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Discrimination of atypical parkinsonisms with transcranial magnetic stimulation

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ABSTRACT

Background: Differential diagnosis of atypical parkinsonian disorders, i.e. dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS) still remains problematic. Furthermore, DLB may overlap with Alzheimer's disease (AD) in the early stages of disease.
Objective: To determine whether transcranial magnetic stimulation (TMS) can be used to classify atypical parkinsonian disorders and AD.
Methods: A paired-pulse TMS multi-paradigm approach assessing multiple intracortical circuits, as short interval intracortical inhibition-facilitation and short latency afferent inhibition, was used to model a decision tree analysis and determine diagnostic accuracy in classifying different neurodegenerative disorders.
Results: We observed a significant impairment in short latency afferent inhibition in AD and DLB and a significant impairment in short interval intracortical inhibition-facilitation in DLB, PSP and CBS patients. These parameters were used to model a decision tree analysis which yielded an overall diagnostic accuracy of 88.3%, with 90.5% for AD, 85.2% for DLB, 76.0% for CBS-PSP, and 94.9% for healthy controls.
Conclusions: The assessment of intracortical connectivity with TMS may aid in the differential diagnosis of AD and the atypical parkinsonian disorders.

Introduction

Atypical parkinsonian disorders (APD) represent a heterogeneous group of neurodegenerative diseases in which parkinsonian symptoms are often accompanied by additional features, including gaze palsy, apraxia, poor response to levodopa, and early cognitive decline [1].

Although the diagnosis is based on established clinical criteria, early differential diagnosis of APD, i.e. dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS) still remains problematic, and in clinical-pathological studies as much as 25% of patients with parkinsonian syndromes can be misdiagnosed [2]. Furthermore, DLB and Alzheimer's disease (AD), which are the most common forms of neurodegenerative dementia, can be difficult to distinguish in the early phase because of common and overlapping clinical features [3,4].

No biological markers are available to corroborate APD diagnosis on clinical grounds, and MRI atrophy patterns have showed good specificity but low sensitivity, especially in the early disease stages [5]. Currently, presynaptic dopaminergic imaging is the most reliable diagnostic tool in the differential diagnosis of DLB and AD [6,7].

As reported, different techniques have succeeded in distinguishing individual disorders, however falling short in providing a comprehensive differential diagnostic approach to distinguish different APD.

In this view, transcranial magnetic stimulation (TMS) has been shown to be a reliable technique to non-invasively assess specific neurotransmitter circuits (i.e. GABA, glutamate, acetylcholine), thus reflecting the underlying neuropathological process.

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In this context, it is now well established that neurodegenerative disorders are characterized by a dysfunction of specific neurotransmitter circuits, and an impairment in cholinergic function has been widely reported in patients with AD and DLB [5]. Similarly, it has been demonstrated that GABAergic and glutamatergic interneurons are impaired by pathological tau inclusions, which are the main hallmarks of PSP and CBS [8,9].

In this view, TMS paired-pulse paradigms, as short-latency afferent inhibition (SAI), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), have been shown to accurately reflect cholinergic, GABAergic and glutamatergic intracortical circuits, respectively [10–13]. Nevertheless, most of these studies have been hindered by the limited number of included patients while none have assessed the diagnostic accuracy of these parameters in distinguishing all these disorders at the same time.

Based on these premises, we assessed SAI and SICI-ICF circuits in a cohort of patients with DLB, PSP, CBS and AD, and developed a diagnostic decision tree to correctly classify patients and healthy controls (HC) according to neurophysiological parameters.

Materials and methods

Subjects

In the present study, patients with APD or AD, according to current clinical criteria [14–17], were recruited from the Centre for Ageing Brain and Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy. Moreover, a group of age-matched healthy subjects were recruited among healthy volunteers (HC).

Patients with a history of epilepsy or with electronic implants were excluded from the study.

Full written informed consent was obtained from all subjects according to the Declaration of Helsinki. The study protocol was approved by the Brescia Hospital ethics committee.

Transcranial magnetic stimulation

TMS was performed with a figure-of-eight coil (each loop diameter 70 mm) connected to a Magstim Bistim^2 system (Magstim Company, Oxford, UK) as previously reported [18]. The magnetic stimuli had a monophasic current waveform (rise time of 100 μs, decaying back to zero over 800 μs). Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle (FDI) through surface Ag/AgCl electrodes placed in a belly-tendon montage and acquired using a Biopac MP-150 electromyograph (BIOPAC Systems Inc., Santa Barbara, CA, USA).

The TMS coil was held tangentially over the scalp region corresponding to the primary hand motor area contralateral to the target muscle, with the coil handle pointed 45° posteriorly and laterally to the sagittal plane.

The motor hot spot was defined as the location where TMS consistently produced the largest MEP size at 120% of the resting motor threshold (rMT) in the target muscle and was marked with a felt tip pen on the scalp to ensure constant placement of the coil throughout the experiment.

rMT was defined as the minimal stimulus intensity needed to produce motor evoked potentials (MEPs) with an amplitude of at least 50 μV in 5 out of 10 consecutive trails during complete muscle relaxation, which was controlled by visually checking the absence of EMG activity at high-gain amplification [13].

SICI-ICF were studied at rest via a paired-pulse paradigm, delivered in a conditioning-test design with the conditioning stimulus (CS) set at an intensity of 70% of the rMT, while the test stimulus (TS) was adjusted to evoke a MEP approximately 1 mV peak-to-peak in the relaxed FDI. Different interstimulus intervals (ISIs) between the CS and TS were employed to investigate preferentially both SICI (1, 2, 3, 5 ms) and ICF (7, 10, 15 ms) [10,11].

SAI was studied using a previously described technique [12]. CS were single pulses (200 μs) of electrical stimulation applied through bipolar electrodes to the right median nerve at the wrist (cathode proximal). The intensity of the CS was set at just over motor threshold for evoking a visible twitch of the thenar muscles while the TS was adjusted to evoke a MEP of approximately 1 mV peak-to-peak. The CS to the peripheral nerve preceded the TS by different ISI ($^-$4, 0, $^+$4, $^+$8 ms, determined relative to the latency of the N20 component of the somatosensory evoked potential).

Ten stimuli were delivered for each ISI for all stimulation paradigms and fourteen control MEPs in response to the TS alone were recorded, for each paradigm, in all participants in a pseudo-randomized sequence. The amplitude of the conditioning MEPs was expressed as a ratio of the mean unconditioned response. The inter-trial interval was set at 5 s (±10%).

SICI-ICF and SAI protocols were performed in a randomized order. Throughout the experiment, complete muscle relaxation was monitored by audio-visual feedback where appropriate. If the study

Table 1
Clinical and demographic characteristics of enrolled patients.

	AD	DLB	CBS	PSP	HC	*p*-value*
Patients (n)	63	27	12	13	39	–
Age (years)	71.7 ± 7.8	71.9 ± 6.3	66.7 ± 6.7	68.4 ± 6.8	68.6 ± 8.1	n.s.
Age at onset (years)	67.5 ± 7.5	69.2 ± 6.5	64.3 ± 6.3	64.8 ± 6.0	–	$p = 0.047$
Gender (% female)	50.8	18.5	42.9	53.8	66.7	$p = 0.004$
MMSE	20.4 ± 6.2	22.6 ± 1.5	26.3 ± 5.7	21.8 ± 4.0	–	$p = 0.001$
BADL	1.2 ± 1.6	1.9 ± 1.4	1.1 ± 1.4	1.3 ± 1.5	–	n.s.
IADL	3.0 ± 2.7	3.5 ± 1.3	1.4 ± 1.6	1.6 ± 2.4	–	n.s.
UPDRS-III	–	15.9 ± 13.3	25.3 ± 9.2	19.1 ± 7.4	–	n.s.
rMT (% MSO)	43.1 ± 8.2	41.6 ± 9.7	48.8 ± 10.4	43.2 ± 9.5	44.5 ± 8.0	n.s.
mean SICI 1, 2, 3 ms	27.3 ± 10.3	64.4 ± 17.4	62.5 ± 41.3	80.2 ± 32.8	24.4 ± 8.4	$p < 0.001$
mean ICF 7, 10, 15 ms	143.5 ± 18.9	91.8 ± 11.9	96.8 ± 29.3	88.6 ± 20.6	145.3 ± 15.7	$p < 0.001$
mean SAI 0, $^+$4 ms	86.6 ± 9.6	78.6 ± 13.7	56.1 ± 14.9	55.1 ± 11.6	51.5 ± 11.9	$p < 0.001$

Demographic, clinical and neurophysiological characteristics are expressed as mean ± standard deviation; rMT is expressed as ratio of the MSO; SICI-ICF and SAI are expressed as ratio of the mean MEP amplitude related to the control MEP.
AD = Alzheimer's disease; DLB = dementia with Lewy bodies; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; HC = healthy controls; MMSE = mini mental state examination; BADL = basic activities of daily living; IADL = instrumental activities of daily living; UPDRS-III = Unified Parkinson's Disease Rating Scale - part III; rMT = resting motor threshold; % MSO = percentage of maximal stimulator output; SICI-ICF = short interval intracortical inhibition-intracortical facilitation; SAI = short latency afferent inhibition; MEP = motor evoked potential.
*significant one-way ANOVA interaction or chi-square test of independence, as appropriate.