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Functional involvement of central cholinergic circuits and visual hallucinations in Parkinson's disease

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Visual hallucinations (VHs) represent a frequent and disturbing complication of Parkinson's disease. Evidence suggests that VH can be related to central cholinergic dysfunction. Short-latency afferent inhibition (SAI) technique gives the opportunity to test an inhibitory cholinergic circuit in the human cerebral motor cortex. This inhibition of motor-evoked potentials can be observed when transcranial magnetic stimulation is delivered with a delay ranging from 2 to 8 ms, after a peripheral nerve afferent input has reached the somatosensory cortex. We applied SAI technique in 10 non-demented patients with Parkinson's disease with VHs, in 12 non-demented patients with Parkinson's disease without VHs (NVH-pts) and in 11 age-matched normal controls. All patients with Parkinson's disease underwent a battery of neuropsychological tests to assess frontal and visuospatial functions, memory and attention. SAI was significantly reduced in patients with VHs compared with controls and patients without VHs. Neuropsychological examination showed a mild cognitive impairment in 16 out of 22 patients with Parkinson's disease. In addition, we found that in our patients with VHs, performance of some tasks evaluating visuospatial functions and attentional/frontal lobe functions was significantly more impaired than in patients without VHs. SAI abnormalities, presence of VH and neuropsychological results strongly support the hypothesis of cholinergic dysfunction in some patients with Parkinson's disease, who will probably develop a dementia. A follow-up study of our patients is required to verify whether SAI abnormalities can predict a future severe cognitive decline. Moreover, SAI can also be very useful to follow-up the efficacy of anti-cholinesterase therapies.

Keywords: Parkinson's disease; TMS; short-latency afferent inhibition; cognitive deficits; visual hallucinations

Abbreviations: MCI = mild cognitive impairment; NBM = nucleus basalis of Meynert; NVH-pts = patients without visual hallucination; Parkinson's disease-CogNL = cognitively normal Parkinson's disease; SAI = short-latency afferent inhibition; VH-pts = patients with visual hallucination

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Introduction

Visual hallucination (VH) in patients with Parkinson's disease is a common complication, having a prevalence range of 8%–40%, and is a risk factor for dementia and higher mortality (Fénelon *et al*., 2000; Aarsland *et al*., 2007). Dopaminergic treatment is not sufficient to explain the occurrence of all VHs, and cognitive impairment. Daytime somnolence and long duration of Parkinson's disease have been identified as risk factors that can induce VH. However, it is not clear whether cognitive changes and hallucinations have a causative link or are independent consequences of pathological processes. Short-latency afferent inhibition (SAI) technique (Tokimura *et al*., 2000) gives the opportunity to non-invasively test an inhibitory circuit in the human cerebral motor cortex that depends mainly on central cholinergic activity (Chen *et al*., 2008). In normal subjects, SAI can be abolished by intravenous injection of the muscarinic antagonist scopolamine (Di Lazzaro *et al*., 2000). However, SAI is abnormal in patients with cholinergic forms of dementia, and can be normalized by acetylcholinesterase inhibitors (Di Lazzaro *et al*., 2002, 2004*b*, 2007). In patients with Parkinson's disease, SAI has been reported to be normal in those who are not on dopaminergic medication and slightly reduced at the more affected side in patients on that medication (Sailer *et al*., 2003). In addition, SAI was found to be enhanced at the affected side in few drug-free patients with Parkinson's disease (Di Lazzaro *et al*., 2004*a*).

However, SAI has never been investigated in patients with Parkinson's disease with hallucinations compared with those without. There is evidence that VHs in Parkinson's disease can be due to cholinergic dysfunction (Manford and Andermann, 1998; Fénelon *et al*., 2000; Oishi *et al*., 2005) and that a moderate cholinergic deficit is present in several cortical regions in non-demented patients with Parkinson's disease (Hilker *et al*., 2005). Therefore, we decided to study SAI in a population of non-demented patients with Parkinson's disease, with and without hallucinations, and with no other historical, clinical, drug assumption and disease duration differences.

Materials and Methods

Twenty-two patients with Parkinson's disease, referred to the University of Naples Movement Disorders Unit, were selected for the present study based on normal general intellectual functioning, as defined by both DSM IV criteria for dementia and the Italian version of the Mini Mental State Examination (MMSE, age- and education-adjusted score $\geqslant$ 23.8). Among the 22 non-demented patients with Parkinson's disease, 10 presented VH (VH-pts) and 12 were free from hallucinations (NVH-pts). The main clinical and demographic characteristics of patients with Parkinson's disease, with and without VHs, are summarized in Table 1. The occurrence of VH was evaluated by means of a structured interview including the Parkinson Psychosis Questionnaire, Part B (Brandstaedter *et al*., 2005). Age, educational level, duration of illness and medication were recorded, and severity of illness was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) Part III.

All patients were treated with L-DOPA alone or a combination of L-DOPA and a dopamine-agonist (pramipexole, ropinorole, etc). In order to compare the amount of all administered dopaminergic drugs, we calculated a L-DOPA-equivalent dose for each patient (Table 1). None of the patients were treated with anti-cholinergic and/or anti-depressant medications.

Neuropsychological examination

All patients underwent a comprehensive neuropsychological battery of tests to assess four cognitive domains: (i) frontal functions, evaluated by means of phonological verbal fluency (Caltagirone *et al*., 1979) and the Wisconsin Card Sorting Test (Milner, 1963); (ii) memory, evaluated by means of immediate and delayed recall of 15 Rey-words (Caltagirone *et al*., 1979); (iii) visuospatial functions, evaluated by means of clock drawing test (Mondini *et al*., 2003) and copying task of the Rey–Osterrieth Complex Figure Test (Caffarra *et al*., 2002); and (iv) attention, evaluated by means of attentional matrices (Spinnler and Tognoni, 1987) and interference task of Stroop test (Barbarotto *et al*., 1998). Patients with Parkinson's disease were considered to have mild cognitive impairment (Parkinson's disease-MCI) when they had subjective cognitive complaint(s) without functional decline, and cognitive deficits of at least 1.5 SD below the expected age-corrected mean score in one cognitive domain (Caviness *et al*., 2007). If a single cognitive domain was impaired, the patient was considered to have single-domain Parkinson's disease-MCI; if there were multiple-domain abnormalities, the patient was considered to have multiple-domain Parkinson's disease-MCI, either with or without an amnestic deficit. Patients with Parkinson's disease without cognitive impairment were considered of having cognitively normal Parkinson's disease (Parkinson's disease-CogNL).

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) of the motor cortex was performed with a high-power magnetic stimulator (MagPro $\times$100, Medtronic, Denmark). A figure-of-eight coil (with external loop diameters of 9 cm) was positioned at the scalp over the right or left (according to the more affected side) hand motor area to evoke motor responses [motor-evoked potentials (MEPs)] in the contralateral first dorsal interosseous (FDI) muscle. MEPs were recorded through surface electrodes with the active electrode on the motor point of the muscle and the reference electrode on the metacarpophalangeal joint of the index finger. MEPs were amplified and filtered (bandwidth 3 Hz to 3 kHz) using a Keypoint electromyograph (Medtronic).

SAI by somatosensory input from the hand

SAI was investigated by applying the technique described by Tokimura and colleagues (2000). Conditioning stimuli were single electrical pulses (200 μs) applied through bipolar electrodes to the median nerve at the wrist (cathode proximal). The intensity of the conditioning peripheral stimulus was set at just over the motor threshold to evoke a visible twitch of the thenar muscles. The N20 wave of cortical somatosensory response was recorded with active electrode attached 2 cm behind C4/C3 (10–20 International System) and reference electrode 2 cm behind C3/C4. A total of 500 responses were averaged twice and superimposed to identify the latency of the N20 peak.

The intensity of the test cortical magnetic shock was adjusted to evoke an MEP in relaxed FDI muscle with peak-to-peak amplitude of $\sim$1 mV.

Table 1 Clinical, neuropsychological and electrophysiological data

	Sex (m/f)	Age (years)	Disease duration (years)	UPDRS (motor)	L-DOPA dose	Memory	Visuospatial	Frontal	Attention	Cognitive profile	SAI (%)
VH											
1	M	70	16	25	950	N	A	A	A	PD-MCI[a]	48.2
2	F	80	18	27	350	N	A	N	A	PD-MCI[a]	**80.2**
3	M	65	3	13	150	A	A	A	A	PD-MCI[b]	**133.7**
4	M	74	5	19	500	A	N	A	A	PD-MCI[b]	**96.8**
5	F	71	3	21	350	N	A	A	A	PD-MCI[a]	**87.1**
6	M	65	2	7	300	N	N	N	N	PD-CogNL	**87.3**
7	M	70	9	9	409	A	N	N	A	PD-MCI[b]	**119.4**
8	M	75	16	11	1150	N	A	A	N	PD-MCI[a]	**86.4**
9	F	72	3	11	550	A	A	A	A	PD-MCI[b]	**103.3**
10	F	62	12	18	650	A	N	A	N	PD-MCI[b]	52.4
	6/4	70.4 (5.3)	8.7 (6.3)	16.1 (6.9)	535.9 (307.8)	5/10	6/10*	7/10	7/10	9/10	89.4 (26.4)
NVH											
1	F	51	17	25	800	N	N	N	N	PD-CogNL	62.1
2	F	52	12	18	1100	N	N	N	N	PD-CogNL	40.0
3	M	70	17	17	750	A	N	A	A	PD-MCI[b]	66.9
4	M	69	16	16	1250	N	N	A	A	PD-MCI[a]	52.8
5	F	71	5	21	500	N	N	A	N	PD-MCI[c]	44.0
6	M	74	5	21	750	N	N	A	A	PD-MCI[a]	20.8
7	M	60	3	13	500	N	N	N	N	PD-CogNL	46.3
8	M	73	3	17	300	N	N	A	A	PD-MCI[a]	43.8
9	F	73	10	21	700	N	A	N	N	PD-MCI[c]	54.4
10	F	79	9	11	750	N	N	N	N	PD-CogNL	42.7
11	M	65	8	12	475	N	N	N	N	PD-CogNL	42.1
12	M	49	3	19	500	A	N	A	A	PD-MCI[b]	42.0
	7/5	65.5 (10.1)	9 (5.5)	17.6 (4.2)	697.9 (271.5)	2/12	1/12*	6/12	5/12	7/12	46.5 (11.8)

M, male; F, female; A, abnormal; N, normal; PD, Parkinson's disease.
Upper normal limit of SAI = 70 (mean + 2 SD of control values), increased values in bold; under the columns are reported M/F ratio, mean value with standard deviation (within parenthesis) and the number of altered tests.
a Multiple domains without amnestic deficits.
b Multiple domains with amnestic deficits.
c Single domain.
*$P = 0.009$, chi-square test.

SAI was tested at different interstimulus intervals (ISIs) determined on the basis of the N20 wave latency. ISIs ranged from 2 to 8 ms after N20 latency and were investigated in steps of 2 ms. For each ISI, we calculated the amplitude of basal MEP (average of five consecutive responses obtained after cortical stimulation alone) and the amplitude of conditioned MEP (average of five consecutive responses obtained after the conditioning peripheral electrical stimulus). The amplitude of conditioned MEP, expressed as a percentage of the basal MEP amplitude at each ISI, was used to evaluate the amount of SAI. All subjects utilized audiovisual feedback of EMG signal at high gain to maintain complete relaxation during experiments. However, patients with tremor score >1 were not included in this experiment. Electrophysiological tests were performed on the more affected side and on patients taking dopaminergic medication. This protocol was decided because it reduces the discomfort level and SAI modifications in patients with Parkinson's disease have been reported on the more affected side, both on and off medication (Sailer *et al*., 2003; Di Lazzaro *et al*., 2004*a*). SAI was also performed in 11 healthy control subjects (five females; mean age ± SD: 62.4 ± 6.2 years). All patients and controls gave their informed consent to the electrophysiological studies. Data of patients and controls, obtained at the ISIs 2, 4, 6 and 8, were analysed and averaged to obtain a grand mean of SAI in order to reduce the data variation. Upper normal limit of SAI was considered to be the mean + 2 SD of control values (70%).

Statistical analysis

Mann–Whitney test was used to compare mean SAI amount in VH and NVH-pts and controls.

For the unpaired sample, *t*-test was used to compare age, educational level, disease duration, UPDRS motor score, L-DOPA equivalent dosage and score values of each neuropsychological test in VH and NVH-pts. Chi-square test was performed to evaluate the difference of involvement of the four explored cognitive domains between VH and NVH-pts. Significance level was set at $P < 0.05$.

Results

Clinical data

Age, gender, motor UPDRS, disease duration and equivalent L-DOPA dosage were not different between VH and NVH-pts

Table 2 Cognitive comparisons among the VH and NVH groups

Neuropsychological parameter	VH group ($n=10$)	NVH group ($n=12$)	*t*-test for unpaired samples *P*
MMSE	27.4 ± 1.6	27.8 ± 1.9	NS
WCST—global score	109 ± 24	91 ± 47	NS
Phonological fluency	22 ± 8	33 ± 14	0.04
ROCF—copy task	20 ± 12	28 ± 7	NS
Stroop test	8 ± 8	10 ± 8	NS
CDT	5 ± 3	8 ± 2	0.02
Attentive matrices	37 ± 10	47 ± 11	0.03
Immediate recall	31 ± 11	40 ± 16	NS
Delayed recall	6 ± 3	8 ± 4	NS

WCST, Wisconsin Card Sorting Test; ROCF, Rey–Osterrieth Complex Figure Test; CDT, clock drawing test; NS, non-significant *P*-value. Significance level was set at $P<0.05$.

(Table 1). There was no difference in educational level between VH and NVH-pts (12 ± 6 years versus 12 ± 5 years; $P=$ NS, *t*-test for unpaired samples).

Neuropsychological examination

Neuropsychological tests showed an MCI in 16 out of the 22 patients (detailed description is reported in Table 1). MCI was present in 9 out of 10 VH-pts and 7 out of 12 NVH-pts ($P=$ NS, chi-square test). In the single cognitive domains, only the visuospatial domain resulted differently impaired between VH (6 out of 10) and NVH-pts (1 out of 12; $P=0.009$, chi-square test). However, the mean scores of phonological fluency, attentional matrices and the clock drawing test were significantly lower in VH than NVH-pts (Table 2).

Electrophysiological tests

All control subjects showed the inhibition of MEPs at ISIs from 2 to 8 ms after N20 latency (mean ± SD: 46.4 ± 11.9% of basal MEP amplitude). The whole population of patients with Parkinson's disease demonstrated a tendency to a reduced SAI, but when compared with controls, data were not significantly different (mean ± SD: 66.0 ± 29.2% versus 46.4 ± 11.9%; $P=0.09$, Mann–Whitney test). When VH and NVH-pts data were analysed separately, NVH-pts had normal SAI (46.5 ± 11.8%), while VH-pts showed a significantly reduced inhibition (89.4 ± 26.4% of basal MEP amplitude) in comparison with controls (46.4 ± 11.9% of basal MEP amplitude) and NVH-pts ($P<0.001$, Mann–Whitney test). Moreover, individual SAI values were outside the normal range (>70%) in 8 out of the 10 VH-pts, whereas none of the NVH-pts had abnormal SAI value (Table 1).

Discussion

In this study involving 22 patients with non-demented Parkinson's disease, we have observed a significant reduction in SAI amount in VH-pts compared with NVH-pts. Moreover, individual SAI values were abnormal (outside upper normal limit) in 8 out of 10 VH-pts, whereas no NVH-pts demonstrated abnormal SAI values (Table 1).

Evidence (Manford and Andermann, 1998; Fénelon *et al*., 2000; Oishi *et al*., 2005) suggests that VH could be due to impairment in the visual stimuli processing related to the degenerative processes in the cholinergic pedunculopontine nucleus (PPN; Manford and Andermann, 1998).

These observations induce interesting speculations about the cholinergic system imbalance and cognitive impairment in patients with Parkinson's disease. The cerebral cortex receives dense cholinergic innervation originating from the nucleus basalis of Meynert (NBM), and the disconnection of cortical areas from their source of cholinergic innervation in the basal forebrain could be responsible for mental-state impairment (Everitt and Robbins, 1997; Selden *et al*., 1998). In fact, degeneration within the NBM has attracted attention in relation to cognitive impairment in Alzheimer's disease (Mufson *et al*., 2003), in dementia with Lewy bodies (Londos *et al*., 2002) and more recently in Parkinson's disease (Bosboom *et al*., 2004). On the other hand, SAI has been suggested to be helpful in exploring the integrity of cortical cholinergic neural circuits, and a reduced SAI has been consistently described both in Alzheimer's disease and dementia with Lewy bodies, in which the NBM is severely affected (Di Lazzaro *et al*., 2002, 2007). However, it is still not clear which neurotransmitters/neuromodulators are involved in SAI regulation. Interestingly, benzodiazepine lorazepam can reduce SAI through GABA-A receptor activation, while quetiapine, which is an antagonist at multiple neurotransmitter receptors (serotonin 5HT1A and 5HT2, dopamine D1 and D2, histamine and adrenergic $\alpha1$ and $\alpha2$), does not modify SAI (Di Lazzaro *et al*., 2005).

In patients with Parkinson's disease, 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). In Parkinson's disease, SAI of drug-free patients has been found to be increased on the affected side (Di Lazzaro *et al*., 2004*a*) and these results have also been confirmed in 10 patients with off-condition Parkinson's disease (Nardone *et al*., 2005). Several autoptic studies on this disease have registered an increased concentration of cholinergic muscarinic receptors in the cerebral cortex (Ruberg *et al*., 1982; Sirvio *et al*., 1989; Lange *et al*., 1993), and positron emission tomography studies have revealed an increased activity of these receptors in the frontal cortex (Asahina *et al*., 1995). The hypothesis of a denervation hypersensitivity of muscarinic receptors, due to a loss of cholinergic ascending input to frontal cortex, has been advanced to explain the enhanced SAI in patients with Parkinson's disease (Di Lazzaro *et al*., 2004*a*; Nardone *et al*., 2005). The loss of cholinergic afferent input to frontal cortex in Parkinson's disease is also confirmed by a pathological study that has recently shown neuronal degeneration within the NBM in non-demented patients with Parkinson's disease (Bosboom *et al*., 2004).

However, here we demonstrate, for the first time, that SAI results in patients with Parkinson's disease can change significantly if patients are grouped according to the presence or absence of VHs. In fact, none of our patients was demented and, with the

exception of VHs, there were no other clinical differences between the two groups of patients with Parkinson's disease.

It is likely that SAI abnormalities and VHs are two epiphenomena—electrophysiological and clinical—of cholinergic system imbalance, sustained by a dysfunction in two different cholinergic circuits. A possible explanation of our results in Parkinson's disease is that VHs—expression of the brainstem cholinergic circuit involvement—together with the neuronal degeneration in NBM, modify the equilibrium of the whole cholinergic system or the balance between it and other neurotransmitter systems. The clinical appearance of VHs could be the signal that in some patients with Parkinson's disease, the frontal cortical cholinergic defect cannot be compensated by denervation hypersensitivity of muscarinic receptors or other feedback control. Only two of our VH-pts did not show SAI abnormalities. It is possible that in these two patients, cortical cholinergic deficiency is still compensated and the degenerative process cannot be detected by the SAI technique. Similar compensation mechanisms have been suggested in patients with mild cognitive impairment having normal SAI (Sakuma *et al*., 2007).

In addition, we found that in our VH-pts, performance of some tasks evaluating visuospatial functions and attentional/frontal lobe functions was significantly more impaired than in NVH-pts. Our neuropsychological findings are consistent with previous studies showing that frontal lobe dysfunctions are predictors of hallucinations (Grossi *et al*., 2005) and that hallucinations, frontal lobe and visuospatial dysfunctions were prognostic factors of subcortical dementia in Parkinson's disease (Mahieux *et al*., 1998; Aarsland *et al*., 2004; Hobson and Meara, 2004; Santangelo *et al*., 2007). Poor performance of tasks assessing visuospatial and attentional/frontal lobe functions can be associated with cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia (Bohnen *et al*., 2006). In fact, the PPN and its cholinergic projections modulate the inputs to the visual cortex, and thus are important in visual processing (Barnes *et al*., 2003; Oishi *et al*., 2005; Uc *et al*., 2005). Moreover, 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).

Therefore, the core feature of cognitive impairment in patients with Parkinson's disease with VHs seems to be related to a widespread cholinergic dysfunction. Non-demented patients with Parkinson's disease have a moderate cholinergic dysfunction and patients with Parkinson's disease-associated dementia present with a severe cholinergic deficit in various cortical regions (Hilker *et al*., 2005).

SAI represents a useful technique to confirm the diagnosis of cholinergic dementia (Di Lazzaro *et al*., 2006; Manganelli *et al*., 2008), and therefore when taken together, our SAI and neuropsychological results support the hypothesis of cholinergic dysfunction in some patients with Parkinson's disease, who will probably develop a dementia. A follow-up study of our patients is required to verify if neuropsychological and electrophysiological abnormalities can predict a future severe cognitive decline.

Moreover, SAI findings are very sensitive to drug assumption and we believe that SAI could be very useful to follow-up the efficacy of anti-cholinesterase therapies.

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