Rehabilitation of disorders of consciousness after traumatic brain injury

Biennial Conference of the Brain Injury and Families/European Confederation (BIF)

Umberto León-Domínguez
Autonomous University of Madrid, Spain
Center for Brain Injury Rehabilitation (C.RE.CER.), Seville, Spain

Vienna International Congress
Vienna Medical Academy, Sep. 19th – Sep. 21st, 2013
Scheme

- Brief summary of topic
  - Etiology
  - Diagnosis
  - Treatment

- Articles about the treatment of Disorder of consciousness
  - Treatment of DOC: A single case study
  - Cortical connectivity in MCS and SND

- Conclusions
What is a Disorder Of Consciousness (DOC)?

*Disorders of consciousness are a medical or functional condition that inhibit consciousness.*
Plum and Posner (1980) clarified that consciousness has two clinical dimensions: wakefulness and awareness.
Etiology of DOC

- Vegetative State
  - Impaired functional connectivity between the Ascending Reticular Activating System (ARAS) and the precuneus (Silva et al., 2010)
  - Lesions confined to the thalamo-cortical system connectivity (Boyle et al., 2009; Fernandez-Espejo et al., 2010)
  - Lesions confined to the thalamus (Adams et al., 1999, 2000; Jennett et al., 2001; Maxwell et al., 2006; Fernandez-Espejo et al., 2010)
  - Impaired Default Mode Network (DMN) Connectivity (Laureys et al., 1999)
  - Impaired functional connectivity between thalamus and posterior cingulate cortex/Precuneus (Fernandez Espejo et al., 2012)
Etiology of DOC

- Minimally Conscious State
  - Diffuse axonal injury damage with possible coexisting functional alteration of subcortical gating systems (Schiff, 2005)
  - Transient from DMN to “task-positive network” (Crone et al., 2011).
Etiology of DOC

- Severe Neurocognitive Disorder
  - Focal cortical injuries drive to cognitive impairments (Luria, 1966; Fuster, 2008)
  - Lesions confined to the cortex drive to impaired neural information processing → content of awareness disrupted (Halligan et al., 2004; Fuster, 2008)
Rehabilitation of patients with DOC
Ethical Code

Management of a patient in a vegetative state or a minimally conscious state requires

1. carefully reaching the correct diagnosis

2. pronouncing an evidence-based prognosis, and

3. thoughtfully considering the medical, ethical, and legal elements of optimum treatment
### Neuropsychological assessment:

<table>
<thead>
<tr>
<th>Vegetative State</th>
<th>Minimally Conscious State</th>
<th>Severe Neurocognitive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>-No evidence of awareness of self or environment and an inability to interact with others</td>
<td>-Intermitent ability to interact with others</td>
<td>-Ability to interact with others</td>
</tr>
<tr>
<td>-No evidence of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli</td>
<td>-Scarce or inconsistent behavioral response to visual, acoustic, tactile or verbal stimuli</td>
<td>-Consistent behavioral response to visual, acoustic, tactile or verbal stimuli</td>
</tr>
<tr>
<td>-No evidence of language comprehension or expression</td>
<td>-Scarce or inconsistent verbal comprehension or expression</td>
<td>-Preserved state of alertness and sleep/wake cycle</td>
</tr>
<tr>
<td>-Intermitent wakefulness manifested by presence of sleep/wake cycles</td>
<td>-Intermitent state of alertness compatible with sleep/wake cycle</td>
<td>-Notable decline from prior level of functioning</td>
</tr>
<tr>
<td>-Sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing care</td>
<td>-Maintenance of autonomic functions alone or with medical or nursing care</td>
<td>-Difficulty with work, study and family</td>
</tr>
<tr>
<td>-Bowel and bladder incontinence</td>
<td>-Inconsistent eye-tracking of objects and people</td>
<td>-Severe deterioration of memory structures and/or processes</td>
</tr>
<tr>
<td>-Variably preserved cranial-nerve reflexes and spinal reflexes</td>
<td>-Scarce or inconsistent response to familiar emotional stimuli</td>
<td>-Severe deterioration of other neurocognitive functions: attention, language, motor abilities, recognition, imagery and/or executive functioning</td>
</tr>
</tbody>
</table>
DOC Diagnosis

- **Neuroimaging Assessment:**
  
  - **Identification of residual cognitive function with fMRI:** (Owen & Coleman, 2008; Coleman, Davis, Rodd, Robson, Ali, Owen & Pickard, 2009; Monti, Coleman & Owen, 2009; Rodriguez Moreno, Schiff, Giacino, Kalmar & Hirsch, 2010; Monti, Vanhaudenhuyse, Coleman, Boly, Pickard, Tshibanda, Owen & Laureys, 2010)

  - **fMRI: Brain computer interface communication:** (Owen, Coleman, Boly, Davis, Laureys & Pickard, 2006)

  - **EEG: cortical wavelength patterns identifications:** (Cruse, Chennu, Fernández-Espejo, Payne, Young & Owen, 2012)

  - **Event-Related cortical potentials (ERPs):** (Guérit, 2005; Kotchoubey, 2005; Luaute, Fischer & Adeleine, 2005; Fischer, Luaute & Adeleine, 2006)

  - **Perturbational complexity index (PCI). TMS + EEG measurements:** (Casali, Gossieres, Rosanova, Boly, Sarasso, Casali, Casarotto, Bruno, Laureys, Tononi & Massimini, 2013)
CAUTION!

The implicit limit of clinical assessments may indeed be one of the major contributors to the estimated rate of about 40% by which MCS patients are misdiagnosed as being vegetative.
Treatment

- 3 principles (Hirschberg & Giacino, 2011):

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Rationale</th>
<th>Method</th>
<th>Aim</th>
<th>Representative Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotherapy</td>
<td>Drug exposure may correct imbalance in inhibitory and facilitory neural systems responsive for symptom expression</td>
<td>Administration of dopaminergic, noradrenergic, and serotonergic medications</td>
<td>Improve arousal, initiation, and attention</td>
<td>Meythaler et al, 2002</td>
<td>Rate of recovery significantly faster in patients treated with amantadine hydrochloride within 3 months of injury relative to placebo group.</td>
</tr>
<tr>
<td>Sensory stimulation</td>
<td>Information processing is dependent on calibration of stimulus intensity and response threshold</td>
<td>Administration of multimodal sensory stimuli (auditory, tactile, visual, olfactory)</td>
<td>Improve breadth and reliability of behavioral response repertoire</td>
<td>Mitchell et al, 1990</td>
<td>Time to recovery of command-following and purposeful movement significantly shorter (mean difference = 5 days) in patients who received a structured sensory stimulation program for 1–2 hours/day over 7–12 days relative to no-treatment controls.</td>
</tr>
<tr>
<td>Deep Brain Stimulation (DBS)</td>
<td>Electro-physiologic stimulation of reticular-activating system produces physiologic changes associated with arousal</td>
<td>Chronic electrical stimulation of mesencephalic structures</td>
<td>Improved arousal and/or cognitive deficits associated with disruption of thalamo-cortical circuits</td>
<td>Schiff et al, 2007</td>
<td>Improvement in arousal ratings, praxis, and swallowing on standardized assessments obtained during DBS-on vs. off periods.</td>
</tr>
</tbody>
</table>
Treatment

- In order to rehabilitate DOC patients we use the Combined Method Therapy (CMT) (Leon-Carrion, 2006):
  - CMT is a methodological engineering process, integrating knowledge of a patient’s intact and non-intact functional brain circuitry with cognition and neuropharmacology.
  - The goal is to achieve a new functional cerebral organization which allows the patient to re-establish functional brain connectivity.
Treatment of DOC: A single Case

Restoring Cortical Connectivity Directionality and Synchronization is Essential to Treating Disorder of Consciousness

Treatment of DOC: A single Case

Patient Profile

- 24-year-old male with TBI resulting from a traffic accident

- MRI showed diffused brain injury with lesions in fronto-temporal areas (predominantly in right and posterior-lateral), as well as inferior-ventral brainstem damage.

- The patient scored 8 on the Glasgow Coma Scale (Eyes 4; Motor 3; Verbal 1), 24 on the Disability Rating Scale, and 2.72 on the Rappaport Coma/near Coma Scale (moderate coma).

- The patient fulfilled international criteria for the VS

CT Scan
Treatment of DOC: A single Case

- CMT Treatment:
  - The patient underwent an intense holistic and multidisciplinary neurorehabilitation program
  - Specific neuropharmacological program
    - The medication included acetylcholinesterase inhibitors, modafinil, dopamine agonists, lamotrigine, and Omega 3 fatty acids
  - TMS
    - PFC stimulation was applied for 20 minutes, 5 days/week. It focused mostly on the DLPFC, although sponge placement centred on F3, following the International 10-20 system (Brodmann areas 8/9). Stimulation intensity was set at 1 milliamp.
  - EEG Monitoring
    - Drug efficacy and dosage were estimated and adjusted using serial QEEG examinations, administered daily and weekly, to restore normative values, decrease slow wave activity, and promote the reappearance of alpha and beta activity.
EEG connectivity data analysis:

- Granger causality which establishes whether a causal connection exists between a pair of EEG channels, based on the statistical significance of the connection strength.
Treatment of DOC: A single Case

- Results

  - The new pharmacological treatment revealed changes in the patient’s cortical connection (16/06/2008) from that of admission (24/04/2008)

  - These changes were due to an increase in the number of connections between the anterior and posterior cortex.

  - Another significant finding was the change in directionality in these connections which took place after beginning the new pharmacological treatment. The initial directionality from anterior to posterior cortex was inverted, and now information was sent from the posterior to the anterior cortex.
Treatment of DOC: A single Case
Synchronization between the anterior and posterior cortex determines consciousness level in patients with traumatic brain injury (TBI).

The present study aims to explore how synchronized nonrandom neural circuits across cortical regions are integrated to generate consciousness.

In this study we compare two groups:

- patients in the MCS
- patients with SND
Hypothesis

Our hypothesis:

1. The emergence of consciousness requires synchronized circuitry to differentially integrate anterior and posterior cortices.

2. Patients with SND should display greater synchrony and connectivity between anterior and posterior regions than patients in the MCS.
Experimental Procedures

- We used functional connectivity analysis to identify brain connectivity networks in task-free resting state EEG recordings.

- Two methods were applied to ascertain the cause and effect relationships among all electrodes:
  - the first measured synchronization activity between pairs of electrodes
  - the second determined the strength and direction of functional connectivity
Experimental Procedures

Patients

- We evaluated two carefully matched severe TBI patient groups (16 patients)
  - 7 patients in MCS
    - 6 M, 1 F
    - mean age = 28.43
  - 9 patients with SND (control group)
    - 6 M, 3 F
    - mean age = 29.5
Results

Our findings:

- preserved consciousness would require simultaneous participation of

- anterior neural cortical structures (responsible for executive functioning) and

- posterior neural cortical structures (responsible for cognitive representations)
Results

- Patients in the MCS showed frontal cortex disconnection from other cortical regions.

- Patients with SND showed high number of functional connections b/t:
  - frontal and parietal regions
  - occipital, frontal and left temporal regions
  - left temporal and parietal occipital regions

- Significant differences also found in delta, theta, alpha, beta bands and in full bandwidth.
Results

- Multivariate modeling to detect the directions of these connections showed connections from all areas to the frontal region.

- These connections reached significance for the beta band (including connections inside the frontal region).
Results

- Our results illustrate the existence of a large scale network surviving in both MCS and SND
  - although patients with SND display a higher level of synchronization
Results
Results
Conclusions

- **Conclusions:**
  - Awareness level depends on the synchronization between retrorolandic (posterior) and frontal (anterior) cortical areas.
  - Patients with TBI presented a higher level of awareness when connections between cortical regions followed a posterior-anterior propagation of beta waves.

- **Clinical application:**
  - These evidence show up the necessity to track the DOC’s treatment with neuroimaging technics to fit the correct pharmacological dose in order to promote posterior-anterior cortical connectivity.
Thank you very much.

• umbertoleon@gmail.com

• www.neurocrecer.es

• www.discovershadow.com/
Disorders of consciousness

Acute Brain Injury → Coma

- Fast Recovery
- Vegetative State
  - 1972 Jennett (Glasgow) & Plum (NY)
  - Locked-In Syndrome
    - 1966 Plum & Posner (NY)
- Brain Death
  - 1952, artificial respirator (Ibsen, Copenhagen)
    - Redefinition of death based on neurological criteria

Recovery of Consciousness

- Minimally Conscious State
  - 2002, Aspen Workgroup
- Permanent Vegetative State
  - 1994, Multi-Society Task Force on PVS
    - >1 year (traumatic)
    - >3 months (non-traumatic; anoxic)
- Permanent Minimally Conscious State

Laureys, *Scientific American* 2007

www.comascience.org
Etiology of DOC

- Coma

- Lesions in Ascending Reticular Activating System (ARAS) (Loeb, 1958; Loeb and Stirling Meyer, 1965; Chase et al., 1968)

- Lesions confined to parabrachial nucleus, locus coeruleus, raphe complex, laterodorsal tegmental and the nucleus pontis oralis (Parvizi & Damasio, 2003)
Prognosis

- Traumatic Brain Injury
  - Coma
    - Fast Recovery
    - Vegetative State
      - Locked-In Syndrome
      - Minimally Conscious State
    - Permanent Vegetative State
  - Recovery of Consciousness (Severe Neurocognitive Disorder)
  - Permanent Minimally Conscious State

Laureys, *Scientific American* 2007