A Review of Transcranial Magnetic Stimulation in Vascular Dementia

Giovanni Pennisi, Raffaele Ferri, Mariagiovanna Cantone, Giuseppe Lanza, Manuela Pennisi, Luisa Vinciguerra, Giulia Malaguarnera, Rita Bella

Departments of Neuroscience and Chemistry, University of Catania, Catania, and Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy

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Vascular Dementia and Transcranial Magnetic Stimulation: An Overview

Vascular dementia (VaD) is considered to be the second most common form of dementia, after Alzheimer’s disease (AD) with a prevalence in European studies of 2.6% in subjects >65 years [1, 2]. However, vascular cognitive impairment, which encompasses any degree of cognitive impairment ranging from an impairment of a specialized cognitive function to VaD [3–5], is deemed to be the most common type of cognitive disorder [6], affecting approximately 5% of the people over the age of 65 years [7].

The traditional concept of the multi-infarct dementia model has been revised and now there is agreement that VaD results from different vascular pathologies, such as subcortical ischemic small-vessel disease as well as cortical infarcts, ischemic-hypoperfusive or hemorrhagic lesions that can lead to numerous clinical phenotypes [8]. This clinical and pathological heterogeneity has caused difficulties and controversies in the diagnosis and classification of VaD [9–11].

Moreover, cerebrovascular disease (CVD), including small-vessel disease and white matter lesions, is frequently observed in AD patients, suggesting an overlap be-
tween VaD and AD [12–14]. Vascular amyloid angiopathy is reported in almost all cases of AD. The risk factors for CVD, such as hypertension, atrial fibrillation, diabetes, hypercholesterolemia, atherosclerosis and apolipoprotein E e4 allele, have been shown to increase the risk of AD [15–21]. The deficit in cholinergic neuronal markers and decreased serotonin metabolism observed in AD have been shown to be associated with VaD too [22, 23]. However, VaD and AD can be distinguished clinically by the mode of onset and progression of the cortical deficits. Whereas memory and language deficits prevail in AD, executive function is more affected in VaD, possibly due to the interruption of frontal networks [24]. Changes in mood and personality occur earlier and are more severe in VaD than in AD [25, 26].

The subcortical ischemic vascular dementia (SIVD), due to small-artery disease and hypoperfusion, identifies a clinically homogeneous group of patients and is a major cause of vascular cognitive impairment and dementia [5, 8]. Data from the Leukoaraiosis and Disability (LADIS) study [27] suggested that subcortical ischemic vascular disease is related to progressive cognitive impairment and a considerable risk of developing dementia [28], it is an independent determinant of global functional decline [29], predicts the development of depressive symptoms [30] and is associated with gait and balance disorders [31] or urinary complaints [32] in older people.

Cognitive alterations in VaD, and particularly in SIVD, were suggested to be the consequence of the disruption of the frontal-subcortical circuits that underlie social behavior, and cognitive and executive cortical functions. Lacunes involving the striatum, globus pallidus or thalamus, and periventricular or deep white matter lesions could cause disruption of the prefrontal-subcortical loop, resulting in a variety of neuropsychiatric symptoms. Interruption of the dorsolateral prefrontal-subcortical circuit leads to executive dysfunction; lesions in the orbitofrontal-subcortical loop result in uninhibited behaviors, personality change and emotional lability, whereas decreased motivation, apathy, abulia and even akinetic mutism are caused by lesions in the anterior cingulate circuit [33].

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. Moreover, 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 [34]. Also, there is a connection between the dopaminergic and cholinergic systems because acetylcholine enhances dopamine release, whereas dopamine modulates cholinergic interneuron activity depending on DA subtype receptors [35]. Moreover, serotonin receptors, present at the level of frontal-subcortical circuits, contribute to the modulation of the dopaminergic pathway [36], 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 [37] and basal acetylcholine and GABA is the main neurotransmitter within the basal ganglia [38]. The interaction between dopamine, glutamate, acetylcholine and GABA underlies the corticostriatal-thalamocortical negative feedback loop in order to limit cortical overstimulation.

White matter lesions may directly affect cholinergic projection [39, 40], and preclinical [41, 42] and clinical evidence [23, 43] suggest that the cholinergic system might also be involved in VaD. Moreover, a severe cholinergic deficit in frontal and temporal cortices has been shown to occur in CADASIL cases [44, 45]. Cognitive decline, associated with subcortical CVD, might be the result of hippocampal and cortical atrophy and, although the cause of diffuse cortical atrophy is not known, it may correlate partially with the severity of white matter lesions [46].

In the last years, the identification of an overlap between VaD and AD and the involvement of multiple neurotransmission systems have led several investigators to use transcranial magnetic stimulation (TMS) in order to define the neurophysiological profile of VaD and to help the differential diagnosis between the 2 forms of dementia. TMS is a noninvasive neurophysiological method specifically able to evaluate the primary motor cortex and the corticospinal tract. TMS was developed as a useful method in order to explore the development of the corticospinal system, the functioning of the healthy brain and to evaluate the involvement of the corticopiramidal tract in a variety of neurological diseases. Many TMS studies have examined motor cortex excitability and motor cortical output after acute stroke, in the poststroke recovery and in brain reorganization, providing relevant data for their prognosis and therapeutic approach [47–53]. TMS has also been applied to study motor cortex changes in patients with cognitive disorders such as AD [54–59], frontotemporal dementia [59] and dementia with Lewy bodies [60].

Various measures of motor cortex excitability and inhibition in normal and pathological conditions have been
evaluated by different TMS techniques. Using single-pulse TMS, motor threshold (MT) at rest or during active movements can be measured. MT is the expression of the level of neuronal membrane excitability because it can be modulated by drugs that block voltage-gated sodium channels [61]. It may reflect the local density of a central core of excitatory interneurons and of corticospinal neurons within the human motor cortex. The interval of suppression of the voluntary electromyographic activity following a single-pulse TMS stimulus, the so-called cortical silent period (CSP), is indeed a measure of motor cortical inhibition and it is due largely to the activation of cortical inhibitory interneurons mediated by GABA-B receptors [62].

Using the paired-pulse paradigm, TMS has revealed the existence of a complex intracortical phenomenon within the human brain by means of the study of short-latency intracortical inhibition (SICI) and intracortical facilitation (ICF) [63]. SICI and ICF are considered to be mediated by different neural circuits: SICI is probably mediated by GABA-A receptors [64], whereas the phenomenon of facilitation seems to originate from intracortical glutamatergic neurons, since dextromethorphan, an N-methyl-D-aspartate (NMDA) receptor antagonist, reduces the ICF [65]. Nevertheless, the interpretation of the ICF seems to be more difficult [66].

Using a different TMS paradigm it is possible to investigate the sensory-motor interaction within the cerebral cortex and the cortical phenomenon of the short afferent inhibition (SAI) [67]. SAI seems to be related to a central cholinergic inhibitory circuit because scopolamine causes its reduction in healthy subjects [68]. SAI might also be connected to GABAergic circuits [69] and could be influenced by other neurotransmitters such as glutamate or dopamine [57]. SAI is reduced in some conditions characterized by an impairment of memory, such as AD [56] and other dementing disorders.

Single TMS pulses delivered in trains are the principle of the repetitive TMS (rTMS), an approach that can transiently influence the function of stimulated brain areas, mainly depending on the frequency of stimulation. rTMS might also have therapeutic and rehabilitative applications since the effects of repeated sessions may persist in time. rTMS as a therapeutic approach is widely suggested in psychiatric disorders [70, 71]. The mechanisms of these changes are not clear, but they seem to be related to synaptic long-term potentiation and long-term depression [72].

**Cortical Excitability in VaD**

TMS has been used to study the motor cortex in patients with vascular cognitive disorders. However, so far we have identified only 5 published reports in the literature on TMS studies in VaD (table 1) and 1 rTMS study in SIVD with executive dysfunction. Currently, these few studies on patients with vascular dementia provide additional information on the underlying mechanism of cognitive complications in CVD.

In 2004, Alagona et al. [73] studied 20 SIVD patients, diagnosed according to the criteria proposed by Erkinjuntti in 2002 [74], 20 AD patients and 20 control subjects. They used the single-pulse TMS technique to evaluate cortical excitability through the assessment of the resting MT (rMT), according to recommended criteria for its estimation [75]. These authors found a reduced rMT in both patient groups with respect to controls. Moreover, SIVD patients showed lower values than AD patients. No statistically significant difference was found in the H/M am-

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**Table 1.** Selected peer-reviewed articles on cortical excitability to TMS in VaD

<table>
<thead>
<tr>
<th>Studies</th>
<th>Demographic and clinical characteristics</th>
<th>TMS parameters</th>
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<tr>
<td>Alagona et al. [73]</td>
<td>20 SIVD, 20 AD, 20 controls</td>
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<tr>
<td>Di Lazzaro et al. [82]</td>
<td>12 SIVD, 12 AD, 12 controls</td>
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<td>Nardone et al. [83]</td>
<td>20 SIVD, 20 controls</td>
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<td>Manganelli et al. [84]</td>
<td>10 CADASIL, 10 controls</td>
<td>figure of eight</td>
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<tr>
<td>Pennisi et al. [85]</td>
<td>20 SIVD, 20 SIDWD, 20 controls</td>
<td>circular</td>
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* p < 0.05; ** p < 0.01. n.s. = Not significant; R = right hemisphere.
plitude ratio between patients and controls, thus the hyperexcitability was not due to increased spinal motor neuron excitability. Furthermore, the CSP was not different in the 2 groups of patients.

This study showed an enhanced motor cortex excitability in SIVD subjects, similar to that of AD patients. The authors hypothesized that the hyperexcitability could be associated with the neurodegeneration mediated by an abnormal glutamate mechanism. In fact, vascular cognitive disorders are the result of ischemic insults that probably trigger the different mechanisms of neurodegeneration also in this form of dementia [76].

Excitotoxicity is a major cause of neuronal loss after hypoxic-ischemic damage [77]. Glutamate is responsible for synaptic transmission through the activation of ionotropic glutamate receptors sensitive to NMDA, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) or kainate. This glutamatergic mechanism underlies neuronal plasticity and normal information processing [78]. The energy deficit following cerebral ischemia increases the release of glutamate by presynaptic membrane depolarization, with a subsequent synaptic activation of voltage-gated Ca$^{2+}$ channels. Moreover, it inhibits the glutamate reuptake by astrocytes and causes an additional accumulation of glutamate in the synaptic space. Excessive activation of ionotropic glutamate receptors leads to neuronal death following the intraneural overload of Ca$^{2+}$ and the subsequent activation of the Ca$^{2+}$-dependent proteins (calpain, cytoplasmic phospholipase A$_2$, protein kinase Ca$^{2+}$-dependent, endonuclease). The accumulation of Ca$^{2+}$ also leads to the production of free radicals through the activation of pro-oxidant processes [79]. Thus, neuronal death occurs through multiple mechanisms causing apoptosis [80].

Moreover, the dysregulation of the delicate balance between excitatory and inhibitory mechanisms may be the cause of the cortical excitability abnormalities. The damage to the cholinergic system may contribute to the cognitive decline of patients with VaD, similarly to AD patients. Therefore, this study suggested that an impaired cholinergic transmission might be a pathologic mechanism leading to the increment of motor cortex excitability in VaD patients, as it occurs in AD [56, 81].

In 2008, Di Lazzaro et al. [82] studied 12 VaD patients with neuroradiological evidence of small-vessel disease, 12 AD patients and 12 age-matched healthy subjects. There was a significant reduction of rMT in VaD and AD patients with respect to controls, but there were no significant differences between the VaD and AD groups. In agreement with the previous study, patients with VaD exhibited increased cortical excitability that might be interpreted to be a functional consequence of subcortical CVD. Moreover, SICI was reduced in a small group of VaD patients, suggesting a possible role for GABAergic circuits in the genesis of hyperexcitability in the motor cortex. Additionally, SAI was found to be decreased in AD patients, while it was normal in most VaD patients, making the cholinergic hypothesis unlikely in this form of dementia. Indeed, SAI was significantly decreased only in 25% of the patients with VaD, suggesting a mixed form of dementia and a possible role for a cholinergic system impairment in this group of patients. SAI was strongly correlated with neuropsychological measures of long-term memory and other higher cortical functions, suggesting a central role for acetylcholine in the memory processes.

Nardone et al., in a different study design [83] including 20 SIVD patients and 20 controls, did not confirm the results of the previous reports. There were no differences between the 2 groups for the neurophysiological parameters measured (central motor conduction time, CSP, SICI, ICF) and, in particular, for MT. The reason of this difference is not clear, even if the inclusion criteria, age and tools were similar. SAI was significantly lower in SIVD patients than in the healthy group. There were no correlations between SAI and neuropsychological results, neuroradiological features, patient age or disease duration. The authors proposed that there was a central cholinergic circuit impairment in this pathology, as in AD [56] and in CADASIL [84]. Therefore, they suggested that the use of cholinomimetics drugs, such as acetylcholinesterase, could be helpful to improve cognitive impairment and cerebral blood flow in VaD subjects. SAI might be a valid tool to evaluate the effects of drugs on the cholinergic system and to predict the clinical response to treatment in these patients.

In a recent study, Pennisi et al. [85] demonstrated that in the subcortical ischemic disease, motor cortex hyperexcitability was a peculiar finding only in patients with dementia. These authors studied 20 SIVD and 20 subcortical ischemic disease without dementia patients (SIDWD) and 20 healthy subjects. rMT was lower in SIVD patients than in SIDWD patients and in healthy subjects. The study confirmed that the enhanced motor cortex excitability is not merely related to cerebrovascular lesions. Despite the cognitive impairment observed in these patients being the result of damage in frontal-subcortical circuits caused by strategic infarcts, CVD itself cannot justify the observed hyperexcitability of the motor cortex. In fact, previous studies showed that strategic...
lacunar infarcts in the pyramidal tract often reduce corticospinal excitability, despite the complete motor recovery [50]. Moreover, it has been reported that chronic cerebrovascular lesions usually do not influence motor cortex excitability [86].

No correlation was found between changes of cortical excitability and neuroimaging data. This can probably be due to the fact that studies have evaluated vascular lesions using simple visual scales that do not allow a precise quantification of the vascular damage. Moreover, as shown by recent imaging studies [87], invisible white matter damage may contribute to the development of vascular cognitive disorders. Thus, further studies should be performed to address also this matter.

TMS Studies in CADASIL

The cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is perhaps the typical hereditary CVD. CADASIL is due to mutations in the Notch3 gene on chromosome 19 and causes progressive cognitive decline until dementia, cerebral ischemic events, psychiatric disorders and migraine with aura. It is a small-vessel disease and represents a pure vascular dementia model; for this reason, patients with CADASIL are particularly suitable for studying the relationship between ischemic brain injury and clinical manifestations.

Neuropathological data in a postmortem single case of CADASIL [44] and immunocytochemical studies [45] showed cholinergic neuronal denervation, anomalies in cholinergic neuronal activities and interruption of axonal projections along the white matter tracts to the frontal cortex.

In 2008, Manganelli et al. [84] first demonstrated with an 'in vivo' electrophysiological study a dysfunction of motor cortex cholinergic innervations, utilizing SAI measurement. In CADASIL patients, rMT and SAI were significantly lower than in healthy individuals, while SAI was normal in the only patient that showed a normal neurophysiological evaluation. These results support the hypothesis of a central cholinergic system impairment in CADASIL [44, 45]. The recurrent vascular insults and the lesional burden in strategic areas [39, 40], such as the external capsule, typically involved in CADASIL [88, 89], lead to the interruption of cortico-subcortical cholinergic circuits [39, 90]. rMT was reduced in CADASIL patients and this cortical hyperexcitability can be caused by cholinergic, GABA and glutamate neurons. The cholinergic system may influence GABA and glutamate circuits, thus CADASIL might involve several neurotransmitter systems, similarly to AD.

TMS Studies in Alzheimer’s Disease

In the last years, many TMS studies were carried out in AD patients with the aim of understanding the changes in motor cortex excitability. Most studies reported that rMT is generally reduced in AD, and this result is interpreted as a marker of increased motor cortex excitability [54–57, 73, 82, 85, 91–93]. Using paired-pulse TMS, some, but not all, studies showed that ICI is reduced in AD patients [59, 94, 95], whereas no changes are observed in ICF [56, 59, 83, 94–96], suggesting a possible involvement of intracortical GABAergic circuits. Finally, an impairment of the central cholinergic transmission is clearly demonstrated in AD [56, 57, 82, 97, 98]. At present, however, it is not clear if the hyperexcitability of the motor cortex in AD is the expression of a selective involvement of excitatory glutamatergic circuits or an impairment of inhibitory cholinergic and, to a lesser extent, GABAergic activity. Although the cholinergic deficit seems to be the most accepted hypothesis, recent results indicate that AD should be considered as a complex neurodegenerative disease, involving different neurotransmitter systems.

Discussion

The reduction of rMT in VaD is a relatively constant result, suggesting a pattern of global increased cortical excitability [73, 82, 85], as already reported in AD. The neuropathological similarity between VaD and AD at TMS evaluation supports the hypothesis that the 2 disorders often coexist as mixed-type dementia.

Cortical hyperexcitability evaluated by TMS can be due to an imbalance of excitatory and inhibitory circuits within the cerebral cortex, leading to a disinhibition of the motor cortex itself. Since the principal excitatory neurotransmitter is glutamate, the glutamatergic system could have a relevant role in the hyperexcitability of the motor areas. In particular, there can be a disproportion between non-NMDA and NMDA neurotransmission in favor of the non-NMDA system [57]. Thus, in VaD patients hyperexcitability could be due to an altered glutamatergic neurotransmission, as observed after stroke [99].

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On the other hand, Di Lazzaro et al. [82] found an impairment of SICI in 16% of their patients, possibly due to an involvement of GABAergic intracortical inhibitory mechanisms.

In fact, Ihara et al. [100] recently affirmed that in leukoaraiosis patients with dementia a bilateral reduction of cortical benzodiazepine receptors exists in the frontopolar and frontal-insular areas, the left tempo-occipital border areas and the left marginal cortical areas, caused by different ischemic lesions in white matter and by disruption of cortical-subcortical circuits.

The impairment of intracortical inhibitory circuits can be linked to GABA-A activity or to inhibitory cholinergic mechanisms. For instance, the blockade of cholinergic muscarinic receptors with scopolamine causes an enhanced cortical excitability measured by TMS [68]. In any case, one possible mechanism is that the reduced corticospinal output activates to a lesser extent recurrent axon collaterals and consequently conducts to a reduced inhibitory effect on corticospinal neurons [101].

The role of the cholinergic system in the development of cognitive impairment is still under discussion also because there are conflicting results on the role of cholinergic circuit activity evaluated by afferent inhibition. Di Lazzaro et al. [82] affirm that in VaD subjects there is no alteration of the central cholinergic circuits. On the other hand, Manganelli et al. [84] and Nardone et al. [83] suggest that the cholinergic neurotransmission can play a role in the cognitive decline of CADASIL and SIVD patients, respectively.

Despite its high sensitivity in evaluating the global weight of several neurotransmitters in VaD, TMS does not provide data about a specific neurotransmission activity [102].

Probably hyperexcitability may be related to the disruption of the integrity of cerebral white matter due to CVD that could damage axons travelling within the white matter, resulting in degeneration of neurons in the subcortical and cortical gray matter.

It is important to note that a diffusion-weighted imaging study conducted in elderly subjects enrolled in the LADIS study showed a significant correlation between ultrastructural abnormalities of the normal-appearing brain tissue and cognition impairment. This suggests that both visible and invisible microstructural white matter alterations are key factors in the evolution of the cognitive impairment [87].

The hypothesis that the described alterations of motor cortex excitability could be related to aging is unlikely. First, in all studies, a control group matched for age has always been included. Secondly, several studies have described the effect of aging on motor cortex circuits reporting results opposite to those found in studies on VaD. An age-related reduction of MEP amplitude has been reported in controls [103], whereas in patients with VaD Alagona et al. found a small (not statistically significant) increase in MEPs size [73].

A significant increase in MT was found in healthy subjects with aging [104], while in patients with VaD, the majority of studies argues that there is a reduction of MT. However Silbert et al. [105] found that white matter hyperintensity volume is associated with decreased rMT.

Aging is also associated with a relative decrease in the excitability of some cortical inhibitory circuits. Shortening of CSP [103] and a reduction of SICI [106] were reported with aging, but these findings were not reported in VaD patients. Finally, no significant effect of aging was found for SAI [103].

The hyperexcitability of motor cortex might be the result of a functional reorganization of cortical areas similar to the compensatory mechanisms that occur in AD [96, 107] and CADASIL patients. In fact, a functional magnetic resonance imaging study of patients with CADASIL showed changes in motor cortex activation in response to the typical subcortical vascular injury. In particular, a greater ipsilateral premotor and primary motor area activation was observed with hand movement that increased with axonal damage. This functional cortical reorganization seems to be an adaptive process to limit motor impairment subsequent to the subcortical injury of CADASIL [108].

To date, the studies on rTMS as a treatment of VaD are scarce and its hypothetical mechanisms are still unclear. The randomized controlled pilot study of Rektorova et al. [109] showed that 1 session of high-frequency rTMS applied over the left dorsolateral prefrontal cortex was able to improve executive functioning, whereas no effects were observed in any other cognitive functions. However, the study was performed on a small group of patients suffering from CVD with mild cognitive impairment but without dementia. Moreover, the efficacy and safety of high-frequency rTMS were tested for the treatment of elderly patients with vascular depression, which is known to be more frequently drug resistant than the early-onset depression [110–112]. A recent study of rTMS in rat models of VaD has reported an improvement of both learning and memory abilities after the administration of low-frequency or high-frequency stimuli. As suggested by the authors, the restoration of cognitive functions could be the result of the biological effects of rTMS that probably
acts by promoting the expression of brain-derived neurotrophic factor and other proteins, such as NMDAR1 and synaptophysin, involved in neuronal cell protection, synaptic transmission and brain plasticity [113].

The majority of TMS results indicate that the cortex of VaD patients is hyperexcitable, a common feature shared also by AD. Literature on TMS in the early stage of VaD is lacking. The few studies on amnestic MCI-early AD failed to detect significant alterations in cortical motor neuron excitability [114, 115]. Future studies using TMS together with biomarkers and neuroimaging could be useful in identifying the brain at risk for dementia and in prognosticating disease progression.

In conclusion, although several neuroradiological reports on VaD have been published, up to now only few neurophysiological studies have examined cortex excitability in patients with cognitive decline following vascular brain damage. All the findings suggest that the use of TMS is already a valuable tool in the study of the neurophysiological basis of cognitive disorders. Further TMS studies are needed to understand the impact of subcortical vascular lesions on cortical excitability and the role of multiple neurotransmitter involvement in VaD patients.

To date, no studies have been conducted at the pre-dementia stage and correlations between cortical excitability and cognitive performance have not been addressed. Moreover, studies on the impact of drugs on cortex excitability of vascular dementia are scarce. However, studies with rTMS are able to provide data for a rehabilitative application with the aim of improving cognitive performance in VaD.

A PubMed-based literature review of English-language studies was performed to acquire publications on VaD and TMS. Key search words were vascular dementia, subcortical ischemic vascular dementia, vascular cognitive disorders, vascular cognitive impairment, Alzheimer’s disease, neurotransmitters, transcranial magnetic stimulation and motor cortex excitability. We have also searched the articles in references to locate data on CVD and TMS.

References


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