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Research report

Unravelling motor networks in patients with chronic disorders of consciousness: A promising minimally invasive approach

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ABSTRACT

Behavioral responsiveness and awareness levels correlate with the degree of functional connectivity within cortical-thalamocortical networks, whose breakdown accounts for chronic disorders of consciousness (DOC). Our study was aimed at assessing the role of the primary motor area (M1) and premotor-M1 circuitry dysfunction in motor output deterioration in minimally conscious state (MCS) and unresponsive wakefulness syndrome (UWS) patients. As a control group, we included a healthy subject (HC) sample in the study. We evaluated the effects of different types of transcranial magnetic stimuli over M1 by recording post-stimulus time histogram (PSTH), which includes a series of peaks of unit firing activity that match with D and I-waves, characterizing the descending corticospinal volleys evoked by transcranial magnetic stimuli. As compared to HC, DOC patients showed a dysfunction of intra-M1 and premotor-M1 circuits, which correlated with the Coma Recovery Scale-Revised scorings. Nonetheless, one UWS patient showed a partially preserved premotor-M1 circuitry, paralleled by a severe intra-M1 circuitry dysfunction. Our data suggest that motor unresponsiveness in some DOC patients may be due to a pure motor output failure, as in the functional locked-in syndrome (fLIS), rather than to a premotor-motor connectivity impairment, which instead characterizes MCS and UWS.

1. Introduction

The presence of purposeful behavioral responses characterizes Minimally Conscious State (MCS) patients, whereas no more than reflex responses are detectable in Unresponsive Wakefulness Syndrome (UWS) individuals (Laureys et al., 2010; Giacino et al., 2012). Behavioral responsiveness and awareness levels correlate with the degree of functional connectivity within cortical-thalamo-cortical networks, whose breakdown accounts for such chronic disorders of consciousness (DOC) (Laureys, 2005; Sarasso et al., 2014). Of note, some DOC patients can show only minimal voluntary movement so that non-invasive brain stimulation, including the transcranial magnetic stimulation (TMS), is a useful way to demonstrate abnormalities of fast corticospinal axons in these patients. Indeed, only some DOC patients have a severe dysfunction of the fast corticospinal neurons although most of them show tetraplegia, decorticate or decerebrate posture (Inghilleri et al., 1994), and a partially preserved cortical-thalamo-cortical connectivity. It has been proposed that these individuals should be labeled as functional locked-in syndrome (fLIS) rather than "UWS with hidden consciousness" or "covert MCS" (Bruno et al., 2011; Formisano et al., 2011a, 2011b, 2013; Di Perri et al., 2014; Gosseries et al., 2014). To this end, we have recently shown that motor unresponsiveness in some DOC patients may be independent of the premotor-primary motor area (M1) circuitry impairment and the degree of cortico-spinal tract deterioration (Naro et al., 2015). In fact, DOC patients with similar premotor-M1 functionality and cortico-spinal tract impairment may show a different level of behavioral responsiveness (Naro et al., 2015). Therefore, these DOC patients may be misdiagnosed when using the Coma Recovery Scale-Revised (CRS-R). The latter represents a reliable tool to identify the awareness level that specifically correlates with the wide connectivity breakdown (Giacino et al., 2004; Kalmar and Giacino, 2005; Gerrard et al., 2014; Lant et al., 2015). We hypothesized that motor unresponsiveness in some DOC patients might be due to an intra-M1 rather than a premotor-M1 dysfunction.

Long since, motor cortex physiology and motor output generation have been investigated through electrical (Merton and Morton, 1980) and magnetic (Barker et al., 1985) brain stimulation methods. Each type of electric and TMS pulses (according to coil design and current flow characteristics) can entrain different subsets of cortical networks within M1 and among premotor areas and M1. In fact, adequate stimuli can generate temporally

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synchronized descending waves in the corticospinal tract. These waves can be recorded either invasively (e.g. at spinal level) or non-/minimally-invasively through single motor unit, F-wave, and H-reflex recording (Boyd et al., 1986; Di Lazzaro and Ziemann, 2013; Berardelli et al., 2002; Day et al., 1989; Mercuri et al., 1996; Mazzocchio and Rossi, 1996). The lateromedial (LM) coil orientation directly activates the axons of fast-conducting corticospinal neurons (thus evoking a D-wave), when using a figure-of-eight coil, near-threshold intensities, and recording descending volleys at spinal level (Di Lazzaro et al., 1998a, 1998b, 1999, 2000, 2001, 2002, 2004, 2006, 2008, 2010, 2012; Di Lazzaro and Ziemann, 2013; Di Lazzaro and Rothwell, 2014; Sakai et al., 1997). The D-Wave is associated with an I_1-wave and late I-waves when increasing the stimulation intensity. The former depends on an indirect trans-synaptic activation of monosynaptic interneuron-corticospinal neuron units; the latter may originate from the high-frequency repetitive discharge of corticospinal neurons induced by reverberating activation of highly connected excitatory interneurons. The posterior-anterior (PA) orientation at low intensity evokes an I_1-wave, at higher intensity late I-waves and, after that, a D-wave with a further increase in stimulation intensity. On the other hand, the anterior-posterior (AP) orientation at a near-threshold stimulation recruits more complex interneuron-corticospinal neuron units (probably including premotor areas) that evoke late I-waves showing slightly different peak latencies in comparison to PA stimulation (Di Lazzaro and Ziemann, 2013). The temporal summation of these waves at spinal level generates the related motor evoked potential (MEP), with growing latency and a non-negligible inter-individual variability (Hamada et al., 2013).

Notably, the non-invasive techniques primarily assess the effects of corticospinal neurons on the excitability of spinal motorneurons, but these are unable to distinguish between D and I waves at spinal level (Ziemann et al., 1998). Nonetheless, valuable studies showed a correspondence between post-stimulus time histogram (PSTH) peaks recorded through single motor unit recording and the peaks of D and I-waves and the inter-I-wave intervals (Day et al., 1987a, 1987b, 1989).

Therefore, our study was aimed at assessing the role of intra-M1 circuitry dysfunction in determining the motor output deterioration in DOC individuals. To this end, we evaluated the effects of different types of magnetic stimuli over M1 on PSTH. We also applied TMS paired pulse protocol, which can be precisely timed at inter-stimulus intervals that are compatible with the inter-I-waves intervals (~1.5 ms) (Tokimura et al., 1996; Ziemann et al., 1996, 1998; Ziemann and Rothwell, 2000).

2. Results

TMS pulses elicited up to four peaks of increased firing probability with growing latency in the PSTH of single motor units. Such peaks had specific latencies according to the coil orientation employed, and were labeled as P_0, P_1, P_2, and P_3 (Fig. 1). Peak distribution was preserved in MCS subjects as compared to HC individuals, and was profoundly abnormal in UWS patients, but one (n.4). The inter-peak interval between P_0 and P_1 was of ~1.1 ms, whereas that between P_2 and P_3 was of ~1.5 ms in HC individuals (similarly to the intervals among D, I_1, and late-I waves). These intervals were increased in MCS patients, in parallel to CRS-R scores (but without significant differences between each

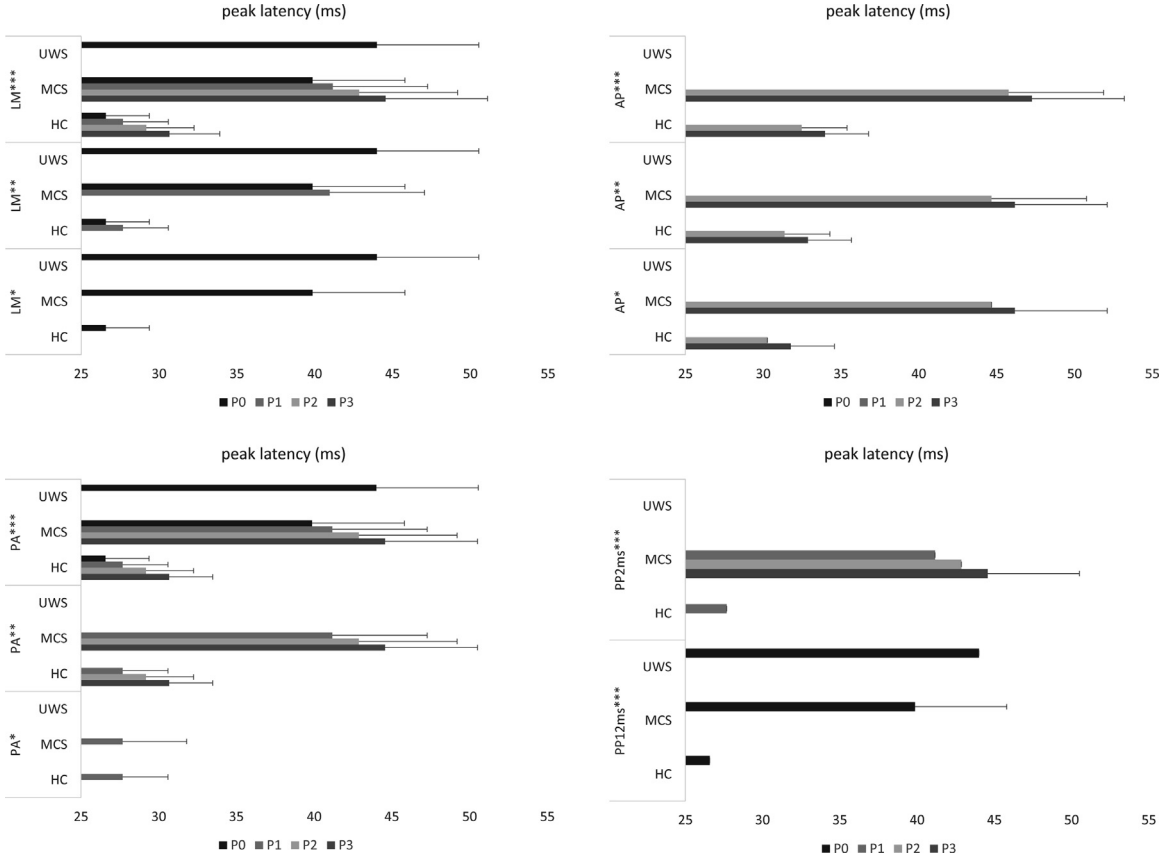

Fig. 1. Shows the mean peak latency (± SD) of each P peak (P_0, P_1, P_2, and P_3) following the different types of single (latero-medial, LM, anterio-posterior, AP, and postero-anterior, PA) and paired-pulse TMS (PP_{2ms} and PP_{12ms}) at different intensity of the test magnetic stimulus (* at resting motor threshold -RMT-,** at 110% RMT, and *** at 120% RMT). UWS patients mainly showed the presence of P_0 peaks, whereas the other peaks were not elicited. Instead, MCS patients showed a better preservation of peak patterns in comparison to UWS individuals, but with increased latencies as compared to HC subjects. PP_{12ms} did not elicit any peak.