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Neurophysiological features of motor cortex excitability and plasticity in Subcortical Ischemic Vascular Dementia: A TMS mapping study

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HIGHLIGHTS

- Motor cortex has enhanced excitability in AD and SIVD patients with respect to control subjects and it is plastically rearranged, without significant differences between the two demented groups.
- In the whole sample of subjects examined a significant direct correlation between parameters associated to cortical excitability and those associated to cortical plasticity is evident.
- Common compensatory mechanisms may act in different kind of dementing diseases.

ABSTRACT

Objective: To evaluate neurophysiological features of M1 excitability and plasticity in Subcortical Ischemic Vascular Dementia (SIVD), by means of a TMS mapping study.
Methods: Seven SIVD and nine AD patients, along with nine control subjects were tested. The M1 excitability was studied by resting thresholds, area and volume of active cortical sites for forearm and hand's examined muscles. For M1 plasticity, coordinates of the hot-spot and the center of gravity (CoG) were evaluated. The correlation between the degree of hyperexcitability and the amount of M1 plastic rearrangement was also calculated.
Results: Multivariate analysis of excitability measures demonstrated similarly enhanced cortical excitability in AD and SIVD patients with respect to controls. SIVD patients showed a medial and frontal shift of CoG from the hot-spot, not statistically different from that observed in AD. A significant direct correlation was seen between parameters related to cortical excitability and those related to cortical plasticity.
Conclusions: The results suggest the existence of common compensatory mechanisms in different kind of dementing diseases supporting the idea that cortical hyperexcitability can promote cortical plasticity.
Significance: This study characterizes neurophysiological features of motor cortex excitability and plasticity in SIVD, providing new insights on the correlation between cortical excitability and plasticity.

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1. Introduction

Motor cortex hyperexcitability is a well defined neurophysiological feature of Alzheimer's disease (AD). It is evident already in the early stages of the disease (Pepin et al., 1999; Alagona et al., 2001; Ferreri et al., 2003, 2011; Rossini et al., 2013), and probably related to disease severity and progression (Ferreri et al., 2011; Khedr et al., 2011; Rossini et al., 2013).

About 10 years ago, along with evidence of a global increase in motor cortex excitability, also a frontal and medial shift of the motor cortical output's center of gravity (CoG) was demonstrated in AD patients without motor deficits by means of transcranial magnetic stimulation (TMS) mapping technique. These findings suggested functional reorganization and plasticity compensating for disease progression at least in its early stages (Ferreri et al., 2003). In the last decade several other researchers confirmed these results, formulating interesting hypothesis and shedding light over the possible mechanisms sustaining these phenomena (Di Lazzaro et al., 2003, 2004 Di Lazzaro et al., 2006; Pierantozzi et al., 2004; Nardone et al., 2006 Nardone et al., 2008; Martorana et al., 2009; Pennisi et al., 2011a; Khedr et al., 2011; Hoeppner et al., 2012).

Vascular dementia (VaD) is considered to be the second most common form of dementia after AD. It results from different types of lesions of vascular origin, including subcortical ischemic small-vessel disease as well as cortical infarcts, ischemic–hypoperfusive or hemorrhagic lesions leading to a variety of clinical phenotypes. Nevertheless, the importance of VaD was overlooked the past century. In recent years new interest has been revived because vascular lesions have been continuously noted to be substantial contributors to the development of dementia by themselves or by their synergetic effects on the pathogenesis associated with AD (Fratiglioni et al., 2000; Roh and Lee, 2014). The Subcortical Ischemic Vascular Dementia (SIVD) represents an important and homogeneous subtype of VaD and it is of particular interest as the relatively slow progression of symptoms and clinical manifestations of the disease often make the differentiation of it from AD difficult (Roh and Lee, 2014). It is related to small vessel disease, which produces either arteriolar occlusion and lacunes or widespread incomplete infarction of white matter due to critical stenosis of medullary arterioles and hypoperfusion (Binswanger's disease). SIVD represents the major cause of vascular cognitive impairment and dementia (Erkinjuntti et al., 2000; Romàn et al., 1993, 2002) thus it is worthwhile to compare SIVD to AD in terms of the pathophysiological mechanisms other than clinical manifestations, bio markers and treatment options (Pantoni, 2010; Roh and Lee, 2014).

To date, only few studies investigating motor cortex excitability in SIVD have been published and in none of them the TMS mapping technique was used (for a comprehensive review see Pennisi et al., 2011b). All these studies (Alagona et al., 2004; Di Lazzaro et al., 2008; Pennisi et al., 2010) but one (Nardone et al., 2008) demonstrated a clear pattern of global increased cortical excitability and, even though a plastic reorganization of motor cortical areas similar to that occurring in AD was suggested (Pennisi et al., 2011b), it has not been demonstrated yet.

The aim of this investigation was to test and characterize neurophysiological features of motor cortex excitability and plasticity in SIVD patients by means of a motor cortex TMS mapping study.

2. Subjects and methods

Data from a representative group of 9 AD patients (9 women; aged 74.3 ± 7.7 years; MMSE 21.1 ± 2.0) and 9 healthy subjects (3 men and 6 women; aged 75.0 ± 15.5 years; MMSE 28.2 ± 1.9) from the previously cited article of our group were used (Ferreri et al., 2003). A new group composed by seven SIVD patients (2 men and 5 women; aged 78.1 ± 4.3 years; MMSE 20 ± 4) is hereby evaluated for comparative analysis.

AD patients were recruited according to the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Dementias Association criteria for a diagnosis of possible or probable AD (McKhann et al., 1984). No clinical evidence of motor disturbances was found in any of the patients after detailed neurological evaluation. SIVD patients satisfied modified clinical and brain imaging criteria for probable diagnosis of VaD of the NINDS–AIREN criteria (Romàn et al., 1993; Erkinjuntti et al., 2000) and fitted with the more recent proposed clinical criteria for the diagnosis of SIVD (Romàn et al., 2002). In some SIVD patients, the clinical examination showed some mild neurological signs such as dysarthria, mild apraxic gait and inconstant dysphagia; however, patients with reduced hand or upper limb motor strength were not included to the study. Hand motor strength was evaluated by means of a rating scale derived from the Medical Research Council (MRC) scale.

To characterize the symptoms of Alzheimer's and vascular dementia patients underwent neuropsychological testing (Looi and Sachdev, 1999; Gainotti et al., 2001; Folstein et al., 1975; Dal Forno et al., 2006), including (I) The mental deterioration battery (MDB) consisting of 7 parts: the Rey's 15 words immediate and delayed recall, word fluency, sentence construction, Raven's progressive matrices 47, immediate visual memory, freehand copying of drawings and copying drawings with landmarks; (II) The Prose memory test; (III) The Corsi block-tapping task; (IV) The mini mental state examination (MMSE) scores; and (V) The trail-making test part A and B. They also underwent a functional evaluation (Instrumental Activity of Daily Living scale; Lawton and Brody, 1969), evaluation of affective symptoms (Burke et al., 1989), magnetic resonance imaging (MRI) and laboratory screening to rule out other causes of dementia than AD or SIVD.

Neither the patients nor the controls had ever suffered from epilepsy or were taking drugs, which are known to influence corticospinal excitability. None of the demented patients was medicated with acetylcholinesterase inhibitors. The international safety standards for TMS were taken into account, patients with metallic prosthesis or fragments in the cranial and thoracic districts, tinnitus, previous retinal detachment, brain hemorrhage, clinical evidence of motor deficits were not accepted to the study (Rossini et al., 1994, 1999; Rossi et al., 2009). The study was approved by the local ethical committee and subjects and caregivers provided informed written consent.

The TMS procedure was performed with the subject lying supine on a bed to facilitate complete muscular relaxation. Two muscles, namely the extensor digitorum communis (ECD) and abductor digiti minimi (ADM), which are known to share the same motor representation area and motor threshold during scalp TMS (Rossini et al., 1994, 2010), were examined (from each arm) bilaterally via Ag/AgCl disks filled with conductive jelly in a belly/tendon montage. Skin/electrode resistances were less than 10 kOhms. Recording of electromyography was conducted using PHASIS equipment (4 channels; Esaote-Biomedica) via 1–2000 Hz filter setting, and a post-stimulus analysis time of 50 ms with a 5 kHz sampling rate. TMS was conducted using MAGSTIM 200 equipment (Magstim Company Limited, Whitland, South West Wales) and an eight-shaped coil with an inner diameter of 70 mm for each wing. To locate the stimulation spots on the scalp the subjects wear a tight elastic cap, which was fixed according to scalp anatomical landmarks (nasion, inion, meatal foramina and vertex, where Cz was located using the international 10–20 system). A hypothetical motor area was mapped with TMS at supra-threshold intensity (approximately 80% of maximal stimulator output) by averaging approximately four stimuli each at various stimulation points. The stimulation location with the highest muscle response was