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LETTER TO THE EDITORS

Exploring the pathophysiology of Mal de Debarquement

Brian C. Clark · Adam Quick

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Dear Sirs,

Mal de debarquement syndrome (MdDS) is a disorder of perceived motion most often occurring following a cruise. We report findings from a patient with MdDS who underwent a transcranial magnetic stimulation protocol to quantify cortical excitability. These data were compared to those from 40 controls. The patient with MdDS exhibited high levels of intracortical facilitation. These findings will provide insight on the pathophysiology of MdDS, and will help guide future work on this rare condition.

Mal de debarquement syndrome (MdDS) occurs when habituation to passive background movement becomes resistant to readaptation to stable conditions and results in a phantom perception of self-motion. MdDS typically disappears quickly after return to stable ground; however, in rare instances the symptoms may persist for months to years (persistent MdDS). While the etiology of persistent MdDS is poorly understood, it does not appear to originate from vestibular dysfunction as vestibular tests are normal and the symptoms do not respond to vestibular therapy [2]. Rather, MdDS appears to be a disorder of neuroplasticity and sensory rearrangement [2]. To our knowledge, there have been no studies examining the neurophysiologic characteristics of the disorder. In this case study we report findings from a patient with persistent MdDS who underwent an extensive transcranial magnetic stimulation (TMS) protocol to quantify motor cortical excitability. Specifically, we quantified the duration of the corticospinal silent period using single-pulse TMS. The silent period is observed when a subject performs a slight contraction and a single TMS stimulus is applied to the motor cortex (Fig. 1a). Additionally, we quantified intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI) using paired-pulse TMS. Paired-pulse TMS combines a conditioning stimulus (CP) with a test stimulus (TP) at different interstimulus intervals, and the relative change in motor evoked potential (MEP) size is expressed relative to an unconditioned test pulse. At a short interstimulus interval of 3 ms, the CP inhibits the MEP in comparison to the TP only (SICI), whereas at a longer interstimulus intervals of 15 ms it facilitates the MEP (ICF) (Fig. 1b).

The patient was a 63-year-old female (160.2 cm, 77.3 kg) who complained of sensations of unsteadiness and a feeling of the floor moving under her feet after disembarking from a 7-day cruise ~3.5 years ago (3/2007). She reported having to regularly reach out to steady herself against stationary objects, and that MdDS had greatly impacted her quality of life (subjective scoring of six out of ten on a visual analog scale for the impact of MdDS on her quality of life). Several other hallmark features of MdDS were present including mild cognitive slowing and transient improvement in symptoms with re-exposure to passive movement [2]. Physical examination was unremarkable. Diagnostic testing including sural sensory and peroneal motor conduction studies, needle EMG, and MRI of the brain were all normal. Additionally, the patient had unremarkable findings on Dix-Hallpike testing and the caloric reflex test. The patient did not have migraine or other primary headache as defined by the International

B. C. Clark (✉)
Department of Biomedical Sciences,
Ohio Musculoskeletal and Neurological Institute (OMNI),
Ohio University, 211 Irvine Hall, Athens, OH 45701, USA
e-mail: clarkb2@ohio.edu

A. Quick
Department of Neurology, The Ohio State University,
Columbus, OH, USA

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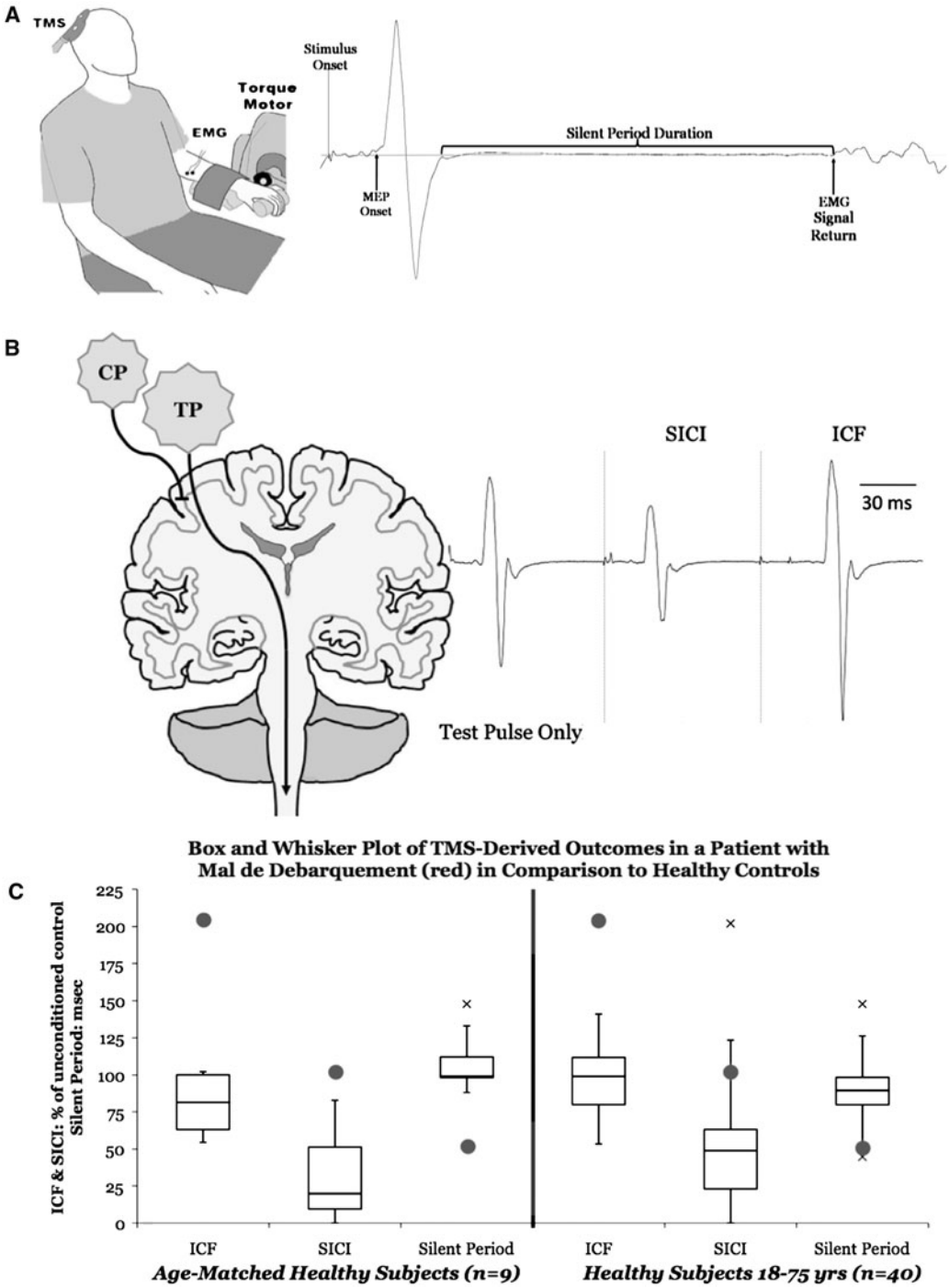

Fig. 1 Intracortical properties were assessed using transcranial magnetic stimulation (*TMS*) (**a**, **b**) in healthy control subjects as well as in a case study patient with persistent Mal de debarquement syndrome (*MdDS*) (**c**). **a** We quantified the duration of the cortico-spinal silent period during a 15% of maximal strength contraction. **b** We quantified intracortical facilitation (*ICF*) and short-interval intracortical inhibition (*SICI*) using paired-pulse TMS. **c** Comparison of the MdDS case patient (shown in *filled circles*) in relation to nine healthy older adults between 60 and 75 years (*left panel*), and 40 healthy adults ranging in age from 18 to 75 years (*right panel*). The *box* and *whisker plot* illustrates the group means for the control subjects as well as the interquartile range. The 'whiskers' are set to 1.5 times above and below the interquartile range, respectively. The patient with MdDS exhibited elevated levels of ICF that were outside the 'normal' range for both age-group cohorts. Additionally, they exhibited low levels of SICI (note that by convention a low level of SICI is indicated by a high numeric value on the graph) and a shorter silent period in relation to age-matched controls; however, these outcomes fell within the 1.5 times interquartile range when younger subjects were included in the analysis. Control subjects that are outside these ranges are shown as outliers (indicated by *cross symbol*). For clarity only the minimum and maximum outliers are shown

Classification of Headache Disorders. The patient was taking fluoxetine (which predated the development of MdDS), but did not report current depression. Serologic studies were unremarkable—except for vitamin B_{12} deficiency. Following the restoration of vitamin B_{12} without a concomitant improvement in symptoms, the patient was diagnosed with persistent MdDS based on her characteristic clinical history. She was not taking benzodiazepines to treat her persistent MdDS.

The TMS protocol was identical to our previous descriptions [4, 7]. In brief, electromyographic (EMG) signals were recorded from the flexor carpii radialis and single-pulse TMS was used to quantify the silent period duration, and paired-pulse TMS was used to quantify intracortical facilitation (ICF) and short-interval intracortical inhibition (SICI). These case data were compared to data from nine healthy, age-matched controls (60–75 years), as well as to 40 controls ranging 18–75 years. Data from the controls were plotted as a box and whisker chart with the ends of the whisker set at 1.5 × the interquartile range to examine whether the MdDS case was an outlier.

The patient with MdDS exhibited elevated levels of ICF (Fig. 1). Additionally, she had low levels of SICI and a shorter silent period in relation to age-matched controls; however, these outcomes fell within the interquartile range when younger subjects were included in the analysis (Fig. 1c).

While data from a single case must be interpreted cautiously, these findings suggest that MdDS may result in alterations in the balance of intracortical properties towards hyperexcitability. Alternatively, individuals with an inherent degree of hyperexcitability may be more susceptible to the development of MdDS. In one study, development of MdDS-like symptoms following an initial motion triggered episode was higher in patients with a history of migraine and there is evidence that migraine is associated with occipital cortical hyperexcitability to TMS [1, 5]. ICF is generally thought to be mediated by excitatory glutamatergic interneurons and NMDA receptors [8], while SICI is mediated by GABA type A receptors [6]. Interestingly, the observation of increased ICF in our MdDS patient is consistent with the finding that patients with MdDS report a moderate improvement in symptoms with benzodiazepines [3], which mechanistically functions to reduce ICF [8].

In summary, we observed that our patient with persistent MdDS exhibited high levels of intracortical facilitation as measured with paired-pulse TMS. These findings will provide insight on the pathophysiology of MdDS, and will help guide future work on this rare condition.

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