

**Defining consciousness: lessons from patients and modern techniques**

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We would like to highlight the great interest recently raised in the scientific community by the increasing number of works on disorders of consciousness (DOC) confined to single subjects or, at most, a few subjects. The purpose of this commentary is to expound the possible role of case-reports in exploring consciousness gradations from the vegetative state (VS) and minimally conscious state (MCS) to full consciousness. Peer-reviewed literature has never produced such meagre case-series and single case reports as in this field, thus suggesting that speculations about DOC should be strictly based upon empirical evidence, although isolated and somehow incidental in nature. Against this backdrop, sheer case reports can teach important lessons about this extremely challenging group of patients and pave the way for further systematic investigations.

To date, the above collection includes short-reports of various kinds related to clinical, prognostic and speculative issues.

Some reports focused on the paradoxical awakening effect of several drugs that might favour the emergence from unconscious states: a transient consciousness improvement has recently been described in a semi-comatose<sup>1</sup> and in a minimally conscious patient<sup>2</sup> during the application of the GABA-A agonist Zolpidem whereas opposite findings were highlighted by others.<sup>3</sup> In this wake, a stable improvement in the level of consciousness has been described in single patients respectively treated with intrathecal baclofen,<sup>4-5</sup> or amantadine.<sup>6</sup> In this respect, we recently reported the awakening effect of intrathecal baclofen in five patients with persistent VS, who showed clinical improvements ranging from a mere increased alertness to a full recovery of consciousness: this observation, although confined to a few subjects, enabled us to make some speculations about the paradoxical effect of intrathecal baclofen and suggest two possible hypotheses on the mechanisms responsible for the reported improvement.<sup>7</sup> Although all these observations deserve further systematic investigation, the above case-series must be given

credit for drawing the attention on the hypothetical awakening effect of these drugs.

Similarly, some authors recently dwelled upon the difficulty in the clinical and prognostic assessment of patients with DOC with a view to provide cases of misdiagnosis supporting this difficulty. It remains very challenging to decide whether the patient is in a VS or MCS, or, alternatively, suffering from a locked-in syndrome: as a result, the VS is often over-diagnosed. An integrated approach, also including neurophysiological and functional imaging paradigms, has been suggested to confirm clinical impressions and avoid misdiagnosis. In this respect the usefulness of case-based lessons comes up again: some case-reports raised questions about the reliability of neurophysiological findings to predict outcomes in these patients.<sup>8-10</sup> Others highlighted the emergent usefulness of functional magnetic resonance imaging (fMRI) to provide reproducible and anatomical specific activation patterns in non communicative patients during tasks implying an external stimulation. The comparison of patterns obtained in patients and healthy subjects respectively may not only provide speculative information on the wide networks underlying normal consciousness but also practical suggestions on the prognosis of patients. There are several experiences that have recently been described on individual patients: for instance, two patients with MCS revealed language-related cortical activation with auditory stimulation using personalized narratives;<sup>11</sup> two patients in VS subsequently emerging to MCS showed an increased activity in the primary auditory cortex and in hierarchically higher order associative temporal areas when their names were uttered by a familiar voice;<sup>12</sup> a patient in VS showed the activation of the supplementary motor area when asked to imagine playing tennis and the activation of regions associated with spatial navigation when asked to imagine moving around her house.<sup>13</sup> What lessons are to be learnt from these case-reports is difficult to

establish: undoubtedly, they suggest that consciousness is not a function that can be localized, but it is certainly active on the vast cortical-subcortical networks with all the ensuing theoretical and neurofunctional issues.

As stated above, case-reports may be very useful in this emerging area of research, since they can contribute to plan a better assessment of patients with DOC, improve their management and identify more reliable prognostic indicators for the recovery of consciousness.

Their contribution is all the more evident if the following aspects are taken into account: firstly, the considerable heterogeneity of patients with DOC does make the collection of vast, homogeneous and rigorous case histories from the point of view of inclusion criteria extremely difficult; secondly, the chronic nature of persistent VS renders the collection of truthful follow-up data on a large number of subjects difficult, with the obvious repercussion that a trustworthy estimate of late improvement incidence is still lacking, probably because of erratic follow-up, incomplete reporting or uncertain diagnoses. Hence, the usefulness of well-designed case series that, even if confined to a few subjects, may best guarantee homogeneity criteria, thus avoiding the legitimization of starting hypotheses which are actually false (type II error) and enabling more prolonged longitudinal observations to be made.

However, although some merits may be recognized in the above case-reports, ethical and scientific prudence suggests forgoing to draw conclusions exclusively based on the data provided by them. Indeed, well-documented case reports may prompt reflections on many issues concerning DOC, provided, though, that robust data can only be gathered by means of following more rigorous studies. This is all the more so if we refer to prognostic issues which, by their nature, raise ethical and legal dilemmas, especially with respect to considerations on the withdrawal of life-sustaining treatments.

Furthermore, within the framework of case reports and case series a clear-cut distinction is called for between simple descriptive case reports and case studies based on single-subject research design: this distinction is fundamental because whereas the former are sheerly narrative in essence,<sup>2,4,5,8</sup> the latter are based on the formulation of a work hypothesis that, through a precise methodology applied to individual cases, is then confirmed or disavowed.<sup>6,7,12,13</sup>

What led to the development of such *case-report based knowledge* covering various aspects of the disorder of consciousness?

This issue will be examined thoroughly by considering the most famous case-report described in the history of neurological science: the "Phineas Gage's" experience.<sup>14</sup> He was a railroad worker who, as a consequence of a traumatic brain injury which only involved his frontal lobes, reported severe effects on his personality and social functioning. From then on, the prefrontal cortex has been regarded as the "organ of civilisation" and a large number of similar behavioural alterations have been recognized in patients with traumatic injuries in the prefrontal region or treated by means of brain surgery because of brain tumours and psychiatric or epileptic disorders.<sup>15</sup>

As a result, the Phineas Gage's case contributed to the evolution of the science involved in localizing brain functions.

Basically, there are three main elements enabling a case report to foster the emergence of fresh research: i) its fortuitous and unpredictable course with improbable and confounding outcomes ii) its occurring in a crucial historical and epistemological moment characterized by arising doubts about an emergent issue iii) its being beyond standard guidelines in terms of diagnosis and therapy.

With vegetative and minimally conscious patients, these main elements arise again: the fact that the essence of consciousness is currently neglected, along with the impossibility to localize it within specific cerebral areas, results in realizing that what we

learn about it originates from fortuitous and irreproducible observations. Moreover, the condition of patients with DOC is the direct result of the period in which they live, although the improvements witnessed by patients in the treatment of the acute stage of their pathology, which has greatly benefited their survival rate, have not been followed by a clearer understanding of consciousness itself. Finally, patients often show unexpected responses to treatments administered for other indications, therefore defying what established by the existing guidelines.

All these features contribute to the intriguing nature of case-reports addressing consciousness and form a considerable component of their success: however, case-reports ~~have to~~ can be considered scientifically **worthy** only if authors are encouraged to formulate specific hypotheses about the clinical events they experienced. These hypotheses may lay the groundwork for subsequent more systematic investigations based on larger samples and more rigorous methodologies, thus contributing to improve our current knowledge on consciousness impairment and recovery.

Moreover, if compared to Phineas Gage, patients with DOC are even more complicated because of their being completely different from each other with respect to the nature and localization of brain lesions. Consequently, they are hardly mutually comparable and each of them should be considered on a case-by-case basis with the result that they turn out to be even more challenging than Phineas Gage's case.

The above heterogeneity prompts reflections on the desirability of future research on consciousness.

In the case of Phineas Gage, a single fortuitous experience suggested the role of the prefrontal cortex in moral and social cognition: modern scientific literature confirmed this pioneering observation by recognizing similar behavioural disorders in a large number of patients with the same lesion thereafter. In this respect,

the science dealing with the localization of brain functions appeared as being the result of an a posteriori knowledge depending on the experience drawn from a large number of comparable subjects.

Apparently, a case-report based culture will not exactly work in the same way as would the unravelling of consciousness: indeed, the striking heterogeneity of patients with DOC makes the systematic verification of intuitions arising from individual subjects difficult and is an indirect sign of the likely delocalized nature of consciousness itself.

In fact, the absence of specific brain damages constantly associated with DOC suggests that consciousness is not localized within confined brain areas and this explains why the assignment of specific regions to an hypothetical domain of consciousness is still far from being resolved. Compared to other simple cognitive abilities, consciousness is less likely to be localized in specific brain structures since it presumably requests the synergy of wide interconnected neural networks whose identification does not seem to respond to the standard methods of cognitive science. This suggests that consciousness does not depend on the performance of single specialized brain areas and should be addressed by investigating how different brain regions communicate with each other according to the concept of functional connectivity. This is also in line with recent studies which regard the VS as the result of a sufficient reduction in global mutual interconnectivity rather than a dysfunction of a single area.<sup>16</sup>

In this respect, a case-report based knowledge of consciousness, although partially invalidated by the heterogeneity of anatomopathological features, might pave the way for ~~further point of view to confront consciousness~~ additional analyses that may help clarifying consciousness and become the most accessible way to tackle it in practical terms.

By way of conclusion, even sheer case reports can teach important lessons on patients with DOC, because they raise important questions that will probably be tackled from the moment they are suggested onwards, just as it occurred with the Phineas Gage's case.

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