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Evoked and event-related potentials in disorders of consciousness: A quantitative review

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ABSTRACT

Sixty-one publications about evoked and event-related potentials (EP and ERP, respectively) in patients with severe Disorders of Consciousness (DoC) were found and analyzed from a quantitative point of view. Most studies are strongly underpowered, resulting in very broad confidence intervals (CI). Results of such studies cannot be correctly interpreted, because, for example, CI > 1 (in terms of Cohen's *d*) indicate that the real effect may be very strong, very weak, or even opposite to the reported effect. Furthermore, strong negative correlations were obtained between sample size and effect size, indicating a possible publication bias. These correlations characterized not only the total data set, but also each thematically selected subset. The minimal criteria of a strong study to EP/ERP in DoC are proposed: at least 25 patients in each patient group; as reliable diagnosis as possible; the complete report of all methodological details and all details of results (including negative results); and the use of appropriate methods of data analysis. Only three of the detected 60 studies (5%) satisfy these criteria. The limitations of the current approach are also discussed.

1. Introduction

Evoked and event-related brain potentials (EP and ERP, respectively) are electrical brain responses strongly phase-locked to a particular event (mostly, a stimulus). Responses largely determined by the properties of this stimulus are usually called EP, or "exogenous responses". In contrast, responses largely determined by individual aspects of brain processing, or by the cognitive task in which the stimulus is embedded, are referred to as ERP or "endogenous responses" (Picton, 1988). Both EP and ERP should be distinguished from the background EEG oscillations, which characterize temporally extended states of cortical functioning (e.g., wakefulness and sleep), and from non-phase locked EEG responses such as event-related synchronization and desynchronization (e.g., Pfurtscheller & Aranibar, 1979).

The term Disorders of Consciousness (DoC) largely encompasses two diagnoses: vegetative state (VS) and minimally conscious state (MCS). The former has a long history of changing names, from apallic syndrome (Kretschmer, 1940) to unresponsive wakefulness syndrome (Laureys et al., 2010), none of which can be regarded as exact. In this paper the most broadly known term VS will be used, although this term can and has been criticized like any other.

In addition to VS and MCS, coma is the most severe DoC. However, pathophysiology and psychology of coma differ from those of VS and MCS. Coma is primarily characterized by the lack of wakefulness which, according to the most prevalent but not unquestioned view, is caused by organic or functional disturbance of the lower brain stem (Husain, 2006; Young, 2009). In contrast, VS and MCS patients are awake, but their subjective awareness is supposed to be lacking (VS) or severely disturbed (MCS). VS and MCS patients are not characterized by any lesion to the lower brain stem; rather, their injuries concern cortical gray matter, or white matter

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(diffuse axonal injury), or the thalamus (Adams, Graham, & Jennett, 2000; Kampfl et al., 1998; Newcombe et al., 2011).

The idea that EP and ERP would open the window into the mind of DoC patients emerged in the late 1980s (Reuter, Linke, & Kurthen, 1989). Larger studies were carried out in the 1990s and early 2000s (Kotchoubey et al., 2005; Witzke & Schönle, 1996). A considerable number of such studies, using a range of different paradigms and experimental designs, has been accumulated to the middle 2010s. But how reliable these studies are? What are their most common features? Which general conclusion(s) can be drawn from their results? A few years ago I (Kotchoubey, 2015) presented an informal, qualitative review of ERP studies performed in patients with severe chronic DoC. However, such informal reviews are always subjective. The aim of the present study was, therefore, to perform a quantitative analysis of the corresponding studies whose main conclusions can be expressed in bare numbers, thus minimizing the role of subjective judgment.

Together with other neurophysiological techniques such as fMRI, EP and ERP are expected to contribute to a better diagnostics of DoC, which is notoriously difficult and error-prone (Childs, Mercer, & Childs, 1993; Schnakers et al., 2009). Furthermore, EP and ERP measures were found to be reliable predictors of the emergence from coma (Daltrozzo, Wioland, Mutschler, & Kotchoubey, 2007; Fischer, Luaute, Adeleine, & Morlet, 2004). Because VS and MCS are chronic conditions, in contrast to the acute coma, these measures can also be investigated in VS and MCS with the hope to reach a more exact prognosis of their long-term outcome.

2. Methods

A search performed using the terms (EEG OR Evoked Potentials OR Event-Related Potentials OR P300 OR MMN OR N400) AND (Disorders of Consciousness OR Vegetative State OR Unresponsive Wakefulness Syndrome OR Minimally Conscious State) yielded, on the first stage, a total of 2275 references. After reading the corresponding abstracts, 996 results were rejected as irrelevant (e.g., the authors did not study any DoC patients, but their data had some implications for DoC, or might be put in some relation to DoC). At the next step, the following publications were removed: (1) double or triple indexed articles; (2) studies of coma that included neither VS nor MCS; (3) studies in which other kinds of EEG activity were recorded, but not phase-locked evoked activity; (4) review articles (e.g., Koch, Massimini, Boly, & Tononi, 2016) and editorials; (5) articles discussing methodological (e.g., Kotchoubey et al., 2013) and ethical aspects of ERP application (e.g., Weijer et al., 2014); (6) studies whose main experimental results were better reported in other publications (Balconi, 2011; Kotchoubey, Lang, Bostanov, & Birbaumer, 2002; Neumann & Kotchoubey, 2004; Witzke & Schönle, 1996); (7) studies that mention patients in vegetative state, but the description of the patients' behavior contradicts this diagnosis[1] (Marosi et al., 1993; Pan et al., 2014; Y. Li et al., 2015); and (8) articles reporting only motor evoked potentials (MEP: Bagnato et al., 2012; Lapitskaya et al., 2013; Pistoia, Sacco, Carolei, & Sarà, 2013). The reason for this latter exclusion is that despite the similar name the brain mechanisms of MEP are very different from that of sensory EP and long-latency "cognitive" ERP.

The final list contained sixty one experimental studies to EP and ERP in patients with the diagnoses (persistent) vegetative state (VS), apallic syndrome, unresponsive wakefulness syndrome (UWS), "prolonged postcoma unawareness", or minimally conscious state (MCS), published in English between 1989 and 2015. The major aim of these studies was description of ERP phenomena in DoC (15 papers, or 25%), a comparison between the diagnoses VS/UWS and MCS (38, or 62%), a comparison between the two subtypes of MCS (Bruno, Vanhaudenhuyse, Thibaut, Moonen, & Laureys, 2011), namely MCS − and MCS + (4 studies, or 7%), exploration of the role of ERPs in outcome prediction (17, or 28%), investigation of the reliability of ERP measures (6, or 10%), or examination of the effect of an intervention (12, or 20%). The sum is larger than 100% because many studies pursued several important goals. In the fourth column of the Table the main aims of each study are indicated.

2.1. Calculation of effect size

As far as possible, results of the studies were converted into Cohen's *d*. The calculation was obvious in the (rare) cases in which *t*-tests and group sizes, or mean values, standard deviations (or standard errors) and group sizes were published (Cohen, 1988). For converting correlation coefficients and odds ratio, the methods proposed by Borenstein, Hedges, Higgins, and Rothstein (2009) were used. Cohen's (1998) ideas were employed for recalculation of ANOVA results with two groups, as well as the results of the non-parametric tests of Wilcoxon and Mann-Whitney. Most frequently, the data were presented as frequencies of occurrence of some ERP effect (e.g., P300) in two predefined groups (e.g., VS versus MCS; or patients who later improved versus those who remained in the same condition). These data were converted into Cohen's *d* following Elis (2010).

It should be said that in some cases only approximate estimations of the effect size could be given. First, some authors reported only the names of the used statistical tests and *p*-values, but not the corresponding statistics (i.e., neither *t*-, nor *F*-, nor χ^2-values). Further, the recalculation of frequencies (Elis, 2010) is based on the χ^2-distribution, which may not be exact when patient groups are very small, which is frequently the case as will be seen below. Furthermore, most methods of conversion into Cohen's *d* presume normal distribution, which was hardly to test in studies with small sample sizes.

[1] Of course, the studies are included in which the neurophysiological data contradicted the clinical diagnosis. In fact neurophysiological methods are expected to provide new information that can partially contradict to clinical data. These studies are, therefore, separated from those in which a declared clinical diagnosis contradicted to behavioral criteria of the diagnosis, e.g., when VS patients were able to perceive complex visual stimuli, although this ability presumes full control of gaze movements.