TRANSCRANIAL MAGNETIC STIMULATION IN VASCULAR COGNITIVE IMPAIRMENT

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[La stimolazione magnetica transcranica nel deterioramento cognitivo vascolare]

ABSTRACT

Transcranial magnetic stimulation (TMS) is ever more used in cognitive impairment, in order to identify alterations in cortical excitability. This review describes the latest updates on the use of TMS in vascular dementia (VaD) and in Vascular Cognitive Impairment-No Dementia (VCI-ND).

Key words: *Magnetic transcranial stimulation, TMS, dementia, vascular dementia, cerebrovascular disease.*

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Transcranial magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a method that exploits magnetic fields varying in time, emitted by a flow of alternating current, to depolarize neuronal membrane and induce a flow of current which is proportional to the rate of variation of magnetic field. The effects of TMS in fact depend on electric field induced in nervous tissue and not by a direct effect of magnetic field. The magnetic fields are produced by coils. There are different modes of stimulation:

Single pulse

Allows to evaluate Motor Evoked Potential (MEP), of which we study latency and amplitude, elicited both centrally (at level of cortex) and peripherally (at level of nerve roots), and from which it derives Central Motor Conduction Time (CMCT), parameter increased in different conditions such as demyelinating disease. Other parameters studied are motor threshold at rest and in action (RMT and AMT), which express the level of cortical excitability. Finally, we evaluate cortical silent period (CSP), expression of intracortical inhibitory phenomena.

Double pulse

Two stimulators can work in parallel to achieve stimuli of greater intensity or, above all, to give two distinct stimuli and evaluate effects of the first on MEP elicited by the second. This method it is named TMS double pulse (paired pulse or ppTMS).

According to the protocol proposed by Rothwell et al.[1], most used, it is given an initial stimulus, called "conditioning", intensity subthreshold motor and a second, called stimulus "test", suprathreshold motor. The crucial element is InterStimulus Interval (ISI) between two stimuli. In healthy subjects, a very short interval (1-6 ms) or very long (50-200 ms) would result in an inhibitory effect (Intra-Cortical Inhibition, ICI); conversely, for intermediate values (8-20 ms) there will be a facilitation (IntraCortical Facilitation, ICF). The interpretation of these phenomena is still controver-

sial. While ICI would be attributable to GABA-A receptors and have a predominantly cortical origin, ICF would derive in cerebral cortex by glutamatergic interneuronal way (with the involvement of the NMDA receptor).

The applications of paired pulse are steadily increasing because it is an elegant and non-invasive method for the study of alterations in cortical excitability and neurophysiological profile of various pathological conditions. A reduction of inhibitory function in motor cortex (with consequent cortical hyperexcitability) seems to be not specific alteration of many neurological and psychiatric disorders, the origin of which may also falls outside primary motor cortex.

Repetitive stimulation (rTMS)

With rTMS is possible both activate certain neuronal populations and modulate their activity for more or less prolonged time. This leads to high potential in therapeutic area both of neurological disorders (m. Parkinson's disease, dystonia) and psychiatric[2,3] (drug-resistant major depression, obsessive-compulsive disorder, auditory hallucinations in schizophrenic patients).

Uses in vascular cognitive impairment

Thanks to its enormous potential, development of technological knowledge and improvement in experimental procedures used, TMS has now become a technique increasingly used in clinical neurology and psychiatry. In this work we will focus exclusively on the use in vascular cognitive impairment.

TMS was applied to study changes of excitability of motor cortex in patients with cognitive disorders such as Alzheimer's dementia (AD), frontotemporal dementia[4], dementia with Lewy bodies[5] and vascular dementia (VaD)[6].

Several studies[7,8,9,10,11,12] have investigated changes of cortical excitability in AD, producing results not always concordant. Most researchers lean towards reduction of rMT, which would indicate the increase of excitability of motor cortex, and a mild and variable reduction of ICI.

Unlike AD, few studies have investigated changes of cortical excitability on VaD. In 2004, Alagona et al.[12] conducted a study over 20 patients with subcortical ischemic vascular dementia (SIVD), 20 with AD and 20 control subjects. Evaluating the rMT using TMS single pulse, researchers have detected a reduction both SIVD group and in AD one, compared to controls. Reduction was greater in SIVD than in AD.

Di Lazzaro et al. study[9] (2008) have monitored 12 patients with imaging demonstration of subcortical vascular disease (SVD), 12 with AD and 12 healthy subjects. It was attested, even in this case, a significant reduction of rMT in both SVD and AD, without particular differences between two groups. In a small group of patients with VaD was significantly reduced ICI, probably due to the involvement of GABAergic circuits. Both this study and the previous one attribute the increased cortical excitability in ischemic damage of some subcortical circuits.

Nardone et al.[19] study, which monitored rMT, CSP, ICI and ICF in a group with SVD and in a control group, did not find significant differences.

In a study of 2010, Pennisi et al.[13] concluded that cortical hyperexcitability, evaluated by monitoring rMT, is a prominent finding in states of overt VaD. Comparing a group with SIVD, one with subcortical ischemic disease without dementia (SIDWD) and a control group, it was found a value of rMT markedly reduced in patients with SIVD than those with SIDWD and with healthy subjects. Therefore, it was possible to deduce such as cerebrovascular lesions do not always determine a reduction of rMT. Site and extent of injury (evaluated with neuroimaging) appear to correlate only partially with excitability alterations, although it is now recognized that white matter lesions (WML) have negative effects on cognition. LADIS study[14], in this context, showed how ultrastructural abnormalities affect cognitive decline. Silbert et al.[15] have shown how volume of white matter hyperintensity (WMH) is associated with a reduction of rMT. Ihara et al.[16] have recently demonstrated how in individuals with dementia and leukoaraiosis there is a bilateral reduction of benzodiazepine receptors in many areas, as expression of damage to cortical-subcortical circuits.

Despite conflicting data, the hypothesis that in VaD, as well as in AD, cortical excitability is increased, is now widely accepted[12,13,17,18]. The interpretation of this finding is still debated. One of the most credible hypothesis is that this is a compensatory mechanism of reorganization that involves glutamatergic neurotransmission, similar to what happens in AD[19,20]. This would include an imbalance between NMDA and non-NMDA transmis-

sion in favor of the second[20]. The excitotoxicity would be responsible for an increase in brain damage; in fact it is the leading cause of neuronal loss after hypoxic-ischemic[21]. The ischemia would enhance glutamatergic transmission both increasing the release of glutamate from the presynaptic membranes and both reducing its reuptake, with consequent accumulation in synapse[22].

Another hypothesis considers that damage will occur on cholinergic pathways, in a manner similar to what happens in AD[23,24]. Many patients with VaD have, in fact, shown alterations of short afferent inhibition (SAI), a parameter related to cholinergic inhibitory circuits, often reduced in subjects with AD. However, finding of reduced level of SAI also in VaD, may be due to a significant number of mixed dementia (VaD + AD). The involvement of cholinergic pathways is therefore still under consideration because opinions on this subject are different. While Di Lazzaro[9] excludes cholinergic neurotransmission involvement, Nardone[25] and Manganelli[26] believe that it is present both in CADASIL than in SIVD.

As we have seen, the few studies on cortex excitability through evaluation of rMT in early stages of predementia (Vascular Cognitive Impairment-No Dementia, VCI-ND) or in SVDWD, showed no abnormalities. Similarly, works conducted on MCI amnestic (early AD) showed no particular changes in excitability of motor cortex[27,28].

According to recent revisions, in concept of VCI belong subjects with mild cognitive impairment but not dementia (VCI-ND). They are people with a single cognitive deficit but normal functional autonomy. This condition, which in some ways can be considered benign (because there is not still an advanced deterioration), however is burdened by serious risks. Patients with VCI-ND, in fact, have an higher risk of death and institutionalization, as well as post-stroke dementia. All this makes it necessary to find as soon as parameters that will help us in making an early diagnosis. This objective, which is basically desirable for any clinical condition, it is even more so for VCI-ND that, for the possibility of identifying vascular risk factors with relative clarity, leave us a good chance of intervention in terms of prevention and therapy. Thus be able to identify subjects with VCI-ND with specific markers would allow us seriously working on their natural history and hence on the incidence of vascular dementia. Therefore the present idea is to be able to detect changes in cortical excitability already in the early dementia, resulting in a possible neurophysiological marker for the early diagnosis of VaD.

The group of subcortical ischemic vascular dementia is one on which research is mainly looking for possible neurophysiological markers, both for its wide prevalence and for its substantial clinical, physiopathological and radiological homogeneity. Compared to flourishing clinical and neuroradiological literature there are only few studies that investigate neurophysiological pattern in patients with SVD and VaD.

As we have seen, search for alterations of excitability in vascular predementia was conducted only through the evaluation of motor threshold. Recent work by Bella et al.[29] has researched, by means of a double pulse TMS, any alterations of cortical excitability in patients with VCI-ND. The hypothesis brought forward by the researchers is that in elderly patients with SVD and neuropsychological profile of VCI-ND is already present functional alteration of neuronal excitatory/inhibitory intracortical circuits induced by age-related WMLs. For this purpose 10 elderly subjects with SVD and 10 control subjects matched for sex and age were recruited. All patients met the neuroradiological criteria for SVD[30], with a predominant context of WMLs, without, however, fulfill the criteria for dementia of the DSM-IV[31]. SVD patients have showed significantly higher scores at Stroop Color-Word Test interference score time (Stroop T), Stroop Color-Word Test interference number of errors (Stroop E) and Frontal Assessment Battery (FAB). There were no statistically significant differences in rMT, CSP, CMCT and A ratio between patients with SVD and controls. Conversely, in patients with SVD the amplitude of MEPs, obtained at ISIs 10 ms from the left hemisphere and at ISIs 15 ms from right, is significantly higher compared to the control group, indicating an enhanced facilitation in SVD patients. A significant reduction of MEP inhibition at ISIs 1 ms from the left hemisphere of SVD patients was also observed, probably due to a not-GABAergic mechanism[32].

This research provides the first evidence of enhanced ICF in SVD patients with clinical features of VCI-ND[33,34]. The greater facilitation of motor cortex might be due to plastic remodeling processes mediated by glutamate-dependent activation of receptors NMDA, even in the absence of cortical excitability changes detected with rMT measure-

ment. The reason of this dissociation between motor threshold and facilitation remains controversial.

The observed increase of ICF does not seem related to aging. Firstly, because a control group of patients matched for age was included in the study, secondly, because in the elderly was observed a reduction of ICF, probably related to an increase of GABAergic tone[35].

The observed motor cortex facilitation, undoubtedly offers an electrophysiological data supporting the hypothesis that age-related white matter lesions, commonly seen on MRI of non demented elderly, are able to determine functional changes in the neural excitatory intracortical circuits.

TMS studies in patients with unilateral stroke showed a motor cortex disinhibition in non-damaged hemisphere[36,37], supporting a possible compensatory role of hyperexcitability in more remote areas of ischemic lesion. Studies of functional magnetic resonance imaging (fMRI) have found widespread activation of non-primary motor areas (such as pre-supplementary motor area) and frontotemporal and occipital regions during a motor task involving lower limbs[38].

According to "disconnection hypothesis"[39], this enhanced activation of specific circuits (motor areas or frontal and parietal neocortical areas) would have a compensatory significance, representing an adaptive response aimed at limiting the functional consequences of ischemic disease of small vessels and maintain a normal cognitive level.

This hypothesis is supported by neurophysiological studies conducted after transient ischemic attacks (TIA), which showed interesting similarities. In patients with TIA, in fact, it has been found an enhanced ICF and a reduced ICI, showing a tendency to motor cortex disinhibition despite the anatomical absence of brain damage. This suggests the activation of neurometabolics protective mechanisms following brief episodes of focal ischemia[40].

If the observed changes in motor areas excitability may represent a neurophysiological marker predictive for dementia, thus allowing preclinical detection of so-called "brain at risk", remains unclear.

Future studies of neuropsychological and neurophysiological follow-up, involving larger case studies, will further clarify the impact of subcortical vascular lesions in motor cortex excitability and tell us whether, and to what extent, the functional alterations observed are predictive of progression towards a framework of full-blown dementia.

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