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Motor cortex excitability in Alzheimer's disease and in subcortical ischemic vascular dementia

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Abstract

Twenty Alzheimer's disease (AD) patients, 20 subcortical ischemic vascular dementia (SIVD) patients and 20 neurologically and cognitively normal subjects underwent transcranial magnetic stimulation to study motor cortex excitability changes. Motor threshold (MT), amplitude of motor evoked potentials, silent period and the H/M ratio (amplitude of maximal Hoffman reflex vs. that of maximal motor response) were considered. MT was lower in SIVD patients when compared with AD patients ($P = 0.003$) and the control group ($P < 0.001$) and lower in AD patients when compared with the control group ($P < 0.001$). The increment of motor cortex excitability in AD and SIVD did not lead us to distinguish clearly the two types of dementia. It is likely that the electrophysiological similarity between AD and SIVD could represent another common mechanism shared from these forms of dementia.

Keywords: Alzheimer's disease; Subcortical ischemic vascular dementia; Motor cortex excitability; Transcranial magnetic stimulation

Alzheimer's disease (AD) and vascular dementia (VaD) are the two most common forms of dementia, which share many pathological, symptomatic and neurochemical features [10]. Subcortical ischemic vascular dementia (SIVD) represents an important and homogeneous subtype of VaD [5]. Transcranial magnetic stimulation (TMS) is the method of choice for non-invasive stimulation of human brain in conscious subjects. It represents a valid tool to study the motor cortex excitability through the evaluation of the motor threshold (MT). In the last years, MT has been investigated in AD patients [1,15,17] but there are no reports available on motor cortex excitability in VaD patients.

In the present work, motor cortex excitability changes were studied in AD and SIVD patients to assess the electrophysiological differentiation and the eventual usefulness of MT for a better clinical evaluation of these two types of dementia.

Twenty SIVD patients (eight men, 12 women, age range 48–84 years, mean age 71.8 ± 9.37 years), 20 AD patients (seven men, 13 women, age range 55–82 years, mean age 72.2 ± 7.53 years) and 20 neurologically and cognitively intact subjects (eight men and 12 women, age range 52–80 years, mean age 68.55 ± 7.96 years) were studied. The study was approved by the local ethics committee and informed consent was obtained from all patients (or from close relatives) and control subjects. All patients and control subjects were free of acetylcholinesterase inhibitors or other medications able to induce cortical or spinal excitability changes. The diagnosis of probable SIVD was established on a modification [5] of the NINDS-AIREN (National Institute for Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neuroscience) criteria for probable VaD [18], while the diagnosis of probable AD was established following the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) [12]. All the patients underwent a magnetic resonance imaging (MRI) study. SIVD patients were included if their cerebral MRI showed subcortical

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lacunes and/or a multiple involvement of the inner white matter. Patients with AD were excluded from the study if they had lacunes or other major pathologies such as brain tumors, hydrocephalus, and trauma, except cortical atrophy. Moreover, AD patients were excluded if their neurological examination showed motor disturbances. Included SIVD patients had no clinical history of stroke. They showed executive frontal lobe dysfunction; in some SIVD patients, the clinical examination showed some neurological signs such as dysarthria, gait disturbances, urinary incontinence, asymmetric tendon reflexes or hemisensory deficit. None of the patients had a history of epilepsy, clinical evidence of myoclonus or extrapyramidal signs. Moreover, they were excluded in the case of reduced hand or upper limb motor strength. Hand motor strength was evaluated by means of a rating scale derived from the Medical Research Council (MRC) scale. All patients showed a normal hand strength score (MRC = 5). An additional inclusion criterion was the finding of motor evoked potentials (MEPs) with normal latency, amplitude and symmetry in both hands. Moreover, patients were excluded if they were unable to respond to simple orders.

Surface recording electrodes were placed over the first dorsal interosseus (FDI) muscle. Magnetic stimulation was performed using a Magstim 200 stimulator (Magstim Ltd., Withland Dyfed, UK) connected to a 9 cm mean diameter circular coil. Resting MT was defined as the lowest TMS intensity able to induce motor responses of an amplitude >20 μV in the relaxed contralateral target muscle, according to internationally established parameters [19]. Cortical stimulation was performed with the coil placed tangentially to the scalp and lateralized on the examined hemisphere with the handle held backward. Stimulation was applied at the 'hot spot' (i.e. the scalp position from which a contralateral MEP of maximal amplitude, minimal latency and lowest threshold was obtained), according to Rossini et al. [19].

Stimulus intensity was set at 30% above the threshold level. The left hemisphere was stimulated by a counterclockwise current and the right hemisphere by a clockwise current. MEPs were amplified using a Medelec Premier (Oxford Instruments) system with gains of 100 μV and 5 mV/div (band pass 30 Hz to 3 kHz). Subjects were studied while producing a weak contraction of the recorded muscle and a post-stimulus period of 100 ms was analyzed. Peak-to-peak amplitudes were measured and five consecutive responses were averaged. The silent period (SP) was estimated as the time between the end of the MEP and the recovery of voluntary activity [9]. It was determined with an approximately 50% of maximum isometric voluntary contraction of the FDI muscle monitored by an acoustic feedback via a loudspeaker and visually on an oscilloscope. The TMS intensity was set at 30% above resting MT. In each experimental condition, the mean SP duration of the five trials was calculated. The analysis time was 500 ms.

In 6/20 SIVD patients, 5/20 AD patients and 5/20 normal subjects it was possible to measure the H/M ratio (amplitude of maximal Hoffman reflex vs. that of the maximal motor response) to examine the spinal motoneurons excitability. The FDI H reflex was evoked from both sides by ulnar nerve stimulation, while the subjects performed a mild contraction of the target muscle. The stimulation was a constant current given at the wrist with the cathode positioned proximally, with an intensity below the threshold for M response appearance. The rate of stimulation was 1 Hz and the stimulus was a square pulse of 0.5 ms. The comparison of the values of the different parameters measured in this study obtained in the three groups of subjects was performed by means of a one-way analysis of variance (ANOVA) followed by post-hoc between-group comparisons when the ANOVA was statistically significant. Values of P lower than 0.05 were considered as statistically significant. Results were expressed as mean $\pm$ 2.5 standard deviation (SD).

The electrophysiological data obtained from AD patients have been reported in Table 1. No significant interside differences were found in the three groups for each TMS parameter and no statistically significant differences were found in the H/M ratio between patients and normal controls. The mean resting MT was 36 $\pm$ 3.02% in AD patients, 32.7 $\pm$ 2.61% in SIVD patients and 49.1 $\pm$ 4.21% in the control group.

The mean MEP/M_{max} values were 48.9 $\pm$ 9.83% in AD patients, 51.9 $\pm$ 13.57% in SIVD patients and 43.7 $\pm$ 8.93% in the control group. The mean values of SP duration were 123.8 $\pm$ 36.33 ms in AD patients, 148.7 $\pm$ 46.41 ms in SIVD patients and 149.8 $\pm$ 43.57 ms in normal subjects.

The ANOVA showed statistically significant differences for MT. In particular, MT was lower in both patient groups than in normal controls ($P < 0.001$) and SIVD patients showed values significantly lower than those of AD subjects ($P < 0.01$). The ANOVA did not disclose significant group differences for the remaining parameters considered in this study; however, there was a tendency for MEP/M_{max} in both patient groups to show values higher than those of normal controls.

MT was significantly decreased in patients (AD and SIVD) compared to cognitively normal subjects. These findings in AD patients confirm and support the previous reports [1,11,15,17]. The hyperexcitability is not due to aging, and in fact it has been shown as an increment of MT in elderly adults when compared with young subjects [14,20]. It could be associated with the neurodegeneration mediated by an abnormal glutamate mechanism [7,8]. Glutamate is the principal excitatory neurotransmitter in the brain. Overstimulation of the *N*-methyl-D-aspartate (NMDA) receptors by glutamate ('excitotoxicity') is implicated in a variety of pathologic conditions, ranging from acute insult such as stroke to chronic neurodegenerative disorders such as Huntington's disease, the acquired immunodeficiency syndrome (AIDS) dementia complex, amyotrophic lateral sclerosis [3] and AD [13]. On the other

Table 1
Statistical comparison between the different groups included in this study

	1-AD		2-SIVD		3-NOR		ANOVA ($P <$)	Post-hoc comparisons		
	Mean	SD	Mean	SD	Mean	SD		1 vs. 2	1 vs. 3	2 vs. 3
MT (%)	36.0	3.02	32.7	2.61	49.1	4.21	0.000001	0.003	0.000001	0.000001
MEP/M_{max} (%)	48.9	9.83	51.9	13.57	43.7	8.93	0.065			
SP (ms)	123.8	36.33	148.7	46.41	149.8	43.57	NS			

hand, motor cortex hyperexcitability does not appear to be due to decreased GABAergic intracortical inhibitory circuits [7], because they have been shown to be normal in AD patients by Pepin et al. [17] using paired TMS. In SIVD patients, caudate nucleus, globus pallidus, paramedian and anterior nuclei of the thalamus and connecting fibers of the frontal subcortical circuits are frequently affected [4]. In these patients, the cognitive alterations were suggested to be the consequence of the disconnections of the executive frontal circuits, due to strategic infarcts. Microinfarction is an important substrate for the development of dementia [2], but CVD (cerebrovascular disease), present in SIVD patients, cannot explain cortical hyperexcitability in this group of patients. In fact, Pennisi et al. [16] showed that a strategic lacunar infarct in the pyramidal tract often reduces corticospinal excitability, despite complete clinical recovery. So, also in SIVD patients, the increased excitability could probably be ascribed to a dysregulation in excitatory or inhibitory circuits. Deficits in cholinergic neuronal markers and degeneration of neuronal circuits could contribute to cognitive decline in VaD patients, like in AD [6]. Liepert et al. [11] showed that motor cortex disinhibition can be transiently corrected by cholinesterase inhibitor drugs, but 1 year of treatment did not stop the progressive increase in motor cortex excitability [15]. The impaired cholinergic neurotransmission in AD and VaD could represent a neurochemical overlap in patients with dementia. In SIVD, we cannot exclude the involvement of GABAergic intracortical inhibitory circuits because no studies with paired TMS have been reported so far. The reduced MT could be due to increased spinal motoneurons excitability, but in the present work we showed an insignificant difference in the H/M amplitude ratio amongst AD, SIVD and control subjects.

In the present study, the SP was not different in both groups of patients when compared with normal subjects. SP showed a negative correlation with aging, which could be partially explained by the tendency for a higher MT in older people [9]. The early part of the SP is probably due to the spinal mechanism, while the latter part could be mediated by cortical structures, probably by stimulation of GABAergic intracortical inhibitory circuits. A previous study [17] showed that GABAergic intracortical inhibition was normal in AD, without any data about SIVD patients.

In conclusion, our data about the increment of motor cortex excitability in AD and SIVD did not lead to a clear distinction between the two types of dementia. The electrophysiological similarity could represent another common mechanism shared from these two forms of dementia or it could support the concept that AD and VaD are not mutually exclusive disorders.

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