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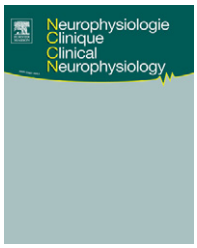

ORIGINAL ARTICLE/ARTICLE ORIGINAL

The relationship between motor cortex excitability and severity of Alzheimer's disease: A transcranial magnetic stimulation study

Étude au moyen de la stimulation transcrânienne de la relation entre l'excitabilité du cortex moteur et la gravité de la maladie d'Alzheimer

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KEYWORDS
Transcranial magnetic stimulation (TMS);
Cortical excitability;
Cortical silent period;
Transcallosal inhibition;
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Summary
Introduction. — In Alzheimer's disease (AD), transcranial magnetic stimulation (TMS) studies have been limited to test motor cortical excitability. The aim of this study was to investigate the inhibitory circuits of the motor cortex and to relate these to measures of cognitive function in AD patients. Results were compared with those of a control group of healthy subjects matched for age, sex and education.
Patients and methods. — Forty-five AD patients and 37 healthy volunteers were included in the study. Each participant received a neurological evaluation, Mini-Mental State Examination (MMSE), and Clinical Dementia Rating (CDR). Neurophysiological evaluations included resting and active motor threshold (rMT and aMT), motor evoked potential (MEP), cortical silent period (CSP), and transcallosal inhibition (TI).
Results. — AD patients showed significantly reduced rMT, aMT and shorter MEP onset latency; in addition there was a prolongation of both CSP and TI. There was a significant positive correlation between the MMSE and CDR, on the one hand, and aMT and rMT, on the other hand, whereas the correlation was negative with CSP and TI durations.
Conclusion. — AD is associated with hyperexcitability of the motor cortex, which supports the hypothesis that changes in GABAb and glutamate function are important factors in cognitive impairment.

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MOTS CLÉS
Stimulation magnétique transcrânienne (TMS) ;
Excitabilité corticale ;
Période de silence cortical ;
Inhibition transcalleuse ;
Maladie d'Alzheimer

Résumé
Introduction. — Les études utilisant les stimulations magnétiques corticales dans la malaise d'Alzheimer se sont limitées à l'évaluation de l'excitabilité corticale. Le but de notre étude était d'évaluer les circuits inhibiteurs du cortex moteur en relation avec les mesures des fonctions cognitives dans un groupe de patients porteurs de la maladie d'Alzheimer (MA). Les résultats sont comparés à ceux d'un groupe de sujets normaux appariés pour l'âge, le sexe et le niveau d'enseignement.
Patients et méthodes. — Nous avons inclus 45 patients atteints de la MA et 37 volontaires sains. Pour chaque participant à l'étude, nous avons réalisé un examen neurologique, un MMSE et un test d'évaluation clinique de la démence (ECD). Sur le plan neurophysiologique, nous avons mesuré les seuils moteurs au repos (SMR) et sous activation volontaire (SMA), le potentiel évoqué moteur (PEM), la période de silence cortical (PSC) et l'inhibition transcalleuse (ITC).
Résultats. — Une diminution significative des SMR, SMA, un temps de latence plus court du PEM et une prolongation de la PSC et de l'ITC furent observés chez les patients atteints de MA. Nous avons trouvé une corrélation positive significative entre, d'une part, le MMSE et l'ECD et, d'autre part, les SMR et SMA. Inversement, une corrélation négative fut trouvée entre MMSE et ECD, d'une part, CSP et TI, d'autre part.
Conclusions. — La MA est associée avec une hyperexcitabilité du cortex moteur, ce qui plaide en faveur de l'hypothèse selon laquelle des modifications des systèmes GABAb-ergiques et glutamatergiques joueraient un rôle essentiel dans les altérations cognitives.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive cognitive decline that leads to dementia. A consistent number of neurophysiological studies have shown increased motor cortex excitability (or decreased inhibition) in response to the application of transcranial magnetic stimulation (TMS) in AD patients long before the occurrence of clinical signs of motor deficit [3—6,16,26,27].

Since neuropathological studies of AD showed an involvement of the primary motor cortex [7], which expresses muscarinic receptors and receives widespread inputs from the cholinergic pathways, it was assumed that this change in excitability was the result of a cholinergic deficit [5,16,28,34]. However, more recent studies suggest that cortical excitability changes may be due to a selective dysfunction of excitatory glutamatergic transmission [4,5,16,26] although this has been questioned by other studies that have reported intracortical facilitation (ICF), which is thought to reflect glutamate-mediated activity, to be normal [16,31]. There is also some evidence that intracortical inhibition (ICI), a probable test of GABAa function, is decreased in AD [16,31]. Thus the true cause of cortical hyperexcitability in AD is still unclear (for a review, see Rossini et al. [33]).

The principal function of the corpus callosum (CC) is to allow the exchange of information between both hemispheres. AD patients show an interhemispheric disconnection syndrome similar in nature to that demonstrated by split-brain subjects, [14]. Disconnection symptoms may stem from the fact that anatomical abnormalities found in the cortex of AD patients affect mainly pyramidal neurons [15], from which callosal fibers originate. These neurons are also the principal recipients of input from the contralateral hemisphere [35]. The distribution of abnormalities is thus coincidental with neurons that form the CC. This has been confirmed by findings that indicate that there is degeneration of this interhemispheric pathway in AD [7,36,38].

To our knowledge there has been few authors [13] measuring the excitability of presumed GABAb-ergic systems in AD. Therefore, we evaluated the cortical silent period (CSP) and transcallosal inhibition (TI), both of which may utilize GABAb [2,37] pathways, in an attempt to establish how different mechanisms interact to promote motor system hyperexcitability in AD. We also tested how these related to the degree of dementia and clinical features.

Patients and methods

Patients

Forty-five consecutive patients (29 females and 16 males, mean age 68.4 years, range 55—82 years) with a diagnosis of probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) [21] were included in this study. In all patients, computed tomography scan (CT) or magnetic resonance imaging (MRI) showed diffuse brain atrophy.

Exclusion criteria were the following: previous history of stroke, metabolic disturbance, other major medical illnesses or epilepsy. Patients with metallic objects in the body, or subjected to a craniotomy in the past, were also excluded. At the time of recruitment, none of the patients were taking cholinomimetic agents, antidepressants, neuroleptics, or sedative-hypnotic drugs for at least one week before the assessment.

The stage of dementia was evaluated by means of the Mini Mental State Examination (MMSE) [9] and Clinical Dementia Rating scale (CDR) [22].