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Ethics, neuroimaging, and limited states of consciousness

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Introduction

Neuroimaging in severely brain-damaged, non-communicative patients raise several methodological and ethical concerns [1-6]. In this lecture we examine the issues of experimental design and reproducibility critical to the eventual success of neuroimaging in delivering new knowledge about disorders of consciousness such as comatose, vegetative and minimally conscious states. Advances in neuroimaging technology now make it possible to produce not only remarkably detailed images of the brain's anatomy, but also to capture images of the brain's physiology and offer new insights in the functional neuroanatomy of these challenging pathologies. At present, patients with disorders of consciousness following an acute brain injury continue to pose problems in terms of their diagnosis, prognosis and therapy. The study of residual brain function and consciousness in these conditions must involve the direct study of these patient populations. This information cannot come from the sole study of healthy volunteers or other pathologies. Research efforts aiming to increase our knowledge about brain function in these conditions remain scarce and are confronted by a series of methodological difficulties, including ethical barriers [7].

Neuroimaging techniques

Neuroimaging encompasses a series of technologies such as positron emission tomography (PET; measuring, for example, the brain's metabolic activity, oxygen extraction or neurotransmitter activity), magnetoencephalography (MEG; measuring the magnetic fields generated by electrical activity within the brain) or advanced magnetic resonance imaging MRI methods such as voxel-based volumetry or morphometry (objectively quantifying changes in brain structure), MR spectroscopy (measuring biomarkers of neuronal integrity, cell membrane turnover or energetic function), and MRI diffusion tensor imaging (assessing the density, integrity and directionality of white matter tracts) [8]. The appropriate experimental protocol will be dependent on the specific methodology employed and on the scientific question asked. In neuroimaging studies of coma, the vegetative state and related disorders, there is a clear need for more data and studies with larger patient numbers. This involves multi-center studies with a shared methodology and experimental protocol.

Unconscious patients and neuroimaging research

Patients with disorders of consciousness should not participate in functional neuroimaging protocols unless it is essential for the goals of the proposed research. Many imaging studies may constitute a small risk to individual patients varying with the technology employed. In our view it is ethically acceptable to perform research if the potential benefits gained by knowledge for the good for the entire patient population is felt to outweigh these risks. We should be cautious that concern about potential risks to individual might inhibit progress in the field - and therefore benefit to the patient. The benefit for severely brain injured patients to participate in a specific neuroimaging study is often very difficult to quantify and at present experts in the field do not seem to have reaches a consensus on the putative benefit at the individual level.

Selection of patients should, at first, aim to include homogeneous populations. The aetiology, time window and structural injury need to be well described and therapeutic and rehabilitation protocols need to be comparable between patients when assessing outcome. Firstly the diagnostic and prognostic accuracy of neuroimaging assessments should be established, as results from validated studies will have implications on end-of-life decisions [9, 10]. At present, although neuroimaging studies in vegetative and minimally conscious states have improved our understanding about the underlying mechanisms of these disorders [11-25], the 'gold standard'

remains careful and repeated neurological examination by a trained examiner [26]. Accurate clinical assessments should be obtained prior to performing neuroimaging in these patients [27], and all relevant clinical details should be made available in publications so that subsequent comparisons and meta-analysis is possible. Patient ineligibility (for example, related to the presence of electric devices or of metal) and artifacts (for example, related to movement) will be specific to the imaging technology used.

Experimental neuroimaging in disorders of consciousness needs a set of standardised, calibrated and validated stimuli. Owen et al have recently proposed a hierarchical paradigm [28] - starting with simple to complex auditory stimuli and ending with the assessment of command-following [29]. Prior to use in patient populations, such paradigms first need to be validated in healthy volunteers. The choice of employed stimuli and experimental paradigm should aim for non-noxious stimulation and patients' discomfort should always be kept to a minimum. In the study of residual emotional processing, positive emotional stimuli should be preferred to negative ones – unless the use of stimuli with negative emotional connotations are the subject of the study or if they show proven benefit in terms of robustness of the obtained neural response. For the study of pain, presentation of noxious stimuli is acceptable as long as the experimental protocol adheres to the published standards of the International Association for the Study of Pain (IASP) Ethical Guidelines for Pain Research in Humans [30]. The minimal intensity of noxious stimulus necessary to achieve the goals of the study should be established and not exceeded.

Pain perception in disorders of consciousness

The study of pain in disorders of consciousness poses very specific and challenging problems. Comatose, vegetative and minimally conscious patients can not, by definition, communicate their pain and possible suffering [31]. The goal of pain research in disorders of consciousness is to acquire new knowledge on the mechanisms, pathogenesis, diagnosis, and treatment of pain - this requires research in these non-communicative patient populations. At present, there is no evidence-based knowledge for guiding decisions regarding the management of pain in these patients [32]. We believe that much more research is needed in order to propose scientific based guidelines for the evaluation and treatment of pain in severely brain injured non-communicative patients. Such research, however, faces major ethical challenges. Some authors believe that noxious stimuli cannot be used in patients unable to give written informed consent. In clinical practice, however, the exploration of behavioral responses to nociceptive stimuli (for example, applying pressure to the fingernail bed with a pencil, applying pressure to the supra-orbital ridge or jaw angle, pinching the trapezium, or rubbing the sternum) is a clinical procedure routinely used to evaluate the level of consciousness. Reactivity to pain is part of widely used 'consciousness scales' such as the Glasgow Coma Scale [33] and Coma Recovery Scale-Revised [34].

Pain is a subjective 'first person' experience. The assessment of clinical or autonomic signs such as changes in heart rate, respiratory frequency, blood pressure, pupillary diameter or skin conductance have shown not be reliable indicators of conscious perception of pain (see studies done during general anesthesia [35]). Only two functional neuroimaging studies have explored brain processing linked to pain in the vegetative state and the results are contradictory. Laureys et al compared cerebral activation to high intensity electrical stimulation of the median nerve at the wrist in fifteen vegetative patients (mean time post-insult was one month; the cause of the coma was non-traumatic in twelve patients and traumatic in three) with fifteen healthy volunteers [18]. The results showed preserved and robust activation of subcortical (brainstem and thalamus) and cortical (primary somatosensory) areas in each and every patient. However, the residual cortical activation was like an island, disconnected from the rest of the 'pain matrix' - including the anterior cingulate cortex which is considered critical in the affective and cognitive processing of pain [36] - and the higher-order cortical network considered necessary for conscious processing [37]. Kassubek et al used similar methodology in seven vegetative patients (mean time post-insult was 1.5 years; the cause was anoxic injury in all cases) and confirmed activation in the primary somatosensory cortex but also – and surprisingly - in secondary somatosensory, insular and anterior cingulate cortices [38].

Some authors [32, 39], considering the current lack of scientific evidence, propose pain treatment in all vegetative and minimally conscious patients, but this view is not present in clinical guidelines [40]. The applicability of the World Health Organization three-step analgesic ladder [41] – applicable to the treatment of pain in palliative care – awaits validation in patients with disorders of consciousness. Pain control using such analgesic ladders are at present not incorporated in symptomatic, palliative or end-of-life care of these patients – for example, Terry Schiavo died without administration of strong opioids. The 'pros' and 'cons' of the use of analgesia in the severely brain damaged, unable to communicate possible perception of pain, is very complex.

Systematic use of narcotic analgesics in these patients might lead to undesired sedation and subsequent underestimation of the level of consciousness. On the other hand, some patients might experience hyperalgesia, requiring more aggressive analgesic therapy, and some patients might fail to show signs of consciousness and be misdiagnosed because the presence of severe pain might further decrease their already impaired cognitive functioning (Laureys et al, unpublished observations).

Concluding remarks

The results from functional neuroimaging studies should be shared with surrogates and, if possible, with patients, but great caution should be used when interpreting the clinical meaning and relevance for the individual patient. Because of the subject matter and the ethical implications of the results of neuroimaging studies with the risk of potential (mis)use for the agenda of social groups, some degree of caution of the interpretation of the data is in order. Conversely, withholding the findings from the scientific community is not recommended, because of concerns about this. In 1994 the position statement of the Multi-Society Task Force on PVS [40] concluded: 'Future PET studies should measure regional cerebral activity in response to visual, auditory, and somatosensory stimulation, to determine whether depressed cortical regions in patients in a PVS can be activated by peripheral sensory stimuli. A confirmation of the absence of evoked activity on the PET scan would help defend the assertion that these patients are completely unaware and insensate'. So far, functional neuroimaging studies have been limited to isolated case reports or small patient series (the largest series included only fifteen patients). Only international collaborative studies and the standardisation of validated experimental imaging protocols can bring the much-awaited evidence-based medicine, permitting an improvement in our care of patients with disorders of consciousness. We feel that caring for severely brain damaged patients represents such an immense humane, affective and social problem that it warrants further research to better understand the underlying cerebral dysfunction of their condition. Unconscious, minimally conscious, and locked-in patients are vulnerable and deserve special procedural protections but they are also vulnerable to being denied potential access to experimental neuroimaging protocols (that can only be undertaken on such patients) if the medical community fails to propose clear ethical guidelines regarding such research.

Key Learning Points

- Neuroimaging studies are redefining our understanding of residual brain function in disorders of consciousness such as the vegetative and minimally conscious states.
- Novel evidence suggests that minimally conscious state patients perceive pain and should receive adequate analgesia.
- More research is needed to validate prognostic neuroimaging markers for the vegetative state.
- An ethical framework for functional neuroimaging studies in disorders of consciousness is needed and is currently being discussed.

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