NeuroImage: Clinical 7 (2015) 588–597

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Review Article

Risk, diagnostic error, and the clinical science of consciousness

Andrew Peterson[a,b,*], Damian Cruse[a], Lorina Naci[a], Charles Weijer[a,b,c], Adrian M. Owen[a,b]

[a] Brain and Mind Institute, Western University, Natural Sciences Centre, London, Ontario N6A 5B7, Canada
[b] Rotman Institute of Philosophy, Western University, Stevenson Hall, London, Ontario N6A 5B7, Canada
[c] Department of Epidemiology and Biostatistics, Western University, Kresge Building, London, Ontario N6A 5B7, Canada

ARTICLE INFO

Article history:
Received 29 May 2014
Received in revised form 14 January 2015
Accepted 18 February 2015
Available online 20 February 2015

Keywords:
Disorders of consciousness
Vegetative state
Minimally conscious state
Unresponsive wakefulness syndrome
Brain injury
Neurology
Statistical methods
Active paradigm
Mental imagery
Ethics
Neuroethics

ABSTRACT

In recent years, a number of new neuroimaging techniques have detected covert awareness in some patients previously thought to be in a vegetative state/unresponsive wakefulness syndrome. This raises worries for patients, families, and physicians, as it indicates that the existing diagnostic error rate in this patient group is higher than assumed. Recent research on a subset of these techniques, called active paradigms, suggests that false positive and false negative findings may result from applying different statistical methods to patient data. Due to the nature of this research, these errors may be unavoidable, and may draw into question the use of active paradigms in the clinical setting. We argue that false positive and false negative findings carry particular moral risks, which may bear on investigators' decisions to use certain methods when independent means for estimating their clinical utility are absent. We review and critically analyze this methodological problem as it relates to both fMRI and EEG active paradigms. We conclude by drawing attention to three common clinical scenarios where the risk of diagnostic error may be most pronounced in this patient group.

Contents

1. Introduction

Recent research suggests that functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) offer diagnostic information ancillary to standard clinical examinations of seriously brain-injured patients. A subset of these techniques, called active

* Corresponding author at: Rotman Institute of Philosophy, Western University, Room 2150, Stevenson Hall, 1151 Richmond Avenue, London, Ontario N6A 5B8, Canada. Tel.: +1 519 661 2111 ext 80947.

http://dx.doi.org/10.1016/j.nicl.2015.02.008
2213-1582/

paradigms (Laureys and Schiff, 2012), utilizes a volitional mental task, such as mental imagery or selective attention, as a proxy for behavioral response to commands. Using these methods, investigators have revealed residual covert awareness in some patients once thought to be in a vegetative state — also referred to as unresponsive wakefulness syndrome (VS/UWS) (Laureys et al., 2010). Given the success of these techniques, clinical application may improve diagnostic accuracy (Giacino et al., 2014; Laureys et al., 2004; Owen, 2013). However, integrating active paradigms into the standard diagnostic protocol poses several difficult questions regarding clinical utility.

Neuroimaging and EEG assessment of brain injury requires powerful statistical tools for data analysis. Whether group-averaged brain activity is tested for statistical significance, individual subject neural anatomy is adapted to standard cortical maps, or regression filters are used to eliminate artifacts, statistical modeling is an invaluable tool for identifying statistically significant findings. However, which statistical methods ought to be used may remain unclear as the majority of techniques used to assess seriously brain-injured patients have not yet been model-tested nor extensively tested against one another (but see Stender et al., 2014).

Given this methodological difficulty, it is possible for different methods to produce conflicting results. Some results may be so heterogeneous that they engender empirically equivalent, yet mutually inconsistent, diagnoses. For example, when working from an identical data set, one task design or method of analysis may detect the presence of awareness in patients previously thought to be in a VS/UWS (Cruse et al., 2011), while another may fail to identify any statistically significant findings (Goldfine et al., 2013). Which results reflect the truth (i.e. whether a patient is aware or not) may remain an open question, as independent confirmation may be technically difficult or precluded on theoretical grounds.

In other domains of medicine, information garnered from clinical assessment may be corroborated with pathophysiological examination. Ideally, multiple sources of diagnostic information converge to form a conciliatory picture of the patient's condition. If diagnostic information is inconsistent, physicians have recourse to further tests that assess the truth of the patient's complaint. Diagnosis after serious brain injury with the aid of active paradigms presents a more complicated puzzle. Because the only accepted clinical procedure for assessing seriously brain-injured patients requires behavioral participation – either through self-report, command following, or functional object use (cf. Giacino et al., 2004) – confirming active paradigm findings by appealing to patients who are already known to be behaviorally unresponsive is problematic. This problem may be resolved by comparing results to other well-established prognostic and diagnostic evidence (Giacino et al., 2014; Young, 2009a). However, as previous research has demonstrated (e.g. Owen et al., 2006; Monti et al., 2010; Cruse et al., 2011; Naci and Owen, 2013; Fernández-Espejo and Owen, 2013; Gibson et al., 2014; Monti et al., 2015), some patients may satisfy all clinical criteria for the VS/UWS while consistently demonstrating awareness through active paradigms. Such patients deviate from standard diagnostic categories (Bruno et al., 2011) and challenge assumptions regarding the attribution of consciousness when conventional evidence is absent (Bayne and Hohwy, 2014; Shea and Bayne, 2010).

Given these methodological obstacles, how can investigators determine which methods ought to be used? Surely the relative accuracy of active paradigms may be determined as this research matures. Promising work on intrinsic cortical networks and their role in modulating consciousness (Demertzi et al., 2014, 2013a; Fernández-Espejo et al., 2012; Soddu et al., 2012; Vanhaudenhuyse et al., 2011, 2010, 2009) may provide a standard experimental benchmark, or gold standard, to validate new methods in the future. However, because this benchmark has not yet been established, investigators may appeal to a different rationale when attempting to identify which methods are most appropriate for clinical practice.

While remaining agnostic to the superiority of any method, we aim to make explicit the normative rationale for utilizing a particular fMRI or EEG active paradigm over others in the absence of a precise estimation of clinical utility. This, we argue, may be an effort to strike a balance between false positive and false negative diagnostic errors. Both false positive and false negative diagnoses in this patient group may have important implications for medical decision-making. These implications may include end-of-life issues (Demertzi et al., 2011), pain management (Boly et al., 2008; Demertzi et al., 2013b, 2009; Laureys et al., 2002; McQuillen et al., 1991; Schnakers and Zasler, 2007), and the concerns of family members (Graham et al., 2014; Jox et al., 2012; Kitzinger and Kitzinger, 2013; Kuehlmeyer et al., 2012). While problems of diagnostic error extend to all neuroimaging methods, we focus our discussion on fMRI and EEG active paradigms that are a source of current disagreement in the disorders of consciousness literature.

2. Assessing consciousness after serious brain injury

Consciousness, as defined in clinical neurology, consists of two components: wakefulness and awareness (Giacino et al., 2014; Laureys et al., 2004; Multi-society task force on PVS, 1994; Plum and Posner, 1982; Jennet and Plum, 1972). Wakefulness is demonstrated by behavioral or electrophysiological manifestations of arousal, while awareness is demonstrated by sustained, reproducible, voluntary behavior, or evidence of language comprehension and expression (Giacino et al., 2004, 2002; Multi-Society task force on PVS, 1994). For any given healthy conscious individual, wakefulness is often, if not always, accompanied by awareness.

Following a period of coma, some seriously brain injured patients may emerge into a VS/UWS or minimally consciousness state (Giacino et al., 2002; Jennet and Plum, 1972; Plum and Posner, 1982). Individuals diagnosed as VS/UWS exhibit semi-regular circadian rhythms, yet evidence no concomitant awareness of visual, auditory, tactile or noxious stimuli (Multi-society task force on PVS, 1994). The VS/UWS is therefore referred to as, "wakeful unresponsiveness" (Jennet and Plum, 1972). By contrast, minimally conscious patients demonstrate regular circadian rhythms with intermittent but reproducible evidence of awareness (Giacino et al., 2002). The fine-grained sub-categorizations of minimally conscious state^{+} and minimally conscious state^{-} have recently been introduced to parse out differences in the complexity of functional recovery (Bruno et al., 2013). Minimally conscious^{+} patients demonstrate higher-order behavioral responses, such as command following or intelligible verbalization, while minimally conscious^{-} patients exhibit lower order responses, such as visual pursuit, localization to noxious stimuli, or stimulus-driven cognition (Demertzi and Laureys, 2014). All such conditions are generally referred to as disorders of consciousness (DoC).

Current methods for diagnosing seriously brain-injured patients utilize a combination of clinical assessment, patient history, structural MRI, and resting state EEG. The primary diagnostic instrument, the clinical examination, probes a patient's preserved awareness through behavior. According to validated behavioral scales, visual fixation, command following, functional object use, localization to noxious stimuli, intelligible verbalization, or intentional communication are evidence of awareness (Shiel et al., 2010) (Giacino et al., 2004; Multi-society task force, 1994; Teasdale and Jennet, 1974). If a patient demonstrates any number of these behaviors in a predictable and task appropriate manner, it is inferred that the patient is, at least minimally, conscious (See Seel et al., 2010 for an extensive review).