TRANSCRANIAL MAGNETIC STIMULATION IN VASCULAR DEMENTIA

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Vascular dementia (VaD) is a clinical syndrome that encompasses a wide spectrum of cognitive disorders caused by cerebrovascular disease.

Vascular lesions contribute to cognitive decline in neurodegenerative dementias, and VaD and Alzheimer’s disease often coexist and share clinical features and multiple neurotransmission involvement.

These similarities have led several investigators to use transcranial magnetic stimulation (TMS) to enucleate a neurophysiological profile of VaD.
Overview:

* Information processing in the frontal-subcortical circuits is mediated by different neurotransmission pathways.
* Dopaminergic transmission, through D1 and D2 receptors, mediates a range of frontal executive cognitive functions, such as working memory, attention processes, response inhibition and motor performance.
* Through nigral connections with the limbic system mediated by D3 and D4 receptors, dopamine is involved in the emotional input and motivation of motor activity.
* Serotonin receptors, present at the level of frontal-subcortical circuits, contribute to the modulation of the dopaminergic pathway [1], suggesting a role for serotonin in mood and behavioral regulation.
* Glutamate and GABA are also involved in this neurotransmission loop because glutamate stimulates the release of striatal dopamine [2] and basal acetylcholine and GABA is the main neurotransmitter within the basal ganglia [3].
* The interaction between dopamine, glutamate, acetylcholine and GABA underlies the corticostriatal-thalamocortical negative feedback loop in order to limit cortical overstimulation.
2. Risk factors for VaD:

* The risk factors for CVD, such as hypertension, atrial fibrillation, diabetes, hypercholesterolemia, atherosclerosis

* Ischemic-hypoperfusive or hemorrhagic lesions

* The deficit in cholinergic neuronal markers and decreased serotonin metabolism
3. Vascular Dementia and Transcranial Magnetic Stimulation:

- Transcranial Magnetic Stimulation (TMS) is based on the law of electromagnetic induction with a pulse of electric current passing through a coil placed over a subject’s head generates a rapidly changing magnetic pulse that penetrates the scalp and skull to reach the cortex with negligible attenuation.
- The pulse of magnetic field in turn induces a secondary ionic current in the brain which can trigger action potentials in cortical neurons.
Clinically introduced approximately 30 years ago as a diagnostic tool to study the central motor pathways, today, TMS goes well beyond the simple assessment of the corticospinal tract.

Indeed, it is able to provide novel insights into the pathophysiology of the neural circuitry underlying neurological and psychiatric diseases and to give in vivo information about the excitability of the human brain cortex and the conduction along corticospinal tract as well as the functional integrity of intracortical neuronal and callosal fibers [2-5].

TMS has also a strong talent to unveil and monitor motor system impairment in the preclinical phase of several neurological disorders [4] or systemic diseases with the central nervous system (CNS) involvement [3, 7].

Moreover, integrated approaches using neurophysiological techniques together with structural and functional imaging have allowed us to study the connectivity across motor and nonmotor areas [8-9].
Finally, by evaluating the effects of agonists or antagonists for specific neurotransmitters, TMS can selectively and noninvasively explore the function of glutamatergic, gamma-aminobutyric acid- (GABA-)ergic, monoaminergic, and cholinergic central circuits (the so-called “pharmaco-TMS”) [10,11].

TMS can be delivered to the same or different brain areas as single pulse, pairs of stimuli, paired cortical and peripheral stimulation, or as trains of repetitive stimuli at various frequencies.
Transcranial Magnetic Stimulation in clinical practice:

- TMS in clinical practice is applied in the form of continuous trains and is named as repetitive TMS (rTMS).
- rTMS can induce changes in neuronal excitability that persist beyond the time of stimulation.
These neuromodulatory effects of TMS are used in patients with neurologic and psychiatric diseases to maintain or restore brain functions.

rTMS at a low frequency (about 1 Hz) induces a decrease of cortical excitability, while higher frequency rTMS, (usually between 5 and 20 Hz), increases cortical excitability.
Single TMS pulses delivered in trains are the principle of repetitive TMS (rTMS), an approach that can transiently modulate the functioning of stimulated and connected brain areas mainly depending on the frequency of stimulation [1, 13,14].

For this reason, rTMS might have therapeutic and rehabilitative applications since the effects of repeated sessions may persist in time [8,11,14,15].

The mechanisms of these changes are not completely clear but seem to be related to the phenomena of synaptic long-term potentiation (LTP) and long-term depression (LTD) within the CNS [16,17].

Similarly, it is possible to induce LTP-like changes in the sensory-motor system by means of the paired associative stimulation [18], which induces a lasting increase of corticospinal excitability that can be considered as a marker of cortical plasticity [18,19].
The majority of TMS studies indicate that the motor cortex of VaD patients is hyperexcitable (reduced resting motor threshold) [21], a common feature shared by AD [20]. This finding has been considered as part of a plastic compensatory mechanism in response to neuronal loss and/or ischemic injury [4, 8]. Accordingly, the enhanced excitability and plasticity might counteract cognitive decline and shed light on the reasons underlying decline or preservation of cognitive domains in dementing population [22, 23].
Repetitive TMS is emerging as promising tool to modulate cortical circuits and related neurochemical pathways in dementing illnesses [24,25].

Several studies, although methodologically heterogeneous, have shown that specific paradigms of stimulation might improve cognitive performance and mood-behavioral symptoms, possibly becoming an alternative to conventional neuroleptic therapy for psychiatric symptoms of dementia [24].

Current pharmacological treatment, indeed, suffers from significant limitations, such as nonspecific mode of actions, an insufficient tailoring to the individual, and a number of adverse effects.
The targets for an ideal nonpharmacological neuromodulatory treatment would be:

(a) modulation of activity in the targeted area,
(b) modulation of activity in a dysfunctional network,
(c) restoration of adaptive balance in a disrupted network,
(d) guiding plasticity for best behavioral outcome, suppression of maladaptive changes for functional advantage.
Very recently, exciting results come from preclinical studies showing the restorative effect of rTMS on cognitive ability in murine model of VaD and its impacts on hippocampal synaptic plasticity [24-25].

In this context, another possible mechanism of action of noninvasive brain stimulation in dementia is represented by the modulation of neurotrophin release.

Moreover, low-frequency rTMS might improve cognitive deficits through the upregulation of the hippocampal BDNF and the expression of the glutamate receptor for N-methyl-D-aspartate (NMDA).

Finally, low-frequency rTMS in VaD patients may improve learning and memory, protect pyramidal cells from apoptosis, and promote hippocampal synaptic plasticity.
5. Conclusion

- To date, the development of dementia cannot be accurately predicted by conventional investigations.
- However, unlike degenerative dementias, VaD can be prevented, at least in part, in most of the patients through a careful prevention and a close monitoring of vascular risk factors.
References:


Thank you for your attention!