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Short Report

Effect of donepezil on transcranial magnetic stimulation parameters in Alzheimer's disease

Yun Tae Hwang[a,b,1], Lorenzo Rocchi[a,1], Paul Hammond[a], Chris JD. Hardy[a], Jason D. Warren[a], Basil H. Ridha[c], John Rothwell[a], Martin N. Rossor[d,*]

[a]Institute of Neurology, University College London, London, United Kingdom
[b]Brain and Mind Centre, University of Sydney, Camperdown, New South Wales, Australia
[c]NIHR Queen Square Dementia Biomedical Research Unit, Institute of Neurology, University College London, London, United Kingdom
[d]Dementia Research Centre, Institute of Neurology, University College London, London, United Kingdom

Abstract

Introduction: There is a need for a reliable, noninvasive biomarker for Alzheimer's disease (AD). We assessed whether short-latency afferent inhibition (SAI), a transcranial magnetic stimulation paradigm that assesses cholinergic circuits of the brain, could become such a biomarker.
Methods: Nineteen patients with AD underwent four SAI testing sessions. The timing of their usual donepezil dose was altered to create different cholinergic states for each session. This was compared to the SAI results from 20 healthy subjects.
Results: SAI was not able to distinguish the different cholinergic states assessed in our study. There appeared to be a diurnal variation in cholinergic function in the control group, which was not present in the AD cohort.
Discussion: SAI does not appear to have a role in diagnosis and assessment of AD patients. The loss of diurnal variation, however, warrants further investigation as it may provide further biochemical insights about AD.

Keywords: Alzheimer's disease; Response to treatment; Transcranial magnetic stimulation; Short-latency afferent inhibition; Acetylcholinesterase inhibitor; Donepezil

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting cognition, usually beginning with memory impairment and executive dysfunction [1]. Biochemically, it is characterized by a cholinergic deficit in the brain [2]. Increasing acetylcholine levels using a cholinesterase inhibitor (ChEI) such as donepezil can produce a modest symptomatic benefit in patients with AD [1]. Cholinergic deficit parallels worsening of cognitive deficits despite treatment with a ChEI [3].

Currently available biomarkers of AD are nonspecific, invasive, and/or expensive. There is a need to develop reliable, noninvasive, safe, and cheap biomarkers for AD that can assess disease progression over time. Such biomarkers will be invaluable in confirming the diagnosis and could act as a quantitative and/or objective marker of potential therapeutic benefit in clinical trials.

Transcranial magnetic stimulation (TMS) is a noninvasive, relatively cheap neurophysiological technique that assesses the excitability of the motor cortex. A specific paradigm—short-latency afferent inhibition (SAI), which couples TMS with a conditioning electric stimulus on the peripheral nerve—has been designed to measure the excitability of cholinergic circuits within human cerebral motor cortex [4,5]. This results in a reduction in amplitude of motor evoked potentials (MEPs) obtained

[1]Equal first author.
*Corresponding author. Tel.: +44 203 448 4773; Fax: +44 203 448 3104 .
E-mail address: m.rossor@ucl.ac.uk

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with TMS. SAI is abolished with administration of intravenous scopolamine, suggesting that it is at least partly mediated by cortical cholinergic activity [5]. In a small study, AD patients had reduced SAI compared to control subjects reflecting their cholinergic dysfunction [6]. In a subgroup of six AD patients in the same study, SAI increased after a single dose of rivastigmine, a ChEI [6]. This study aimed to assess whether SAI can be used as a biomarker of AD pathology and response to treatment with a ChEI.

2. Materials and methods

2.1. Participants

Nineteen AD patients meeting the consensus criteria for typical mild-to-moderate AD [7] treated with donepezil once daily and 20 healthy subjects (HS) participated in the study. Their demographics and clinical characteristics are summarized in Table 1. This study has been approved by the appropriate local and national research ethics committees, and all participants gave informed consent in accordance with the Declaration of Helsinki.

Table 1
Demographic and neurophysiological profiles of the participants

	Control	AD
Gender (M:F)	9:11	9:10
Age (years ± SD)	66.3 ± 7.0	71.0 ± 8.1
Handedness (R:L)	19:1	19:0
MMSE (/30 ± SD)	29.8 ± 0.5	23.4 ± 3.3
MMSE < 24	0	11
Symptom duration (years ± SD)	N/A	4.0 ± 2.0
Range of symptoms (years ± SD)	N/A	2–8
Donepezil taken (night:day)	N/A	12:8
Donepezil dose (10 mg:5 mg)	N/A	18:1*
Donepezil treatment duration (years ± SD)	N/A	1.7 ± 1.1
Interval between 2 visits (days ± SD)	13.7 ± 1.0	14.4 ± 2.3
Sensory threshold (mA ± SE)		
Morning	2.60 ± 0.96	2.80 ± 1.08
Afternoon	2.55 ± 0.78	2.88 ± 0.91
SEP stimulation intensity (mA ± SE)		
Morning	7.79 ± 2.89	8.36 ± 3.30
Afternoon	7.64 ± 2.45	8.78 ± 2.74
N20 latency (ms ± SE)		
Morning	20.43 ± 1.24	20.26 ± 1.42
Afternoon	20.44 ± 1.43	20.11 ± 1.45
N20-P25 amplitude (μV ± SE)		
Morning	6.19 ± 3.28	6.37 ± 3.53
Afternoon	6.45 ± 3.32	6.54 ± 3.88
Resting motor threshold (%MSO ± SE)		
Morning	47.65 ± 8.17	49.24 ± 12.22
Afternoon	47.60 ± 9.84	49.95 ± 12.70
1 mV motor threshold (%MSO ± SE)		
Morning	64.41 ± 14.44	71.74 ± 17.89
Afternoon	62.49 ± 13.74	72.34 ± 21.09

Abbreviations: AD, Alzheimer's disease; SD, standard deviation; SE, standard error; M, male; F, female; R, right; L, left; MMSE, Folstein Mini–Mental Status Examination; N/A, not applicable; SEP, sensory evoked potential; MSO, maximum stimulator output.

NOTE. Resting motor threshold and 1-mV motor threshold are measured as a percentage of the maximum stimulator output.

*One patient on 5 mg did not tolerate titration to 10 mg and was stepped down to 5 mg several months before enrollment in this study.

2.2. Experimental procedures

SAI was tested four times over two separate visits in all participants. There were two sessions per visit, 4 hours apart ("morning" and "afternoon" sessions). The AD group was asked to delay their daily dose of donepezil preceding the visit until immediately after the completion of the morning TMS session, for an interval of at least 24 hours between donepezil ingestion and the morning TMS session. This timing was based on the pharmacokinetic properties of donepezil to create a relatively deficient cholinergic state for the morning session, compared to the afternoon session occurring 4 hours later, when the serum level of donepezil is expected to be at its peak [8,9].

2.3. Resting motor threshold and SAI

Resting motor threshold was defined as the lowest TMS intensity applied over the left primary motor cortex able to evoke an MEP of at least 50 μV in 5 of 10 consecutive trials during rest in the right first dorsal interosseous muscle. SAI was performed using the method previously described by Tokimura et al. [4]. Briefly, SAI was obtained by coupling a TMS pulse applied over primary motor cortex, at an intensity able to elicit a MEP of around 1 mV amplitude from the right first dorsal interosseous (1 mV-int), with an electric stimulus of 200 μs duration and a somatosensory stimulation intensity (SST) of 300% of the somatosensory threshold over the right median nerve. The interstimulus interval (ISI) between electric and magnetic pulse was adjusted based on individual latency of the N20 component of somatosensory evoked potentials recorded over the left hemisphere according to current guidelines [10], using the same SST of SAI. Fifteen trials for single, control TMS pulse and for each ISI (N20 +2, +4, +6 and +8 ms) were collected in a randomized order. SAI was then calculated as the ratio between the averages of conditioned and control MEP at each ISI.

2.4. Statistical analysis

Age and neurophysiological variables (SST, somatosensory evoked potential N20 latency, somatosensory evoked potential N20-P25 amplitude, resting motor threshold, and 1 mV-int) were compared between AD