsychological rehabilitation, and endeavoured to establish the point at which cognitive deficits ceased to present signs of spontaneous recovery. Our study involved 28 subjects with severe TBI who were neuropsychologically assessed at 8 months post-TBI and again, 19 months later. Results showed no significant differences between the two neuropsychological exams and no spontaneous recovery beyond the 8 month post-TBI. Neurocognitive deficits consequential to TBI appeared to be established within the first 8 months post-trauma.

The present study reports on the outcome of 19 adults with severe TBI in the post-acute phase after undergoing a holistic, intensive, and multidisciplinary programme in a highly specialized neurorehabilitation centre in Europe.

METHODS

Subjects

Nineteen patients with severe head trauma (3 female, 16 male; mean age 23.57 years) and a median Glasgow Coma Scale (GCS) score of 5 (interquartile range (IQR): 4 –7) at admission. Patients were recruited from the Center for Brain Injury Rehabilitation (C.RE.CER) in Seville, Spain. No control group was used in this descriptive study. Inclusion criteria included emergence from coma, a GCS score of ≤ 8 within 24 h post-TBI, and the presence of at least 3 impaired cognitive functions

 doi: 10.2340/16501977-0982
 ISSN 1650-1977

(deterioration of mental process involving symbolic operations, such as orientation, memory, attention, mental control, automation, and planning). All patients began the neurorehabilitation programme approximately 24 months post-injury. Patients' mean GCS score, mean time from brain injury to programme admission and demographic data are shown in Table I.

Treatment programme

Patients enrolled in a holistic, intensive and multidisciplinary rehabilitation programme at Center for Brain Injury Rehabilitation (7–11). Patients underwent daily 4-h rehabilitation, 4 days a week, for 6 months. Each rehabilitation session lasted 60 min, and was given by a specialized therapist (neuropsychologist, physical therapist, speech therapist, or occupational therapist) in accordance with the patient's needs. In general, patients received a combination of these rehabilitation sessions, which were specifically tailored to meet the physical, emotional, behavioural and cognitive needs of each patient, and could include pharmacological treatment, as reflected in previous studies by León-Carrión (1, 12, 13). Cognitive rehabilitation included exercises in orientation, memory, attention mechanisms (automation and mental control), calculation, planning and executive functioning (14) (Appendix I).

Outcome scoring system

Each cognitive function was clinically scored on a scale from 1 to 10 by the therapist who conducted the session. Baselines for cognitive functions were obtained at admission, using the CRECER Clinical Outcome Scale (CRECERCOS) and neuropsychological assessments prior to rehabilitation (Table II). Patients received a score of normalcy when performance achieved pre-morbid levels of functioning. This normalcy was clinically established through interviews with the patients' families and closest associates. A score of 1–2 was assigned to subjects with severe impairment (almost no response) in a specific function (10–20% normalcy); 3–4 indicated impaired, although inconsistent, response (30–40% normalcy); 5–6 showed consistent, but scarce, response (60% normalcy); 7 indicated a good response, but too scarce to be considered at normal level (70% normalcy); 8–9 reflected near normal response in quantity and quality, but not at pre-morbid levels (80–90% normalcy). A score of 10 was assigned when patient performance showed either his/her previous level of functioning (100%) or statistical normalcy.

Statistical and data analysis

The following analyses were carried out: comparison of initial scores with scores after discharge; mean number of sessions completed for each cognitive function; percentage of functional gain obtained after rehabilitation, and percentage of functionality at discharge compared with admission. The percentage of functional gain is calculated from the CRECERCOS baseline at admission and the final level of functionality obtained after neurorehabilitation, with a maximum score of 10. For example, a patient with a 6 on the CRECERCOS scale has a potential gain of 4 points to achieve the maximum score of 10. If the functional gain of this patient after treatment is 2 points, his/her percentage of functional gain is 50% (half of the potential 4 points). The equation used to determine the latter is as follows:

$$FG\% = \frac{MI - M0}{10 - M0} \times 100$$

Ml is the score obtained by the patient in the last month of rehabilitation. M0 represents the patient's score at admission. FG% is the percentage of functional gain for each specific function obtained in the final assessment. Statistical analyses were performed using SPSS 15.0 software for Windows, with alpha set at 0.05 for all tests. Fisher's exact test was applied to analyse categorical variables. Given the asymmetrical distribution of most of the variables, non-parametric analyses were performed. Means, standard deviations, medians and interquartiles are displayed in Tables I, III, IV and V. We applied the Mann-Whitney *U* tests to analyse independent samples and the Wilcoxon test for related samples. Correlation analysis was carried out using the Spearman's rank order correlation (rho). We used mean values and standard deviations (SD) to summarize our results due to their higher illustrative capacity for presenting and comparing our data.

Table I. *Patient demographic data: age, Glasgow Coma Score (GCS) score within 24-h post-traumatic brain injury (TBI) and time from injury to programme admission*

Patient data $n = 19$	Mean (SD)	Median (IQR)
Age	23.57 (7.04)	23 (19–28)
GCS Score	5.37 (1.89)	5 (4–7)
Time from injury to programme admission, months	23.94 (58.62)	11 (4–17)

GCS: Glasgow Coma Scale; SD: standard deviation; IQR: interquartile range.

RESULTS

CRECERCOS score analyses

Table III displays patients' mean scores on the CRECERCOS scale at admission and discharge from the neurorehabilitation programme. At admission, the group mean for the different cognitive functions was 4.59. The lowest mean scores were for *automation* and *short-term memory*, while *orientation* received the highest score. At discharge, the group mean for all areas increased to 7.52, with *calculation* scoring the lowest, and *orientation* the highest mean score.

Functional gain increased in all areas. The global mean score reached 56.24%, with patients achieving the highest gains in *orientation* and *automation* and the least gain in *calculation* and *mental control*. Comparative analysis between areas showed the most significant gain in *orientation*, particularly compared with *calculation* and *mental control* ($p < 0.01$). Significant differences were also found between short-term memory and calculation (Table III).

Statistical comparisons were carried out between number of rehabilitation sessions and cognitive function. Table IV illustrates the number of sessions (60 min per session) which patients underwent during the rehabilitation programme. The mean number of sessions was 43. *Planning* received the most rehabilitation sessions, whereas *mental control* received the

Table II. *Classification for Center for Brain Injury Rehabilitation Clinical Outcome Scale (CRECERCOS). The first column shows CRECERCOS scores; the second indicates percentage of cognitive functionality compared with pre-morbid levels of normalcy; the third shows level of impairment associated with each score*

CRECERCOS score	Impairment score, %	Specific function/s
1–2	10–20	Severe impairment (almost no response) in a specific function
3–4	30–40	Impaired, inconsistent response
5–6	50–60	Consistent response
7	70	Good response
8–9	80–90	Near normal response in quantity and quality, but not pre-morbid level
10	100	Previous functioning level

Table III. *Classification for Center for Brain Injury Rehabilitation Clinical Outcome Scale (CRECERCOS) scores at admission and discharge, and overall functional gain*

Cognitive functions	*n*	CRECERCOS at admission Mean (SD)	CRECERCOS at admission Median (IQR)	CRECERCOS at discharge Mean (SD)	CRECERCOS at discharge Median (IQR)	FG% Mean (SD)	FG% Median (IQR)	CRECERCOS Differences admission–discharge Wilcoxon (Z value)	FG% Differences between cognitive functions Mann-Whitney U test
Long-term memory	19	4.27 (1.68)	4 (3–6)	7.7 (1.44)	8 6.75–8.625)	57.26 (24.4)	56.47 (33.33–72.32)	–3.73**	c*
Short-term memory	19	3.86 (1.97)	4 (2–5.5)	7.4 (61.16)	7.5 (7–8)	56.69 (18.03)	55.55 (47.77–71.4)	–3.82**	c*, d*
Orientation	15	7.45 (3.15)	8.5 (6.1–10)	9.47 (1.46)	10 (9.875–10)	88.33 (20.61)	100 (77.5–100)	–2.66**	a*, b*, d**, e*, f**, h*
Calculation	14	4.3 (1.77)	4.5 (3.75–5.35)	6.87 (1.61)	7 (7–7.75)	43.32 (20.06)	40 (31.78-58.33)	–3.18**	b*, c**
Attention	8	4.58 (1.60)	5 (4.12–5.8)	7 (1.64)	7 (5.75–7.87)	46.3 (25.69)	44.44 (26.25–56.25)	–2.52*	c*
Mental control	16	4.53 (1.73)	4.5 (4–6)	7.03 (1.71)	7.5 (6.12–8)	44.6 (30.54)	50 (22.72–66.66)	–3.24**	c**
Automation	8	3.28 (2.27)	4.5 (1–5)	7.28 (2.15)	7 (6–10)	60.43 (33.79)	66.66 (25–100)	–2.37*	
Planning	18	4.34 (1.46)	4.3 (3–5.5)	7.41 (1.43)	7.5 (7–8)	53.05 (24.76)	53.84 (37.5–72.5)	–3.77**	c*

a: significant differences for *long-term memory*; b: significant differences for *short-term memory*; c: significant differences for *orientation*; d: significant differences for *calculation*; e: significant differences for *attention*; f: significant differences for *mental control*; g: Significant differences for *automation*; h: significant differences for *planning*.
*$p<0.05$; **$p<0.01$.
SD: standard deviation; FG: functional gain; IQR: interquartile range.

least. The comparative study between cognitive functions showed significant differences between *calculation* and the following: *short-term memory* ($p<0.01$), *orientation* ($p<0.05$), and *planning* ($p<0.01$). Significant differences were also found between number of sessions for *mental control* compared with *long-term memory, orientation, and planning* ($p<0.01$). Correlation analysis between functional gain and number of sessions was also performed for each cognitive function (see Table IV). Only *planning* showed a linear correlation between the two variables, as more sessions associated with greater functional gain (rho = 0.63, $p<0.01$).

Correlation analysis between patients' total functional gain and time from injury to programme admission was carried out for each cognitive function. The analysis revealed significant negative correlations between these variables for *long-term memory* (rho = –0.63) and *planning* (rho = –0.62). No other functions correlated with the time from injury to programme admission (Table IV).

To determine whether the initial state of a patient affected his/her subsequent rehabilitation, we relied on the GCS score at time of injury. We were able to obtain this information for 16 of the 19 patients in our study. All scores fell below 8 on

Table IV. *Number of sessions, time elapsed from brain injury to rehabilitation programme admission and functional gain (FG)*

Cognitive functions	Sessions, *n* Mean (SD)	Sessions, *n* Median (IQR)	Mann-Whitney U test Number of sessions Differences between cognitive functions	Spearman correlation (rho) Correlation FG%–number of sessions	Spearman correlation (rho) Correlation FG%–time from injury to programme admission
Long-term memory	46.53 (26.44)	54 (23–70)	f**	–0.08	–0.63**
Short-term memory	50.16 (23.63)	58 (43–70)	d**	0.03	–0.29
Orientation	55.67 (31.05)	53 (22–88)	d*, f**	–0.48	–0.55
Calculation	28.29 (27.65)	14.5 (4–53.5)	b**, c*, h**	0.36	–0.13
Attention	37 (32.89)	25.5 (7.25–72)		0.38	–0.25
Mental control	23 (18.62)	13.5 (10.25–40.5)	a**, c**, h**	0.26	0.09
Automation	42.2 (33.97)	43 (5.75–76.5)		0.2	–0.16
Planning	69 (42.39)	53.5 (41.75–83.75)	d**, f**	0.63**	–0.62**

a: significant differences for *long-term memory*; b: significant differences for *short-term memory*; c: significant differences for *orientation*; d: significant differences for *calculation*; e: significant differences for *attention*; f: significant differences for *mental control*; g: Significant differences for *automation*; h: significant differences for *planning*.
*$p<0.05$; **$p<0.01$.
IQR: interquartile range: SD: standard deviation.

Table V. *Between-group comparison of lowest and highest GCS scores*

Patient demographic data	Low GCS score ($n=7$) Mean (SD)	Low GCS score ($n=7$) Median (IQR)	High GCS score ($n=9$) Mean (SD)	High GCS score ($n=9$) Median (IQR)	Between-group differences Mann-Whitney U test (z score)
Gender (M/F)	5/2		8/1		0.55[a]
Age, years	21.57 (4.81)	22(19–23)	22.89 (8.27)	25(16.5–28)	–0.48
GCS score	3.57 (0.53)	4 (3–4)	7.22 (1.92)	7 (5.5–8)	–3.38**
Time from injury to programme admission (months)	10.85 (8.39)	15 (1–16)	39 (84.72)	11 (3.5–21.5)	–0.42

Cognitive functions ($n_{low\ GCS}/n_{high\ GCS}$)	Functional gain % Low GCS score ($n=7$) Mean (SD)	Low GCS score ($n=7$) Median (IQR)	High GCS score ($n=9$) Mean (SD)	High GCS score ($n=9$) Median (IQR)	Between-group differences Mann-Whitney U test (z score)
Long-term memory (7/9)	60.9 (27.80)	62.5 (33.3–85.07)	50.47 (19.68)	50 (29.16–69.04)	–0.79
Short-term memory (7/9)	58.78 (16.11)	58.33 (50–64.28)	58.52 (12.72)	55.55 (48.88–72.38)	–0.05
Orientation (4/4)	88.75 (13.14)	90 (76.25–100)	85 (30)	100 (55–100)	–0.33
Calculation (6/6)	47.45 (25.13)	50.86 (25.45–64.58)	35.79 (12.77)	36.92 (28.57–43.33)	–0.96
Attention (2/5)	54.16 (5.89)	54.1 (50–58.33)	42.41 (33.06)	30 (21.59–69.4)	–1.16
Mental control (6/8)	28.40 (28.94)	38.18 (–3.57 to 50.08)	59.56 (23.78)	58.33 (50–72.9)	–2.02*
Automation (5/2)	49.60 (33.49)	36.36 (22.5–83.33)	87.5 (17.67)	87.5 (75–100)	–1.37
Planning (7/9)	44.53 (33.30)	45.94 (33.33–75)	60.23 (14.24)	62.5 (49.65–69.58)	–1

[a]Fisher's exact test.
*$p < 0.05$; **$p < 0.01$.
GCS: Glasgow Coma Scale; SD: standard deviation; IQR: interquartile range; M: male; F: female.

the GCS. We divided these patients into two groups: the low GCS group ($n=7$), with scores ≤ 4, and the high GCS group ($n=9$), with scores >4. As shown in Table V, both groups had similar distributions of gender and age ($p>0.05$), as well as time from injury to programme admission ($p>0.05$). However, mean GCS scores between the two groups (3.57 for low GCS and 7.22 for high GCS) did show significant differences ($p<0.01$).

Table V displays the percentage of functional gain obtained by both GCS groups in each cognitive function throughout the rehabilitation programme. The low GCS group showed a mean functional gain of 53.09%, whereas the high GCS group mean reached 61.74%. The highest functional gain for both groups was in orientation. The lowest gain was found in *mental control* in the low GCS group and in *calculation* in the high GCS group. We also compared the mean functional gain of each group in these cognitive functions, as shown in Table V. Significant differences were found in *mental control* ($p<0.05$), with the highest gain shown by the high GCS group.

DISCUSSION

The main results of this study may be summed up as follows. Firstly, percentage of functional gain in all cognitive areas did not differ between low and high GCS score groups, with the exception of mental control. Secondly, cognitive functions improved significantly from rehabilitation admission to discharge. Thirdly, functional gain was related to the number of sessions the patient underwent during the course of rehabilitation. Fourthly, not all cognitive functions required the same number of sessions to recover statistic or clinical normalcy. Finally, total functional gain and time from injury to cognitive rehabilitation showed an inverse relationship between long-term memory and planning.

The first aim of this study was to ascertain whether the severity of the lesion at admission determined the severity of the cognitive sequelae observed as a consequence of the physical damage to the brain. To determine the severity of the lesion, we used the patient's worst GCS score during the first 24 h post-injury. The GCS score, since its introduction, has been considered one of the most important predictors of outcome after head injury, although different studies have demonstrated that a correlation does not always exist after brain trauma (15). Our results showed a partial correlation between severity of lesion (GCS) at admission and patients' cognitive functional gain. This correlation was only found in mental control. Our data did indicate that patients scoring higher within the GCS 5–8 range tended to achieve higher functional gain than those with lower scores, although a comparison of mean functional

gain between groups in each cognitive function only showed significant differences in *mental control*. As a cognitive function, *mental control* is related to the part of executive functioning that engages and directs different mental activities (16). This function is directly related to an individual's capacity to be independent (17).

Our CRECERCOS analysis of scores at rehabilitation admission (4.59) and discharge (7.52) found significant differences between number of treatment sessions and the patient's cognitive functional gain. This functional gain is observed in all cognitive areas, with a global mean of 56.24%. Our results support those of other authors, who maintain that the period of cognitive rehabilitation may vary (18).The course of cognitive recovery after post-traumatic coma is irregular, with many ups, downs, and plateaus. Our results indicate that, to achieve a good response and outcome nearing normalcy, a patient needs over 300 h of intensive rehabilitation. This data supports and validates Prigatano's (3) earlier statement that the effects of cognitive rehabilitation are not observed in patients with TBI who receive less than 100 hours of treatment. Our data is also in accordance with Cicerone et al. (2), whose comprehensive review of the empirical literature on cognitive rehabilitation found evidence supporting this treatment and its advantages over conventional forms of rehabilitation.

It is important to note that patient scores increased and decreased throughout the treatment period. Progress during any rehabilitation programme, whether it is physical or cognitive, is not uniform. In our study, each cognitive function required a mean of 43 training sessions, with planning requiring the most (69), and mental control the fewest (23). Our results also indicate that not all cognitive functions require the same number of sessions to recover statistic normalcy. For example, long-term memory, orientation and planning differed in terms of time and effort needed to achieve recovery.

In a previous study, we found that consolidation after an initial gain required more rehabilitation time. Each achievement must be consolidated, and this takes time and repetition, which is reported to have significant physiological effects on learning and working memory (19). In clinical practice, we have observed that if the patient is discharged as soon as s/he obtains a score of 7 or 8, the possibility of a drop or regression persists. Time is also required for structural and functional reorganization in the brain. Training cannot be given all at once, although it should be consistent and progressive. Hence, we recommend that this rehabilitation period be scheduled as 4-h daily sessions, 4 days a week. Treatment should not be abandoned if for a short period of time the patient does not show improvement, or if s/he regresses somewhat. Nonetheless, if regression or stalls persist, their causes should be sought before continuing with the rehabilitation programme. Our results indicate that not all cognitive functions require the same type of treatment; some are more costly to recovery in terms of time and effort.

Another finding is of particular relevance to the planning and timing of TBI rehabilitation. We found that the sooner patients receive treatment after injury, the better their cognitive outcome, especially in long-term memory and planning. However, this treatment requires time, especially to consolidate recovery. Memory is a time-dependent process, as shown by McGaugh & James (20). Furthermore, the duration of post-traumatic memory problems, such as amnesia, has traditionally been a better predictor of cognitive outcome than admission GCS score, as shown by Miller et al. (21).

In conclusion, the rehabilitation of cognitive deficits in TBI patients who have emerged from deep coma is advisable when a holistic, intensive and multidisciplinary programme is applied. However, the course of cognitive recovery after TBI is not uniform, and depends on which cognitive functions are impaired, and on the severity of this impairment. Successful treatment of these deficits varies in terms of time and effort. The number of sessions needed to rehabilitate impaired cognitive functions differs from function to function. For example, our results showed that planning and memory require the highest number of rehabilitation sessions to achieve near normalcy. We should also note that cognitive functions are interrelated, and their rehabilitation must be structured to maximize outcome. Furthermore, the consolidation of cognitive gain also requires time, proper training, and well-programmed therapy. We suggest that patient discharge should occur only after cognitive improvements are consolidated. This study provides an approximation of recovery time after TBI. More studies, involving different technology and theoretical bases, could help expand our knowledge of effective post-TBI cognitive rehabilitation.

ACKNOWLEDGMENTS

This research has been funded by a contractual agreement between the Center for Brain Injury Rehabilitation (C.RE.CER) and the Human Neuropsychology Laboratory at the University of Seville, Spain. We would also like to extend our appreciation to Dr Fernando Machuca Murga for his assistance in collecting data, and Ignacio Solís Marcos for his contributions to data organization and analyses.

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Appendix I. *The Center for Brain Injury Rehabilitation integral, intensive and multidisciplinary model of rehabilitation for people with acquired brain injury*

Interdisciplinary holistic and intensive programmes
- involve brain damage specialists from different fields: neuropsychologists, speech therapists, neurologists, psychiatrists, neurosurgeons, physical therapists, etc.
- ecologically-valid
- divided into synchronized phases (aims, methods and professionals)
use quantitative and qualitative methods
each deficit is allotted the necessary time and dedication to provide best possible outcome

Basic operational requirements:
- rehabilitation treatment designed by specialized personnel, adapted to patient's needs
patient/specialist – at least one professional per three patients
- adequate installations, apparatus and rehabilitation techniques for efficient treatment

Multidisciplinary Programme Structure:
Neuropsychological Rehabilitation
- based on neurological evaluation of patient's cognitive capacities and emotional state
- outcome goals based on clinical and statistic results of this evaluation
- main goal: patients attains maximum degree of functional independence
- treatment sessions include individual (and family) psychotherapy – rehabilitation may continue when patient goes home

Speech rehabilitation
fluidity, auditory comprehension, denomination, reading, writing, repeating, automatic mechanisms, comprehension of written language and presence of paraphasic errors:
- fluency tasks: articulatory agility, length of phrases, verbal agility, etc.
- auditory tasks: differentiating, identifying/obeying orders
- denomination tasks: visual confrontation, free association, etc.
- deficits appearing in reading/writing process are re-taught

Physical rehabilitation
spasticity, posture control, balance, trembling, emotional reactivity
we use NeuroBird system of computerized muscular training as well as other physiotherapy techniques (e.g. Bobath)

Occupational therapy/functional therapy
focus on patient's environment, his/her interests and motivation, culture, values, beliefs and the role the patient plays in his/her surroundings

Efficiency of treatment
CRECER programmes undergo daily evaluation and progress control
- neurofunctional state of patient
- efficacy of methods applied

J Rehabil Med 2012; 44: 512–516

ORIGINAL REPORT

Included in the special issue:
CONSCIOUSNESS AND THE VEGETATIVE STATE: TODAY
J Rehabil Med 2012; 44: 481–516

NEUROREHABILITATION FOR SEVERE DISORDER OF CONSCIOUSNESS: THE S. ANNA – RAN OPERATIONAL MODEL

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The operational model and strategies designed for use in the S. Anna – Research in Advanced Neurorehabilitation Institute for the care and neurorehabilitation of subjects in the vegetative or minimally conscious states are described here. A total of 722 patients were admitted, cared for and discharged from the institute in the period 1998–2009. Application of the model approach has progressively shortened the time of hospitalization and rehabilitation and reduced costs.

Key words: severe disorder of consciousness; vegetative state; minimally conscious state; healthcare; neurorehabilitation, outcome.

J Rehabil Med 2012; 44: 512–516

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Submitted September 27, 2011; accepted January 30, 2012

INTRODUCTION

The S. Anna Institute – Research in Advanced Neurorehabilitation (RAN) for the care and neurorehabilitation of subjects with acquired severe brain damage and disorder of consciousness has been operative in Crotone, Italy, since 1998. The institute aims to meet the needs of a local population of 3–4 million; to date it has admitted, treated and discharged a total of 722 subjects. In the process, dedicated units have been designed and set up to care for subjects with different clinical conditions and at different stages of evolution after brain injury. The functional organization and care and neurorehabilitation procedures in each unit have been designed to respond to the subjects' needs, particularly for those patients who cannot be discharged or treated at home, who need long-term hospitalization. The aim of continuous reorganization since 1998 was to achieve a progressive, cost-efficient reduction in the length of hospitalization in the semi-intensive units for acute patients and in the duration of the rehabilitation protocols, and to help improve outcomes. The objective of this paper is to describe the model and the strategies designed to operate it.

PATIENTS AND DIAGNOSIS

Subjects with severe acquired brain damage and disorder of consciousness are routinely admitted to the institute upon referral from intensive care or neurology/neurosurgery units. There are no pre-determined admission criteria, other than autonomous breathing, stability of vital parameters, and absence of indications for further (neuro)surgery. Patients are classified as being in a vegetative state (VS; also referred to as unresponsive wakefulness syndrome (UWS)) by the current clinical criteria and applicable scales; evolution into a minimally conscious state (MCS)[1] (1–6) is diagnosed when reproducible or sustained behavioural patterns associated with evidence of awareness of self or environment are observed (7–11). Outcome is conventionally assessed with the Glasgow Outcome Scale (GOS) (12, 13) despite occasional ambiguities in this scale in the classification of VS or MCS (14, 15).

A total of 722 patients were admitted in the period 1998–2009. Of these, 503 were diagnosed as being in VS/UWS according to the current criteria; demographics, aetiology and outcome are summarized in Table I. At admission approximately 25% of referred subjects ($n = 219$; 30.3%) featured some consistent, although not constant, behavioural responses compatible with the diagnostic criteria for the atypical VS or MCS. The percentage is consistent with the reported misdiagnosis between the VS and MCS (up to 25–40%) (16, 17); however, the continuous interaction between the S. Anna Institute and the staff of intensive care or neurology/neurosurgery units in the area appears to be incompatible with such a percentage of error. These subjects' demographics, aetiology and outcome are summarized in Table I and compared with the subjects in VS/UWS at admission in order to infer about evolution and outcome.

[1]The MCS (8–10) was not defined until 2002 and the revised Coma Recovery Scale (7) was not in use in Italy before 2008 (18). Subjects admitted to the S. Anna–RAN in 1998–2002 were initially diagnosed as being in a VS with ("atypical" VS) or without any consistent behavioural responsiveness; in this regard, the Aspen Neuro-behavioral Conference Workgroup guidelines (9, 10) were informally followed. The clinical records have been revised for the present study and the diagnosis of VS and MCS reformulated according to these guidelines, but this re-classification did not change the perspective of the study. The VS is currently also referred to as UWS (19); this label is intended to help characterize a condition with somehow unclear boundaries, that shares aetiology and underlying pathophysiology with the MCS, but differs as to prognosis, medical, legal, or popular perception of the bioethical issues (20), allocated resources, healthcare policies, etc.

Table I. *Demographics and outcome of 503 subjects diagnosed and 219 not diagnosed as being in a vegetative state (VS) at admission. The length of time in the intensive care units before admission and in the dedicated semi-intensive care units for VS are shown. The Glasgow Outcome Scale (GOS) ranking classes were: 1 = death; 2 = VS exceeding 1 year in duration; 3 = recovery, with severe disabilities; 4 = recovery, with mild disabilities; and 5 = full recovery or recovery with minimal disabilities not interfering with everyday life (12, 13)*

Subjects	*n* (%)	Age, years Mean (SD)	Time in intensive care unit before admission, days Mean (SD)	Time in the semi-intensive care unit for VS, days Mean (SD)	GOS rating at discharge, %				
					1	2	3	4	5
Diagnosed (*n* = 503)									
All patients	503	39 (15)	58 (45)	154 (117)	17	16	23	24	20
Post-traumatic	302 (60)	29 (14)	50 (47)	140 (118)	5	16	20	29	29
Vascular	160 (32)	56 (15)	56 (39)	144 (113)	34	15	31	18	4
Anoxic-hypoxic	37 (7)	45 (19)	63 (53)	174 (127)	45	21	18	9	6
Others	4 (1)	59 (12)	34 (16)	63 (33)					
Not diagnosed (*n* = 219)									
All patients	219	44 (19)	37 (20)	74 (72)	5	3	16	30	46
Post-traumatic	120 (55)	39 (21)	39 (22)	72 (61)	5	3	14	19	59
Vascular	81 (37)	49 (18)	36 (19)	81 (55)	4	4	20	44	28
Anoxic-hypoxic	5 (2)	36 (12)	40 (24)	46 (42)	0	0	50	25	25
Others	13 (6)	56 (16)	24 (20)	61 (46)	25	0	0	50	25

SD: standard deviation; GOS: Glasgow Outcome Scale.

INSTITUTE STRUCTURE AND ORGANIZATION

The institute units were designed and sequentially organized in compliance with the country regulation, and in order to guarantee clinical care and neurorehabilitation programmes that meet patient's individual pathophysiological conditions, evolution during rehabilitation, and needs.

Operative units

The following units are operative: a 10-bed (2 rooms with 6 and 4 beds, respectively) semi-intensive care unit, also termed the "Awaking Unit" (Semi-Intensive Care Unit for the severe disorder of consciousness, Fig. 1), is dedicated to subjects with severe disorder of consciousness who meet the criteria for diagnosis of VS/UWS in the acute phase at admission. Three dedicated physicians, 5 therapists and nurses rotate to provide a total of 10 h' assistance per day. Temperature and humidity are kept constant and sterile air is circulated (8 times/h). All beds can be moved to upright positions to promote the patients' adaptation to a vertical position and to help recover autonomic balance. The staff schedule and rotation guarantee an overall level of 8-h/day/patient medical, nursing and neurorehabilitation assistance. Each patient is monitored by conventional procedures. All subjects undergo a 3 h/day minimum neurorehabilitation, compatible with their clinical condition and stability. The protocols for neurorehabilitation are purported to: (*i*) favour the recuperation of circadian rhythms by providing changes in illumination; start feeding with regular timing as early as possible; schedule all activities during the 24-h period; (*ii*) minimize all problems due to bedding; and (*iii*) transfer the subject from bed to wheelchair; adapt the subject to an upright position; and start the procedures or assisted mobilization as soon as possible. All subjects are treated regularly in a swimming pool at 38ºC to help counterbalance spasticity and provide the muscle relaxation needed for all rehabilitative procedures to be carried out. The neurorehabilitation protocols include assisted passive mobilization, postural positioning, orthoses, relaxation, stimulation of buccal mucosa, single and group mirror excercises, assisted drawing (Fig. 2a), training in swallowing, training in breathing (clapping, assisted coughing), inhibition of pathological postures, hydrotherapy, automatic walking (Fig. 2b), protocols to withdraw the tracheal cannula, etc. Uni- or multi-modal sensory stimulations are presented regularly to help provide communication with the environment.

In the framework of the MIMERICA[2] project, an ambient intelligence platform combining traditional and innovative sen-

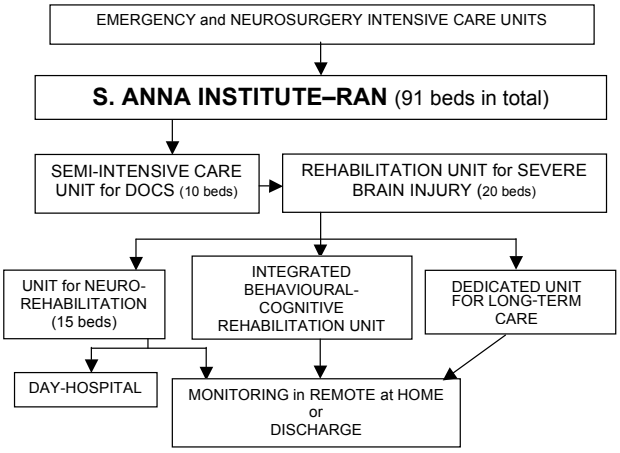

Fig. 1. S. Anna–RAN model for the care and neurorehabilitation of subjects with severe acquired brain damage and disorder of consciousness. RAN: Research in Advanced Neurorehabilitation; DOC: severe disorder of consciousness.

[2]The project and development of MIMERICA were supported by the Italian Ministry of University and Research with dedicated funds for competitive pre-industrial research (2004–2007).

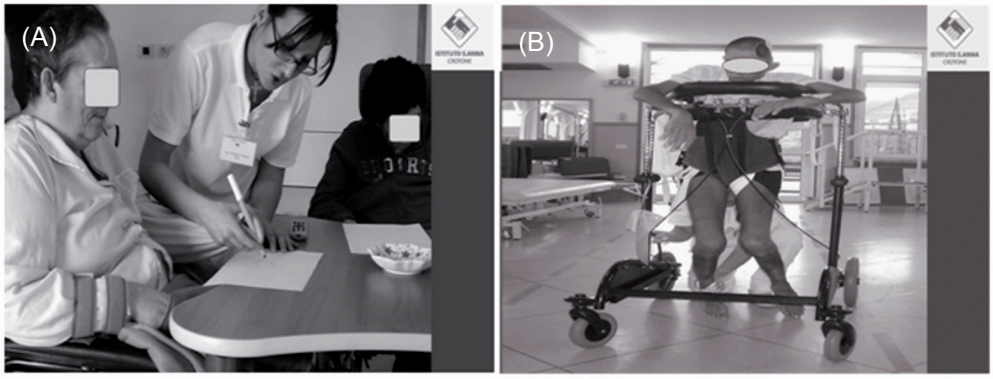

Fig. 2. Examples of rehabilitation treatment of patient with disorder of consciousness in S. Anna Institute–Research in Advanced Neurorehabilitation. (A) Assisted drawing. (B) Automatic walking.

sors for the ambient (temperature and humidity, oxygen, light/dark cycles, noise, etc.) and the relevant functional parameters (body temperature, heart rate and systolic/diastolic blood pressure, breathing, oxygen saturation level, spontaneous movements, voicing, eye movements and blinking, and heart rate variability) of a sub-sample of subjects has been implemented for monitoring. Ambient intelligence collectively indicates pervasive and non-invasive hardware/software infrastructures allowing two-way human interaction with, and full control of, the environment at varying levels of functional complexity. Research into the effects of spontaneous or environment-induced changes in non-neural factors on brain function (e.g. responsiveness) or evolution is in progress. To this end, the platform architecture is interfaced for compatibility and interplay with advanced tools for knowledge management and knowledge discovery, processing data to infer new knowledge and potentiate intelligent processing through intensive and iterative processes (21–23).

Subjects emerging from the VS/UWS and recovering into a MCS clinical condition (7–9) are transferred to the 20-bed unit dedicated to the patients with acquired severe brain injury (brain injury care in Fig. 1). In this unit, monitoring is limited to the vital parameters, depending on the patient's clinical needs; and assistance is provided for a total of 7 h/day/patient. Subjects are treated with standard motor, speech therapy and cognitive rehabilitation procedures, depending on the disabilities observed when consciousness is (partially) recovered.

A 36-bed unit is dedicated to the long-term care of patients who have not evolved from a VS/UWS or MCS and are unsuitable for discharge or homecare (long-term care in Fig. 1). Transfer to this unit is made at a time after brain injury that depends on aetiology: 12 months for post-traumatic subjects, 6 for those with major vascular injury and 3 for those who have had massive anoxia-hypoxia. Full nursing and medical assistance, proper feeding/hydration, adaptation to a wheelchair, and passive motor treatments are guaranteed and the possible evolution towards a (partial) recovery of consciousness is monitored by *ad hoc* protocols. When practicable, the family is trained to be able to take care of the subject at home for limited periods of time, with the aim of re-adjusting the patient to the home environment. Following an increase in the number of beds in this unit from 16 to 36, the turnover along the institute units increased significantly (black vertical bar in Fig. 3) ($\chi^2 = 3.679$, $p = 0.05$).

Subjects further evolving from a MCS and (partly) recovering consciousness with residual cognitive impairment and/or behavioural disorders that are incompatible with discharge or untreatable at home are transferred to the 10-bed integrated unit for cognitive-behavioural rehabilitation, with appropriate nursing and psychological support and cognitive rehabilitation.

Subjects (partially) recovering consciousness with residual major motor disabilities are transferred to the 15-bed unit for motor functional rehabilitation and trained to adjust to future, fully-monitored, remote treatment, at home.

This re-organization has progressively reduced the length of hospitalization in the semi-intensive unit for subjects with VS/UWS and has increased the turnover rate, therefore combining an optimal utilization of the institute facilities with the fulfilment of each patient's needs (Fig. 3).

Work to extend healthcare and neurorehabilitation to patients at home under remote control is in progress. To this end, collaboration between the S. Anna – RAN and the local government and healthcare organization (the Oberon project) has been

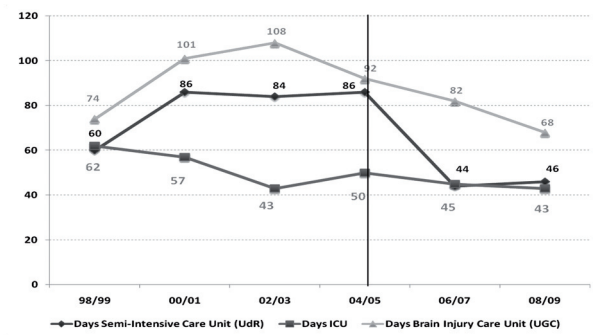

Fig. 3. Mean length of hospitalization (days) in intensive care or neurology/neurosurgery units of local hospitals and in the Institute S. Anna–Research in Advanced Neurorehabilitation dedicated units. Note how the increased number of patients in institute acute and the long-term units has contributed to reducing hospitalization in local hospitals. The turnover between units increased significantly after increasing the number of available beds in the long-term unit (*black vertical bar*) ($\chi^2 = 3.679$, $p = 0.05$).

established, in order to develop and test the potentialities of remote monitoring and homecare of 54 subjects in a persistent VS/UWS or MCS over a 3-year period.

EARLY RECOVERY AND OVERALL OUTCOME

The evolution from VS/UWS to MCS to recovery and the overall outcome were studied retrospectively by referring to two established major descriptors, namely the GOS (12–13) and the re-appearance of a visual pursuit response (24, 25). In general (and in agreement with previous evidence), post-traumatic patients had better outcomes than vascular patients, and anoxic-hypoxic subjects had the worst outcome irrespective of their condition at admission (24–26).

Subjects not in VS/UWS at admission because of the short time between their emerging from coma and their referral to the S. Anna had shorter hospitalization times, both in the intensive and dedicated semi-intensive care units, and better GOS ratings at discharge than those in VS, irrespective of aetiology (χ^2= 27.6, $p < 0.0001$), with a higher probability of scoring a GOS class 5 (χ^2= 11.375, $p = 0.0004$) and a lower probability of scoring a GOS class 1 (χ^2= 3.309, $p = 0.03$). Comparable results were obtained when considering post-traumatic and vascular subjects separately (χ^2= 22.26, $p = 0.0002$, and χ^2= 61.31, $p = 0.0001$, respectively) (Table I).

Visual pursuit ("the pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli") is a predictor of favourable outcome, with recovery of consciousness in 73% of subjects in VS/UWS (45% in the absence of eye tracking); it is an established key descriptor of the subject's evolving from the VS/UWS into the MCS (8–11, 24–27). No differences were observed by testing for a visual pursuit response in the evolution of subjects in VS/UWS due to traumatic or vascular brain injury, who were found to have developed into a MCS in 46% and 49% of cases, respectively, after 50 days. These percentages had increased by 8 months after brain injury, to 89% and 88%, respectively, and had increased further to approximately 90% at discharge or at the end of follow-up (> 235 days). The evolution of subjects with brain anoxia-hypoxia was less favourable, with percentages of evolution increased to a MCS up to 63% at the end of follow-up. Only 12.6% of subjects were diagnosed 8 months after brain injury as still being in a VS/UWS; a later evolution (2 years or more) was observed in 7% of the total group of subjects classified as being in a VS/UWS at admission (25).

The visual pursuit response reflects (partial) recuperation after severe brain injury of the brainstem-cortical interaction and functional organization, which are thought to sustain consciousness and are interfered with by the pathophysiological disconnection resulting in a VS/UWS (25). Its early re-appearance (deemed equivalent to early evolution into a MCS) correlates with a better outcome, confirming the predicting role of this neurological sign (24). However, evolution from the VS to the MCS (at least as indicated by recovered visual tracking) also appears possible several months after brain injury (25).

COMMENT

The extent to which the neurorehabilitative procedures now in use at the S. Anna – RAN Institute or elsewhere are individually or collectively capable of promoting an evolution from the VS to the MCS to recovered consciousness remains, to a relevant extent, undocumented, but a role of the therapeutic milieu, i.e. the synergic effects of the environment and the trainers' and nurses' assistance, appears indisputable. Following this rationale, units dedicated to the care and neurorehabilitation of subjects with severe brain injury and consciousness disorders, such as the VS or MCS, are operative in developed countries. The commitment as to resources, logistics, dedicated nursing, rehabilitation and medical care has substantially reduced mortality and the percentage of the so-defined persistent (>1 year) VS. It has improved the chance of favourable outcome, which, in our experience, nevertheless remains worse than for patients with severe acquired brain damage who have never entered into a VS. In our institute, approximately 80% of subjects in VS/UWS due to brain trauma recovered consciousness, while 60% attained recuperation to levels compatible with autonomy or allowing quasi-normal life conditions. To this end, healthcare and neurorehabilitation in dedicated units should be made available as early as possible, with a flexible therapeutic continuum congruent to the functional brain organization attained at each phase during the evolution from coma to a VS or MCS, to recovered consciousness. In our operative model, hospitalization only exceptionally exceeds 6 months, unless cognitive/behavioural disturbances occur after recovery of consciousness. Later evolution from a VS/UWS to a MCS, further improvement to higher levels of functional brain organization, or recovery of consciousness are also possible.

ACKNOWLEDGEMENTS

This study was supported by the Institute S. Anna – RAN. The authors thank Professors Leon Sazbon (University of Tel Aviv, Israel) and Walter G. Sannita (University of Genova, Genova, Italy, and State University of New York, Stony Brook, NY, USA) for continuing support and valuable advice.

The authors have no conflicts of interest to declare.

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