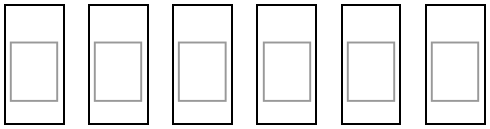

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Original Research Article

Motor Cortex Excitability Changes in Mild Alzheimer's Disease Are Reversed by Donepezil

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Key Words
Transcranial magnetic stimulation · Alzheimer's disease · Active cortical motor threshold · Resting motor threshold

Abstract
Background: Recent neuroimaging studies in humans support the clinical observations that the motor cortex is affected early in the course of Alzheimer's disease (AD). ***Methods:*** We used transcranial magnetic stimulation to measure the active cortical motor threshold (ACMT) in AD patients in the very early stage of the disease, and we explored whether and in which way the pharmacologic manipulation of the cholinergic system could have a direct effect on the excitability of the motor cortex. ***Results:*** An increase of the ACMT was observed in AD patients in the early stage in comparison to controls. After 2 months of treatment with donepezil, the threshold did not differ significantly from normal subjects. ***Conclusions:*** The results suggest an early functional impairment of cholinergic neurotransmission in AD, which is associated to early changes in the excitability of the motor system.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting cognitive functions and particularly memory. These signs reflect a dysfunction of the associative cortical areas and the limbic system. Until now, the motor cortex was supposed to be relatively spared by the neurodegenerative process. However, studies of animal models in AD showed that

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direct connections between the basal forebrain and the motor cortex are affected [1–3]. From a clinical point of view, changes in facial expression, speech, body movements and muscular tone of AD patients have been described and measured throughout the course of the disease [4, 5]. A link between executive dysfunction and gait abnormalities has been established in demented patients [6]. A recent study using functional MRI has provided experimental evidence of impaired connectivity between the motor cortex and other brain areas in early AD patients [7]. Transcranial magnetic stimulation (TMS) is a noninvasive electrophysiological tool to investigate the motor cortex excitability in normal human brain and in neurological diseases [8]. Different paradigms of stimulation can be used, such as single-pulse or double-pulse stimulation, monophasic or biphasic stimulation, and TMS can be subject to several methods of conditioning whose qualities have been evaluated through international consensus [9]. The lowest intensity of single-pulse TMS required to evoke a reproducible electromyographic response is called the motor threshold. It can be measured at rest (resting motor threshold, rMT) or during a slight voluntary contraction (active motor threshold, aMT). rMT is commonly defined as the minimum stimulus intensity required to elicit motor evoked potentials (MEPs) of more than 50 μV peak-to-peak amplitude in at least 50% of the successive trials. In contrast, aMT is usually defined as the minimum stimulus intensity needed to produce MEPs of approximately 200 μV in 50% of the consecutive trials during isometric contraction of the tested muscle (at about 20% of the maximum voluntary contraction). Due to the hyperexcitability of the motor cortex induced by the voluntary contraction, aMT is lower than rMT. The results of different studies on TMS in AD give conflicting results concerning the motor threshold [10–14]. Most studies found a significantly reduced rMT in AD patients compared to healthy controls. However, in one study [14], rMT was found to be higher in AD patients than controls. aMT was assessed in several studies, with the results being somewhat divergent from those for rMT, even within the same study. Some found significant decreases in aMT, along with rMT, in AD patients as opposed to normal subjects [10, 15]. Others found no significant differences in aMT in AD patients versus controls [11, 16].

The physiological mechanisms underlying these changes in motor threshold in AD are not known even though multiple mechanisms of modulation of cortical inhibition have been explored, such as paired- pulse TMS, short-latency afferent inhibition, intracortical inhibition or facilitation [17, 18]. Cortical plasticity and functional connectivity have also been advocated as playing a role in the changes in cortical excitability [19]. Using TMS to measure the motor threshold, we examined whether and in which way the pharmacologic manipulation of the cholinergic system in AD patients in the early stage of the disease could have a direct effect on the excitability of their motor cortex.

Patients and Methods

Patients

Twelve right-handed AD patients (6 males, 6 females, mean age 72.6 ± 9.3 years) were studied. All patients were diagnosed with probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association. According to the Clinical Dementia Rating Scale, they were in the early stage of the disease. The Mini-Mental State Examination (MMSE) was performed in all patients (table 1). The mean MMSE score was 23.5 ± 2.47. Patients who exhibited signs of other neurological diseases or were under medications with a possible effect on cognitive function or excitability of the nervous system were excluded. The neurological motor examination was normal. The patients were independent in the elementary activities of daily living even if some instrumental activities of daily living were impaired. A brain MRI to exclude cerebral vascular lesions or any cause of reversible dementia was performed in all patients. All AD patients underwent the experiment before treatment initiation with a cholinesterase inhibitor (10 mg/day of donepezil administered orally). The whole procedure was repeated after 2 months of treatment in all patients except 1 (patient 11) who did not present to follow-up.

Table 1. Description of age, MMSE score and ACMT threshold in the studied patients with mild AD

Patient	Age, years	MMSE score before donepezil	MMSE score after donepezil	ACMT before donepezil	ACMT after donepezil
1	73	26	26	34	34
2	83	21	25	33	30
3	58	26	28	33	35
4	66	24	23	42	27
5	75	18	18	40	40
6	81	23	22	37	33
7	70	23	24	39	36
8	74	25	27	38	35
9	75	21	22	33	30
10	81	24	25	37	37
11	81	25	NA	47	NA
12	54	26	26	37	32

The age-matched (71.5 ± 8.4 years) control group consisted of 13 right-handed normal subjects (7 males, 6 females) with no history of neurological disease and a completely normal neurological examination (table 1).

All patients and normal subjects were able to participate in the electrophysiological procedure. They gave their informed consent to participate in the study, which was approved by the local ethics committee.

Methods

The patients and normal subjects were seated comfortably on a chair in a quiet examination room. The compound muscle action potential of the right abductor digiti minimi was recorded with a Nicolet Viking IV IES 405-1 EMG machine to assess the response to TMS.

TMS was used in accordance with the consensus guidelines [20]. It was applied by a Magstim 200 stimulator (Magstim Ltd., Withland Dyfed, UK) through a circular coil with a diameter of 9 cm, located at the vertex area of the scalp. The circular coil was chosen instead of a more focal eight-shaped one to reduce the procedure duration. The center of the coil was measured on the line between the nasion and the inion point in each patient to ensure the reproducibility of the procedure from the first session to the second one performed 2 months later. The circulating current was turning clockwise in order to elicit a response in the target muscle. The subjects were asked to perform a slight isometric voluntary contraction of the right abductor digiti minimi (around 10% of the maximum voluntary muscle contraction) during the TMS, with an auditory feedback. This active cortical motor threshold (ACMT), defined as the minimal intensity of cortical stimulation, which produces MEPs of approximately 200 μV in 50% of the consecutive trials during isometric contraction of the tested muscle (at about 20% of the maximum voluntary contraction), was determined by lowering the stimulator output gradually from 60% of the maximal output. The aMT method was preferred to the resting one because AD patients showed difficulties in maintaining absolute rest during the duration of the experiment.

The results were compared and statistically analyzed between the groups by using the unpaired Student t test. A correlation between the MMSE score and the motor threshold in untreated patients was investigated by the Pearson correlation test.

Results

The mean ACMT in normal subjects was 32.77% (SD ±7.68). Before treatment with donepezil, the mean ACMT was 37.50% (SD ±4.18) in AD patients. The difference in the ACMT between AD patients before treatment and normal subjects was significant ($p < 0.05$). In the 11 AD patients who underwent the experiment after being treated with donepezil for 2 months, the mean ACMT was 33.54% (SD ±3.67).

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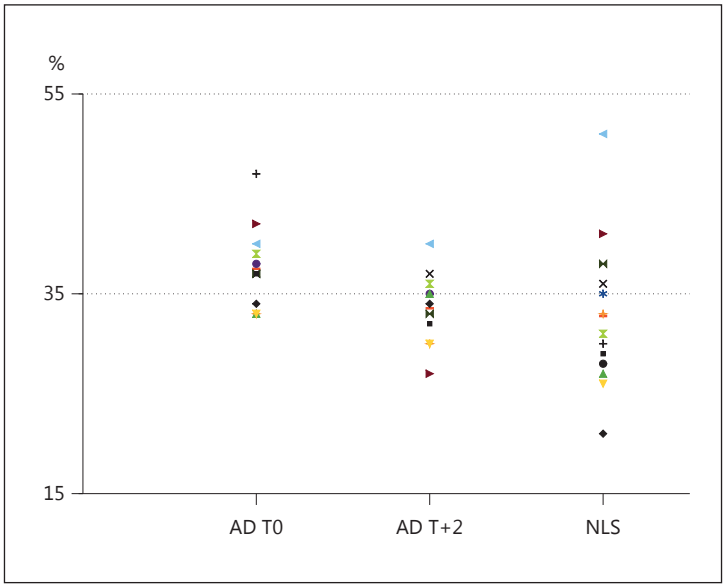

Fig. 1. Distribution of individual values of aMT (expressed in %) in AD patients before treatment with donepezil (AD T0), in AD patients after 2 months of donepezil treatment (AD T+2) and in normal subjects (NLS).

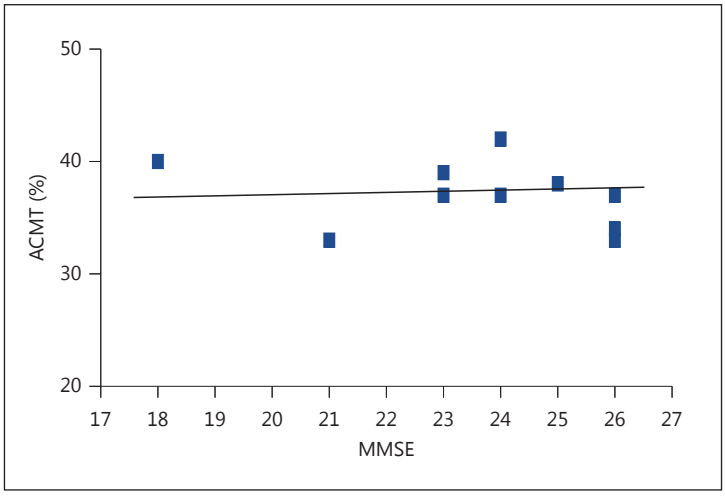

Fig. 2. Relationship between values of MMSE in untreated AD patients and the ACMT. A weak positive correlation (R = 0.04) was found.

The difference in the ACMT between treated AD patients and normal subjects was not statistically significant. The difference in the ACMT in AD patients before and after treatment was significant ($p < 0.05$), either after inclusion or exclusion of patient 11 (fig. 1). Similarly, the mean MMSE score was slightly increased in the treated patients (24.18 ± 2.82) compared to the group before treatment (23.5 ± 2.47), however, without a statistical difference. When a Pearson correlation test was performed between the MMSE value and the value of the ACMT in untreated patients, the obtained R showed a weak value of 0.04. Nevertheless, this was a positive value indicating a trend of the ACMT to increase with the MMSE score (fig. 2).

Discussion

Our results show a significant increase in the ACMT of TMS in early-stage AD patients compared to normal subjects. There is even a positive but weak correlation between the MMSE and aMT value. The limitations of this study include the following: the small number

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of patients, the lack of an extensive neuropsychological battery and the focus on the aMT measure only. Nevertheless, our results show that the cortical motor threshold is increased in mild AD in contrast to previous studies [10–13], which have shown a decrease in the cortical motor threshold in AD patients. However, in another study [21], rMT and aMT were studied in patients with very mild AD. Both were found to be increased in the group of AD patients compared to controls, even if this increase did not reach statistical significance. Perretti et al. [14] had also shown a slight increase in the motor threshold, particularly in severely affected patients. This was explained by cortical atrophy, which increases the distance between the site of stimulation on the scalp and the motor cortex. Vascular mechanisms are also advocated, but in non-demented vascular patients there is no change in rMT [22]. It could be more common in the later stage of AD [23] and influence the level of the motor threshold. This was not the case in our patients as they were in the early stage of the disease, and their brain MRIs showed neither atrophy in the area of the motor cortex nor vascular damage. Moreover, the fact that the motor threshold is modulated by a cholinesterase inhibitor suggests a functional mechanism rather than a technical effect of atrophy.

One of the explanations for the different results of our study in comparison with the previous ones is the disease stage of our patients. Indeed, contrary to the study by Pepin et al. [10], in which most of the patients had moderate or severe AD (mean MMSE score 17.1 ± 3.78), in the present study, we have recruited patients who were all in the early phase of the disease (mean MMSE score 23.5 ± 2.47). In the study by Di Lazzaro et al. [12], which showed a reduced active threshold in AD, the mean MMSE score was 19.35 ± 3.8 (range 9–28). For mild cognitive impairment, there is also data on rMT with either an increase [24] or a trend to decrease [25, 26] compared to controls and AD patients. There is also data available on aMT in MCI, which show no difference with the control group [27]. This increase in aMT that we observed in our experiments in mild AD could reflect the clinical changes seen in patients in the early stage of the disease when they appear to be less reactive, slower in their movements and with diminished facial expression [5], while AD patients in a more advanced stage are often hyperkinetic with motor disinhibition. Thus, we could hypothesize that in AD, there is a modulation of the excitability of the motor cortex in function of the stage of the disease, with an initial increase in the motor threshold and a secondary decrease as the disease progresses. This change in the excitability of the motor cortex during the course of AD is also advocated to explain the discrepancies in the motor threshold during the time course of amyotrophic lateral sclerosis [28]. It could be a common adaptive phenomenon in neurodegenerative diseases, seen like a trial to compensate a functional disequilibrium in the motor output. Vascular mechanisms could be added in later stages of the disease.

It is known from neuroimaging and pathological studies in humans and from animal experiments [29] that in the early disease course, there is no loss of cholinergic neurons in the brains of AD patients. There is a modulation of the synaptic cleft associated to a dysfunction of the cholinergic neurons and a loss of signaling by the nerve growth factor in the cholinergic neurons [30]. This leads to a mild loss of the acetylcholinesterase activity without significant neuronal loss. There is recent evidence from animal experiments [1] showing that beside the already known indirect pathway between the limbic system and the motor cortex via the basal ganglia and the prefrontal cortex, there are also direct connections from the basal forebrain and particularly from the nucleus basalis of Meynert to the motor cortex in rats. The increased motor threshold in the early stage of AD could reflect the dysfunction of these direct connections. Another argument for the implication of these cholinergic connections in the excitability of the motor cortex in AD patients is the effect of donepezil on the motor threshold observed in our study, where the threshold is restored to the normal range by the medication. This is in agreement with the study by Ferreri et al. [31] who showed a decreased rMT after

chronic cholinesterase inhibitor treatment in AD patients. It is also an argument for a loss of function and not a loss of neurons, at least in early AD.

The results of our experiment confirm the imaging studies from a neurophysiologic point of view suggesting an early impairment of cholinergic neurotransmission in AD [32] and support the concept of functional changes in the motor system in early AD. The normalization of the ACMT by donepezil is a strong argument in favor of this hypothesis. Further studies are needed to evaluate the time course of the excitability of the motor cortex in parallel to the progression of AD.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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