

Functional evaluation of central cholinergic circuits in patients with Parkinson's disease and REM sleep behavior disorder: a TMS study

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Abstract Central cholinergic dysfunction has been reported in patients with Parkinson's disease (PD) and hallucinations by evaluating short latency afferent inhibition (SAI), a transcranial magnetic stimulation protocol which gives the possibility to test an inhibitory cholinergic circuit in the human brain. REM sleep behavior disorder (RBD) was also found to be associated with cognitive impairment in PD patients. The objective of the study was to assess the cholinergic function, as measured by SAI, in PD patients with RBD (PD-RBD) and PD patients without RBD (PD-nRBD). We applied the SAI technique in 10 PD-RBD patients, in 13 PD-nRBD patients and in 15 age-matched normal controls. All PD patients and control subjects also underwent a comprehensive battery of neuropsychological tests. Mean SAI was significantly reduced in PD-RBD patients when compared with PD-nRBD

patients and controls. Neuropsychological examination showed mild cognitive impairment in 9 out of the 10 PD-RBD patients, and in 5 out of the 13 PD-nRBD. SAI values correlated positively with neuropsychological tests measuring episodic verbal memory, executive functions, visuoconstructional and visuo-perceptual abilities. Similar to that previously reported in the idiopathic form of RBD, SAI abnormalities suggest a cholinergic dysfunction in PD patients who develop cognitive impairment, and present findings indicate that RBD is an important determinant of MCI in PD.

Keywords Parkinson's disease · REM sleep behavior disorder · Transcranial magnetic stimulation · Short latency afferent inhibition

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Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a clinical condition characterized by an intermittent or complete loss of muscle atonia and an increase of phasic muscular activity during REM sleep, leading to complex nocturnal motor behaviors (Mahowald and Schenck 2000).

RBD affects mainly older men and may occur alone (idiopathic form) or in association with a variety of neurological disorders. In particular, RBD is frequently associated with synucleinopathies (Boeve et al. 2001; Iranzo et al. 2006; Postuma et al. 2009), including Parkinson's disease (PD) (Schenck et al. 1996a; Comella et al. 1998; Gagnon et al. 2002a, b). RBD often precedes the clinical onset of the neurodegenerative disease.

The pathophysiological mechanisms of RBD are still matter of debate. Animal models studies (Jouvet and

Delorme 1965; Hendricks et al. 1982) and neuropathological observations in humans (Uchiyama et al. 1995; Schenck et al. 1996b; Turner et al. 2000; Arnulf et al. 2000) suggest that some brainstem structures, in particular the ventral mesopontine junction, the pedunculopontine nucleus (PPN), the laterodorsal tegmental nucleus, the locus coeruleus (LC), and the peri-LC area, are involved in the pathogenesis of the disease. From PPN and LC originate the most numerous cholinergic and noradrenergic neurons within the brainstem reticular formation, respectively (Jones 2000). These pontine structures play a critical role in arousal, cortical activation, and cognitive functions (Berridge et al. 1993; Kleiner and Bringmann 1996; Steckler et al. 1994, Winn 1998; Aston-Jones et al. 1999).

A modulatory role of the dopaminergic system in behavioral arousal and alertness has been documented; however, abnormalities in dopaminergic neurotransmission are not sufficient to explain the occurrence of RBD and cognitive impairment in all PD patients.

There is evidence that a moderate cholinergic deficit is present in several cortical regions in patients with PD (Hilker et al. 2005). Moreover, poor performance of tasks assessing visuospatial and attentional/frontal lobe functions can be associated with cortical cholinergic denervation in patients with PD and dementia (Bohnen et al. 2006).

In vivo evaluation of some cholinergic circuits of the human brain has recently been introduced using a transcranial magnetic stimulation (TMS) protocol that may reveal information about the function of some cholinergic circuits in the human brain. This technique relies on short latency afferent inhibition (SAI) of the motor cortex (Tokimura et al. 2000). SAI is significantly reduced in cholinergic forms of dementia, such as AD and dementia

with Lewy bodies (Di Lazzaro et al. 2002, 2004b, 2005a, 2007) and in AD patients it can be increased by ACh inhibitors (Di Lazzaro et al. 2005a), while SAI is normal in non-cholinergic forms of dementia, such as fronto-temporal dementia (Di Lazzaro et al. 2006). Recently, SAI was also found to be reduced in patients with amnesic mild cognitive impairment (MCI) in multiple domains (Nardone et al. 2012a) and in patients with idiopathic REM sleep behavior disorder (iRBD) (Nardone et al. 2012b). SAI has never been investigated in patients with PD and RBD compared with those without.

The aim of the present study was to evaluate whether there is a cholinergic dysfunction, as evaluated by means of SAI testing, in PD patients with RBD. We also examined the relationship between neurophysiological findings and the cognitive performances in neuropsychological tests.

Materials and methods

Patients

Ten PD patients with concomitant RBD (PD-RBD; 2 women, mean age 65.9 ± 6.5 years), 13 PD patients without RBD (PD-nRBD; 4 women, mean age 63.7 ± 6.4 years), and 15 male healthy control subjects (4 women, mean age 66.4 ± 7.0 years) were recruited for the study. Demographic and clinical features are shown in Table 1.

Subject underwent one-night polysomnography (PSG). The PD-RBD patients fulfilled standard clinical criteria for RBD (American Academy of Sleep Medicine 2005), and showed excessive phasic or tonic electromyography

Table 1 Demographic and clinical characteristics of the patients with Parkinson disease (PD) and REM sleep behavior disorder (PD-RBD), PD patients without REM sleep behavior disorder (PD-nRBD) and control subjects

	PD-RBD patients ($N = 10$)		PD-nRBD patients ($N = 13$)		Controls ($N = 15$)	
	<i>M</i>	(SD)	<i>M</i>	(SD)	<i>M</i>	(SD)
Age (years)	65.9	(6.5)	63.7	(6.4)	66.4	(7.0)
Education (years)	10.1	(3.8)	10.5	(3.7)	10.9	(4.0)
PD disease duration (years)	5.0	(2.3)	6.0	(2.8)	–	
RBD disease duration (years)	6.0	(2.5)	–		–	
L-Dopa equivalent dose (mg)	578	(2.9)	627	(341)	–	
BDI-II	7.9	(1.8) ⁺	5.2	(1.9)	3.7	(1.5)
UPDRS part III	17.5	(4.3) [*]	18.3	(4.3) [*]	2.7	(1.1)
MMSE	26.6	(1.4) ⁺	28.2	(1.3) [*]	29.5	(0.6)
DRS	135.8	(2.7) [*]	140.2	(4.0)	141.0	(1.6)

Data are expressed as mean values (SD)

BDI-II Beck-II Depression Inventory, *UPDRS* unified Parkinson's disease rating scale, *MMSE* mini-mental state examination, *DRS* dementia rating scale

* Significant difference ($P < 0.01$, Tukey-HSD) compared to control group, ⁺significant difference compared to PD-nRBD group

(EMG) activity during REM sleep defined as tonic chin EMG activity for more than 20 % of the total REM sleep episode (Gagnon et al. 2002a).

None of the patients or control subjects had a history of other neurological, psychiatric, or cardiovascular disorder. All patients completed the Unified Parkinson's disease Rating Scale (UPDRS) part III (Fahn et al. 1987), and were screened for depression according to the Beck Depression Inventory (BDI)-II (Beck et al. 1996). In order to control for vigilance impairment, the four choice reaction time test (FCRTT), a sensitive tool measuring attentional decrement, was administered to each subject (Wilkinson and Houghton 1975; Glenville and Wilkinson 1979). Cut-off values of BDI-II and FCRTT were score of 14 and 1 s (upper reaction time), respectively.

All patients were treated with L-DOPA alone or in combination with a dopamine-agonist. An L-DOPA equivalent dose was calculated for each patient using a conversion formula (Williams-Gray et al. 2007; Rowe et al. 2008) and shown in Table 1. None of the subjects were treated with anticholinergic medication or other drugs known to influence the motor cortex excitability. In particular, none of the patients were treated with benzodiazepines before the examination.

Patients provided informed consent before participation in this study, which was performed according the Declaration of Helsinki and approved by the local Ethics Committee of the Christian Doppler Clinic.

Neuropsychological examination

The battery included two tests of global cognitive function: the MMSE and the dementia rating scale. Executive functions were assessed by the Trail Making test parts A and B (outcome measure = time in seconds), the Stroop color word test (outcome measure = time in seconds and number of errors on the interference condition), and the letter and semantic (fruit/vegetable, and animal items) fluency tests. Episodic verbal memory was assessed by the Rey auditory verbal learning test (outcome measure = total number of words in trials 1 to 5, immediate recall, delayed recall, and correct recognition). Visuospatial abilities were assessed by the copy of the Rey-Osterrith complex figure and the block design subtest from the Wechsler Adult Intelligence Scale-III (adjusted score). Finally, visuo-perceptual (visual exploration) abilities were assessed by the Bells test (outcome measure = number of omissions) (for reference and description of all tests, see Lezak et al. 2004).

The diagnosis of MCI was made according to the revised criteria of Petersen and Morris (2005), with a cut-off of 1.5 SD.

Transcranial magnetic stimulation

TMS was performed using a High-power Magstim 200 magnetic stimulator (Magstim Co., Whitland, Dyfed, UK) connected to a Bistim module throughout all measurements. A figure-of-eight coil with external loop diameters of 9 cm was held over the motor cortex at the optimum scalp position to elicit motor responses in the first dorsal interosseous (FDI) muscle. The dominant hemisphere was selected for stimulating patients and healthy subjects. The induced current flows in a postero-anterior direction. Motor evoked potentials (MEPs) were recorded via two 9-mm diameter Ag–AgCl electrodes with the active electrode applied over the motor point of the muscle and the reference on the metacarpophalangeal joint of the index finger. MEPs were amplified and filtered (bandwidth 3–3,000 Hz) by D150 amplifiers (Digitimer, Welwyn Garden City, Hertfordshire, UK).

All patients were examined in the on state.

We evaluated the following TMS parameters: the resting motor threshold (RMT), the central motor conduction time (CMCT), the short latency intracortical inhibition (SICI), and intracortical facilitation (ICF) to paired TMS, and the SAI.

RMT was defined as the minimum stimulus intensity that produced a minimal motor evoked response (about 50 μ V in 50 % of 10 trials) at rest. CMCT was calculated by subtracting the peripheral conduction time from spinal cord to muscles from the latency of responses evoked by cortical stimulation with the formula: MEP latency – (F latency + M latency – 1)/2 (Rossini et al. 1994).

SICI and ICF were studied using the technique of Kujirai et al. (1993). Two magnetic stimuli were given through the same stimulating coil over the motor cortex and the effect of the first (conditioning) stimulus on the second (test) stimulus was investigated. The intensity of the conditioning stimulus was set to 80 % RMT; the second (test) shock intensity was adjusted to evoke a MEP in relaxed FDI with an amplitude of approximately 1 mV, peak-to-peak.

The timing of the conditioning shock was altered in relation to the test shock. Inhibitory interstimulus intervals (ISIs) of 2, 3, and 5 ms and facilitatory ISIs of 7, 10, and 20 ms were investigated. Ten stimuli were delivered at each ISI also for test stimulus and single MEP. For these recordings, muscle relaxation is very important and the subject was given audiovisual feedback at high gain to assist in maintaining complete relaxation. The presentation of conditioned and unconditioned trials was randomised. The amplitude of the conditioned EMG responses was expressed as the percentage of the amplitude of the test EMG responses. The amplitudes of the conditioned

responses were averaged obtaining grand mean amplitudes of the three inhibitory and of the three facilitatory ISIs.

SAI was studied using the recently described technique (Tokimura et al. 2000). Conditioning stimuli were single pulses (200 μ s) of electrical stimulation (with the cathode positioned proximally), applied through bipolar electrodes to the median nerve at the wrist. The intensity of the conditioning stimuli was set at just over motor threshold for evoking a visible twitch of the thenar muscles. The intensity of the test cortical magnetic shock was adjusted to evoke a muscle response in relaxed FDI with an amplitude of approximately 1 mV peak-to-peak. The conditioning stimulus to the peripheral nerve preceded the test magnetic cortical stimulus. ISIs were determined relative to the latency of the N20 component of the somatosensory evoked potential evoked by stimulation of the median nerve. In right-handed subjects, the active electrode for recording the N20 potential was attached 3 cm posterior to C3 (10–20 system), and the reference was 3 cm posterior to C4 (vice-versa for left-handed subjects). Five hundred responses were averaged to identify the latency of N20 peak. ISIs from the latency of the N20 component plus 2 ms to the latency of the N20 component plus 8 ms were investigated in steps of 1 ms.

Eight stimuli were delivered at each ISI also for test stimulus and single MEP. We calculated the average of the MEP obtained after cortical magnetic stimulation alone, and the average of the MEP obtained by conditioning cortical magnetic stimulus with a peripheral stimulus to the median nerve at the wrist at the seven different ISIs studied. The amplitude of the conditioned MEP was expressed as a percentage of the amplitude of the test MEP. The percentage inhibition of the conditioned responses at the seven different ISIs was averaged to obtain a grand mean. Subjects were given audio–visual feedback at high gain to assist in maintaining complete relaxation.

In order to clarify a possible spinal or peripheral contribution on the motor cortex excitability parameters, supra-maximal stimulation (0.2 ms square-wave constant current pulses) of the ulnar nerve at the wrist was used to assess spinal and peripheral motor excitability. While FDI was relaxed, the peak-to-peak amplitude of F waves (average, 20 trials) and CMAP (maximum, 3 trials) were determined. We identified the F waves according to the criteria reported by the International Federation of Clinical Neurophysiology as responses that are variable in their latency, amplitude and configuration, but that occur grouped with a consistent range of latency (Kimura et al. 1994).

Statistical analysis

The demographic and clinical data, the neurophysiological parameters (SAI, RMT, SICI, ICF, CMCT, CMAP and

F-wave), and all the neuropsychological measures were analysed by means of an ANOVA for repeated measures. If the ANOVA reveals a significant group effect, groups were compared by means of Tukey HSD post hoc comparisons.

To evaluate the relationship between the electrophysiological parameters and the examined neuropsychological measures, a partial correlation analysis controlling for the variables age and educational level was carried out. This analysis was conducted for patient and control groups separately.

P value <0.01 was taken as the significance threshold for all tests.

To illustrate on a single-subject level the possible deviation from the mean values of the control data, we also calculated in all patients individual z -scores for all neuropsychological measures and SAI.

Results

The neurophysiological data are summarized in the Table 2.

MEPs in healthy controls were inhibited when the median nerve stimulus was given before TMS of the cerebral cortex at an interval corresponding to the N20 latency plus 2 ms to the N20 latency plus 8 ms. The amount of inhibition over this period was significantly smaller in PD-RBD patients than in PD-nRBD patients and control subjects, as confirmed by a significant ANOVA group effect for SAI ($F_{(2, 35)} = 30.65$, $P < 0.001$) and post hoc Tukey-HSD group comparisons (see Table 2). ANOVA group effects were not found for any other neurophysiological measures in either of the patient groups ($F_s < 1$, $p_s > 0.74$).

In both patient groups, the other TMS parameters did not differ significantly from the controls ($p_s > 0.01$ for all tests).

9 out of the 10 PD-RBD patients and five out of the 13 PD-nRBD patients were diagnosed as having MCI (see Table 3). Compared with control subjects, these PD patients performed significantly worse on the neuropsychological tests measuring global cognition, episodic verbal memory, executive functions, and visuoconstructional and visuosperceptual abilities.

SAI was abnormal in the PD-RBD patients with impaired cognitive performances.

Partial correlation analyses controlling for age and educational level for each group separately revealed that almost all examined neuropsychological test scores highly correlated with SAI in PD-RBD patients and less highly in the PD-nRBD patients. Correlations are shown in Table 4. No significant correlations were found for control subjects. Significant correlations were not found between disease

Table 2 Neurophysiological parameters of the PD-RBD patients, the PD-nRBD patients, and the control subjects

	PD-RBD patients (<i>N</i> = 10)		PD-nRBD patients (<i>N</i> = 13)		Controls (<i>N</i> = 15)	
	<i>M</i>	(SD)	<i>M</i>	(SD)	<i>M</i>	(SD)
SAI (%)	77.4	(8.1)* ⁺	49.0	(12.6)	45.4	(10.1)
RMT (% maxStim)	51.1	(10.1)	50.7	(8.2)	49.8	(8.6)
SICI (%)	31.6	(13.7)	32.2	(15.2)	34.5	(16.6)
ICF (%)	117.4	(18.0)	122.8	(16.0)	122.4	(20.4)
CMCT (ms)	6.3	(0.5)	6.3	(0.6)	6.3	(0.6)
CMAP (mV)	11.1	(1.3)	11.1	(1.3)	11.3	(1.3)
F-wave (μV)	225.1	(28.1)	231.5	(27.9)	229.3	(33.5)

Data are expressed as mean values (SD)

SAI short afferent inhibition, RMT resting motor threshold, SICI short latency intracortical inhibition, ICF intracortical facilitation, CMCT central motor conduction time, CMAP compound muscle action potential

* Significant difference ($P < 0.01$, Tukey-HSD) compared to control group, ⁺significant difference compared to PD-nRBD group

duration and SAI in either of the patient groups. Only a borderline significant correlation between RBD disease duration and SAI was observed ($r_{(6)} = 0.66$, $P = 0.076$), indicating a trend towards reduced inhibition with higher disease duration.

Discussion

We report a significant reduction in SAI amount in PD-RBD patients compared with PD patients without RBD. Similar SAI abnormalities have been recently described in PD patients with visual hallucination (Manganelli et al. 2009). Notably, four patients with RBD and none of the patients with RBD reported visual hallucinations. There is evidence that visual hallucinations in PD can be due to cholinergic dysfunction. Therefore, our observations suggest a cholinergic system imbalance also in PD patients with RBD.

In fact, SAI is thought to be related to central cholinergic activity because in normal subjects it can be reduced or abolished by intravenous injection of the muscarinic antagonist scopolamine (Di Lazzaro et al. 2000) or modulated by ACh (Di Lazzaro et al. 2005a; Fujiki et al. 2006). However, it is still unclear if other neurotransmitters/neuromodulators are involved in the regulation of SAI. Indeed, SAI is influenced by GABAergic drugs such as some benzodiazepines in healthy subjects (Di Lazzaro et al. 2005b, c), and by dopaminergic drugs in patients with PD (Sailer et al. 2003), while quetiapine, an antagonist at multiple neurotransmitter receptors in the brain such as serotonin 5HT1A and 5HT2, dopamine D1 and D2, histamine, and adrenergic $\alpha 1$ and $\alpha 2$ receptors, does not modify SAI in healthy subjects (Di Lazzaro et al. 2005b). On the other hand, it has been reported that dopamine modifies SAI in AD (Martorana et al. 2009). Therefore, it should be

considered that other neurotransmitters such as dopamine may be able to modulate cortical cholinergic function in AD patients. Interestingly, RMT [which is thought to reflect both neuronal membrane excitability and non-NMDA receptors glutamatergic neurotransmission (Ziemann et al. 1996; Di Lazzaro et al. 2003)], as well as SICI [which is considered to reflect mostly the GABA_A-mediated intracortical inhibitory interactions (Kujirai et al. 1993)] and ICF [which is believed to reflect intracortical excitatory neurotransmission, which is largely mediated by NMDA receptors (Ziemann et al. 2008)] did not differ significantly between either group of patients and the control group.

SAI abnormalities, the presence of RBD, and neuropsychological results strongly support the hypothesis of cholinergic dysfunction in some patients with PD, who will probably develop dementia. Our findings are thus consistent with a recent perspective study (Postuma et al. 2012), showing an evolution toward dementia in PD patients with RBD and not in those without RBD.

In PD patients, SAI has been found to be normal or slightly increased in off condition and reduced more on the affected side with drug administration (Sailer et al. 2003). SAI of drug-free PD patients has been found to be increased on the affected side (Di Lazzaro et al. 2004a), and these results have been confirmed in 10 patients with off-condition PD (Nardone et al. 2005). A denervation hypersensitivity of muscarinic receptors has been proposed to explain the enhanced SAI in patients with PD (Di Lazzaro et al. 2004a; Nardone et al. 2005). A possible explanation of our results is that RBD—expression of the brainstem cholinergic circuit involvement—can modify the equilibrium of the whole cholinergic system or the balance between it and other neurotransmitter systems. The appearance of decreased SAI values could be the signal that, in some patients with PD, the frontal cortical

Table 3 Individual raw data and z-scores of short latency afferent inhibition (SAI), demographic/clinical data and neuropsychological measures of PD-RBD and PD-nRBD patients

	PD-RBD patients																							
	1*	2*	3*	4*	5*	6*	7*	8*	9*	10	1*	2*	3*	4*	5*	6	7	8	9	10	11	12	13	
Neurophysiology																								
SAI raw data	88	84	84	82	78	78	76	74	70	60	66	65	62	62	60	48	46	44	42	40	38	36	28	
SAI z-score	4.2	3.8	3.8	3.6	3.2	3.2	3.0	2.8	2.4	1.4	2.0	1.9	1.6	1.6	1.4	0.3	0.1	-0.1	-0.3	-0.5	-0.7	-0.9	-1.7	
Demographic/clinical data																								
Age (years)	70	72	68	77	54	65	61	68	61	63	54	70	56	69	58	66	66	74	68	78	64	68	72	
Education (years)	8	13	6	8	13	17	8	5	10	13	13	8	8	5	13	17	10	10	8	12	8	8	17	
PD disease duration (years)	4.2	9.8	6.5	7.5	4.0	4.5	4.4	3.6	2.5	3.0	5.0	3.0	4.2	4.4	4.8	2.2	3.5	10.0	8.8	11.2	7.0	8.0	6.2	
RBD disease duration (years)	6.2	10.8	7.8	8.8	5.2	5.2	5.0	4.6	2.8	3.6														
Global cognition																								
DRS	-4.2	-4.9	-4.2	-3.6	-4.9	-3.0	-3.6	-1.8	-0.6	-0.6	-3.0	-3.6	-3.6	-3.0	-3.0	1.8	1.8	0.6	-0.6	0.6	2.4	0.6	2.4	
DRS raw data	134	133	134	135	133	136	135	138	140	140	136	135	135	136	136	144	144	142	140	142	145	142	145	
MMSE	-7.1	-7.1	-7.1	-5.5	-4.0	-4.0	-4.0	-4.0	-2.4	-0.8	-4.0	-5.5	-4.0	-4.0	-4.0	-0.8	-2.4	-0.8	-2.4	-0.8	0.7	-0.8	0.7	
MMSE raw data	25	25	25	26	27	27	27	27	28	-0.8	27	26	27	27	27	29	28	29	28	29	30	29	30	
Verbal memory																								
Learning	-4.3	-4.3	-3.7	-4.0	-3.5	-2.9	-3.2	-2.3	0.0	-0.6	-3.5	-3.5	-3.7	-3.7	-3.2	-0.6	0.6	-2.9	0.0	0.0	-1.7	-1.2	1.4	
Delayed recall	-2.6	-3.3	-3.3	-3.3	-1.2	-0.5	-1.9	-0.5	0.2	0.2	-1.9	-1.9	-1.9	-1.9	-1.9	0.2	0.2	1.0	1.0	0.2	1.7	-0.5	-0.5	
Recognition	-2.3	-2.3	-2.3	-2.3	-1.2	-1.2	-1.2	-1.2	-1.2	-0.1	-1.2	-1.2	-1.2	-1.2	-2.3	-1.2	0.9	-0.1	-0.1	-0.1	0.9	-0.1	-0.1	
Attention/executive function																								
Digit span	-4.0	-2.3	-3.1	-4.8	-4.0	-3.1	-2.3	-1.5	1.0	-1.5	-1.5	-0.7	-1.5	0.2	-3.1	1.0	0.2	1.0	0.2	1.8	0.2	-0.7	1.0	
Stroop time	5.0	4.0	4.6	3.7	2.9	2.9	3.6	2.0	1.5	1.3	2.0	1.7	-0.1	1.9	2.4	0.5	-0.1	-1.0	-0.7	0.1	0.3	-0.8	-1.8	
Stroop errors	8.4	6.0	6.0	7.2	6.0	4.9	4.9	3.7	2.6	1.4	3.7	2.6	2.6	1.4	1.4	0.2	0.2	-0.9	-0.9	-0.9	0.2	-0.9	-2.1	
Semantic fluency	-3.0	-3.3	-3.0	-3.9	-2.0	-1.4	-1.7	-1.7	0.4	0.1	-3.6	-3.0	-3.3	-3.0	-3.3	1.0	-0.8	-1.4	0.1	1.6	-0.5	1.0	0.7	
Letter fluency	-2.5	-3.1	-2.5	-2.8	-0.8	-0.2	-1.1	-0.8	-0.2	0.6	-2.2	-1.7	-2.0	-2.2	-2.0	2.9	-0.2	0.6	1.2	-0.2	0.3	0.6	-0.5	
TMT A	4.7	4.5	3.9	3.6	3.3	2.8	2.8	2.2	-0.6	0.0	3.3	3.1	2.4	2.8	-1.7	0.0	1.4	-0.6	1.1	-0.8	-0.3	0.3		
TMT B	7.5	5.9	3.8	6.1	5.5	2.8	3.2	1.3	1.3	0.5	1.9	0.3	1.3	0.0	-0.5	-1.7	2.2	1.0	2.4	0.2	-1.3	-0.3	0.1	
Visuospatial ability																								
Block design	-1.6	-2.1	-2.1	-2.1	-1.0	-1.0	-1.0	-1.6	-1.0	0.1	-1.0	-1.6	-1.6	-1.6	-1.6	0.7	0.1	-0.4	0.1	0.1	0.1	0.7	0.1	
Rey figure copy	-4.0	-3.2	-3.2	-3.2	-1.6	-2.4	-2.4	-2.4	-1.6	-0.8	-3.2	-2.4	-2.4	-2.4	-2.4	0.1	0.9	-1.6	-0.8	-0.8	0.1	0.1	0.9	
Visuoperceptual ability																								
Bells test	4.6	3.2	3.2	3.2	1.8	1.8	1.8	1.8	0.4	0.4	1.8	1.8	3.2	-1.0	0.4	0.4	-1.0	1.8	1.8	0.4	-1.0	0.4	-1.0	

z-scores in bold type indicate difference >2 SD of controls mean, asterisk indicates patients diagnosed with mild cognitive impairment
MMSE mini-mental state examination, *DRS* dementia rating scale, *TMT* trail making test, and *RAVLT* rey auditory verbal learning test

Table 4 Correlations (controlled for age and educational level) between SAI values and results of neuropsychological tests

	PD-RBD		PD-nRBD		Controls	
	r(6)	<i>p</i>	r(8)	<i>p</i>	r(11)	<i>p</i>
Global cognition						
DRS	−0.90	**	−0.83	**	0.24	n.s.
MMSE	−0.95	**	−0.90	**	0.16	n.s.
Verbal memory						
RAVLT, total	−0.87	*	−0.71	*	−0.08	n.s.
Delayed recall	−0.78	*	−0.64	*	−0.20	n.s.
Recognition	−0.94	**	−0.64	*	−0.31	n.s.
Attention/executive function						
Digit span	−0.60	n.s.	−0.32	n.s.	−0.34	n.s.
Stroop time	0.89	**	0.73	*	0.49	n.s.
Stroop errors	0.93	**	0.91	**	0.08	n.s.
Verbal fluency, semantic	−0.84	**	−0.75	*	−0.03	n.s.
Verbal fluency, letter	−0.86	**	−0.43	n.s.	0.35	n.s.
TMT A	0.90	**	0.43	n.s.	0.41	n.s.
TMT B	0.85	**	0.15	n.s.	0.11	n.s.
Visuospatial abilities						
Block design	−0.82	*	−0.75	*	−0.30	n.s.
Rey figure copy	−0.95	**	−0.70	*	0.43	n.s.
Visuoperceptual abilities						
Bells test, omission	0.91	**	0.61	n.s.	0.13	n.s.

MMSE mini-mental state examination, DRS Dementia rating scale, TMT trail making test, RAVLT Rey auditory verbal learning test, n.s. not significant
 ** $P < 0.01$, * $P < 0.05$
 (“borderline significance”)

cholinergic deficit cannot be compensated by denervation hypersensitivity of muscarinic receptors or other feedback control (Di Lazzaro et al. 2004a; Nardone et al. 2005).

The findings of the present study are also in agreement with previous neuropsychological studies demonstrating that cognitive impairment in patients with PD is closely related to the presence of RBD (Gagnon et al. 2002a; Vendette et al. 2007). Moreover, waking EEG spectral analysis performed in non-demented PD patients showed EEG slowing only in patients with concomitant RBD, and not in patients with PD without RBD (Gagnon et al. 2004). Association between waking EEG slowing and cognitive impairment has been reported previously in patients with mild or severe cognitive disturbances (Prichep et al. 1994; Babiloni et al. 2006).

On the other hand, several studies have demonstrated neuropsychological impairment (Ferini-Strambi et al. 2004; Massicotte-Marquez et al. 2008; Terzaghi et al. 2008) and EEG slowing (Fantini et al. 2003) even in patients with the idiopathic form of RBD. Interestingly, mean SAI was also found to be reduced in patients with iRBD (Nardone et al. 2012b).

Many studies have demonstrated that MCI is present in patients with PD at various stages of their illness (Green et al. 2002; Emre 2003; Janvin et al. 2003, 2006; Foltynic et al. 2004; Muslimovic et al. 2005). Deficits in executive function tasks requiring the integrity of the frontostriatal pathway, episodic memory impairment, as well as

visuospatial and visuoperceptual dysfunctions have often been reported in PD (Helkala et al. 1988; Levin et al. 1991; Green et al. 2002; Emre 2003; Janvin et al. 2003; Foltynic et al. 2004; Muslimovic et al. 2005).

Poor performance of tasks assessing visuospatial and attentional/frontal lobe functions has been associated with cortical cholinergic denervation in PD and Parkinsonian dementia (Bohnen et al. 2006). In our previous study, we found that iRBD patients show impairments in verbal memory and executive functions (Nardone et al. 2012a) while, in line with previous studies (Gagnon et al. 2002a; Vendette et al. 2007), in PD-RBD patients lower performances in visuospatial and visuoconstrual tests were also detected.

Neuropathologic and brain imaging studies performed in PD with cognitive impairment and in patients with RBD showed common neural alterations in several brainstem nuclei (i.e., substantia nigra, PPN, LC-subcoeruleus complex, and raphe nucleus) and anomalies in their corresponding neurotransmitters (i.e., dopaminergic, cholinergic, noradrenergic, and serotonergic systems) (Emre 2003; Iranzo et al. 2006; Braak et al. 2005). All of these brainstem structures have diffuse projections to the cerebral cortex and perturbations of these neural networks may explain the presence of cognitive deficits in patients with PD-RBD. In particular, the PPN is an important part of a network for maintaining attention, and may control attentional processes through its direct projections to the forebrain

cholinergic system or indirectly through activation of thalamocortical projection (Perry et al. 1999; Inglis et al. 2001).

Non-demented patients with PD have a moderate cholinergic dysfunction and patients with PD-associated dementia present with a severe cholinergic deficit in various cortical regions (Hilker et al. 2005).

Therefore, the core feature of cognitive impairment in PD patients with RBD, as well as in patients with iRBD, seems to be related to a widespread central cholinergic dysfunction.

In conclusion, our SAI findings and neuropsychological results support the hypothesis of cholinergic dysfunction in some patients with PD, who will probably develop a dementia, and raise the possibility that the presence of RBD may indicate increased risk of cognitive impairment in patients with PD. Longitudinal studies of the patients are required to verify whether SAI abnormalities can predict a future severe cognitive decline.

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