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The improvement of movement and speech during rapid eye movement sleep behaviour disorder in multiple system atrophy

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Multiple system atrophy is an atypical parkinsonism characterized by severe motor disabilities that are poorly levodopa responsive. Most patients develop rapid eye movement sleep behaviour disorder. Because parkinsonism is absent during rapid eye movement sleep behaviour disorder in patients with Parkinson's disease, we studied the movements of patients with multiple system atrophy during rapid eye movement sleep. Forty-nine non-demented patients with multiple system atrophy and 49 patients with idiopathic Parkinson's disease were interviewed along with their 98 bed partners using a structured questionnaire. They rated the quality of movements, vocal and facial expressions during rapid eye movement sleep behaviour disorder as better than, equal to or worse than the same activities in an awake state. Sleep and movements were monitored using video-polysomnography in 22/49 patients with multiple system atrophy and in 19/49 patients with Parkinson's disease. These recordings were analysed for the presence of parkinsonism and cerebellar syndrome during rapid eye movement sleep movements. Clinical rapid eye movement sleep behaviour disorder was observed in 43/49 (88%) patients with multiple system atrophy. Reports from the 31/43 bed partners who were able to evaluate movements during sleep indicate that 81% of the patients showed some form of improvement during rapid eye movement sleep behaviour disorder. These included improved movement (73% of patients: faster, 67%; stronger, 52%; and smoother, 26%), improved speech (59% of patients: louder, 55%; more intelligible, 17%; and better articulated, 36%) and normalized facial expression (50% of patients). The rate of improvement was higher in Parkinson's disease than in multiple system atrophy, but no further difference was observed between the two forms of multiple system atrophy (predominant parkinsonism versus cerebellar syndrome). Video-monitored movements

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during rapid eye movement sleep in patients with multiple system atrophy revealed more expressive faces, and movements that were faster and more ample in comparison with facial expression and movements during wakefulness. These movements were still somewhat jerky but lacked any visible parkinsonism. Cerebellar signs were not assessable. We conclude that parkinsonism also disappears during rapid eye movement sleep behaviour disorder in patients with multiple system atrophy, but this improvement is not due to enhanced dopamine transmission because these patients are not levodopa-sensitive. These data suggest that these movements are not influenced by extrapyramidal regions; however, the influence of abnormal cerebellar control remains unclear. The transient disappearance of parkinsonism here is all the more surprising since no treatment (even dopaminergic) provides a real benefit in this disabling disease.

Keywords: paradoxical kinesis; multiple system atrophy; rapid eye movement sleep behaviour disorder

Abbreviations: MSA = multiple system atrophy; RBD = rapid eye movement sleep behaviour disorder; REM = rapid eye movement

Introduction

Multiple system atrophy (MSA) is a rare, sporadic neurodegenerative disorder that is characterized by autonomic failure, parkinsonism or cerebellar ataxia. When parkinsonism (bradykinesia, rigidity and gait instability) is predominant, this disorder is called MSA-P, whereas it is referred to as MSA-C when cerebellar ataxia is predominant (Gilman *et al.*, 1999, 2008). Patients with MSA die 6–9 years after the onset of symptoms, with a yearly rate of ~10% (Wenning *et al.*, 1994; Testa *et al.*, 2001; Watanabe *et al.*, 2002). The primary cause of death in MSA is related to the development of bulbar palsy, which predisposes patients to aspiration pneumonia. Glial cytoplasmic inclusions composed of filamentous alpha-synuclein are a criterion for definite neuropathological diagnosis of MSA with degenerative lesions of the striato-nigral and olivo-ponto-cerebellar structures (Papp *et al.*, 1989). Even when parkinsonism predominates, the motor response to levodopa is poor or absent. This is due to the loss of putaminal neurons, in which dopamine post-synaptic receptors are located, in addition to the death of nigro-striatal neurons (Churchyard *et al.*, 1993).

Most patients with MSA (Plazzi *et al.*, 1997; Vetrugno *et al.*, 2004) develop rapid eye movement sleep behaviour disorder (RBD), wherein vigorous, complex movements that correspond to dreams are performed during sleep (Schenck *et al.*, 1986). The normal abolition of muscle tone is incomplete during rapid eye movement (REM) sleep in these patients, possibly as a result of lesions in the pontine REM sleep atonia system allowing the patients to act out their dreams (Sastre and Jouvet, 1979; Lu *et al.*, 2006). Because of the large dispersion of lesions in the brainstems of patients with MSA, it is possible that these neurons have been destroyed.

We have recently reported that parkinsonism disappears during RBD movements in patients with Parkinson's disease. The bed partners of these patients noticed faster, stronger and smoother movements, as well as louder and more articulated speech in these patients during sleep, which sharply contrasts with their movements when awake. The restoration of motor control was confirmed by video surveillance. No bradykinesia, tremor or hypertonia was observed during these REM sleep-associated movements. We hypothesize that these improvements derive from either a transient re-establishment of dopamine transmission (as suspected in other paradoxical kinesias) or a transient bypass of the basal ganglia (De Cock *et al.*, 2007).

The aim of this study was to determine if this REM sleep-associated motor improvement could also be observed in patients with poor levodopa-sensitive parkinsonism (MSA). In addition, we also wanted to determine if cerebellar symptoms (MSA-C) and parkinsonism (MSA-P) disappear.

Materials and methods

Patients

From January 2007 to March 2010, 49 patients with MSA and their bed partners were recruited from the French National Reference Centre for MSA in Toulouse ($n = 36$), the neurology department and sleep disorders unit of the Pitié-Salpêtrière University hospital in Paris ($n = 8$) and the Gui de Chauliac University hospital in Montpellier ($n = 5$). All of the included patients met the criteria for probable MSA (Gilman *et al.*, 1998). They slept most nights with a bed partner who was able to observe their behaviour during sleep. Only 31 bed partners were able to precisely describe the quality of movements, vocalizations and facial expression in the sleeping patients. All participants provided written informed consent. Additional consent for the video-polysomnography was obtained from 22 of the 49 patients. These 22 patients did not differ in age, gender, disease course or motor disability from the 27 unmonitored patients (data not shown); however, they had more frequent clinical RBD (100% versus 77%, $P = 0.04$), which suggests they were more motivated to undergo sleep monitoring.

We also extracted 31 patients with Parkinson's disease from our previous study (De Cock *et al.*, 2007) who were matched for age (64 ± 9 years) and gender (20 males) to the patients with MSA whose bed partners were able to evaluate the quality of their movements during sleep. Among them, 19 had overnight sleep and video monitoring.

Clinical evaluation

Data concerning demographic characteristics, medical history, MSA course and treatment (with particular attention to the use of psychoactive drugs) were collected during a face-to-face interview. The total daily levodopa equivalent dose was calculated using a previously reported formula (Hobson *et al.*, 2002). The extent of motor disability was assessed in patients at the optimal effectiveness of their

anti-parkinsonian treatment using the Unified MSA Rating Scale (UMSARS-I, historical and -II, motor examination) evaluating parkinsonism and cerbellar signs, (Wenning *et al.*, 2004). Neuropsychological examination included the Mini Mental State Examination (Folstein *et al.*, 1975) and the Frontal Assessment Battery (Dubois *et al.*, 2000).

In addition, patients were interviewed about their sleeping habits during the current year using a structured questionnaire that was adapted from an RBD questionnaire (Comella *et al.*, 1998). The patients and their bed partners were separately interviewed about RBD in the presence of one another. Clinical RBD was defined when the bed partner reported significant, purposeful limb or body movements during sleep (as if patients were acting out their dreams) and when these movements were associated with a dream recall when the patient was awake. The structured questionnaire also assessed the quality of movement during RBD. We asked the bed partners to compare patients during RBD versus wakefulness for movements (speed, smoothness and strength), facial expressions and quality of speech (volume of the voice, articulation and intelligibility). They were asked to score each item as 'better than awake', 'similar to awake', 'worse than awake' or 'do not know'. They were also invited to provide some demonstrative examples founding their impression. This questionnaire had been validated in our previous work regarding movement control during RBD in Parkinson's disease (De Cock, 2007). When confronted with objective video-polysomnography criteria of RBD, it reached a 97.2% (35/36) sensitivity to diagnose RBD, the single false positive being a sleepwalker with Parkinson's disease.

Sleep monitoring

Sleep and nocturnal movements were monitored during a single night in the sleep unit for 22 patients with MSA and 19 patients with Parkinson's disease. The monitoring included Fp1-Cz, O2-Cz and C3-A2 electroencephalography; right and left electro-occulogram; nasal pressure monitoring through a cannula; tracheal sounds via a microphone; thoracic and abdominal belts for assessing respiratory efforts; electrocardiography; pulse oximetry; EEG-synchronized infra-red video monitoring and an ambiance microphone. We monitored the EMG of the levator menti and tibialis anterior muscles. The sleep stages, arousals, respiratory events, periodic leg movements and muscle activities were scored through visual inspection according to standard criteria (Iber *et al.*, 2007).

Video and electromyography movement analysis

We determined the presence or absence of RBD in this group of patients through sleep monitoring. RBD was defined as the presence of complex motor behaviours as observed from the video-audio recordings during REM sleep (American Academy of Sleep Medicine, 2005). Alternatively, if no motor behaviour was observed in the video, we required the presence of REM sleep without atonia, defined as the time containing REM sleep epochs with at least 50% of the duration of the epoch having a chin EMG amplitude greater than the minimum amplitude in non-REM sleep muscle tone divided by total REM sleep time (American Academy of Sleep Medicine, 2007) during $>30\%$ of the REM sleep time and a history of clinical RBD (Gagnon *et al.*, 2002; Montplaisir *et al.*, 2010).

The collected movements were then rated in a single session by a group of movement disorder specialists (M.V., I.A., V.C.D.C. and E.R.) who were blind to the patient diagnosis and sleep-wake stage. We visually characterized the facial expression (especially when there were apparent associated emotions such as crying, laughing and fear) and the movement patterns, including part of the body, speed and amplitude, along with any vocalizations. The four movement disorder specialists, by pairs, rated the video clips if the movement speed was slow, normal or rapid, ample or not, if speech was intelligible or not, with high, low or normal volume, and if facial expression was present or not, while being blind to the sleep or wake stage, using a measure for each of these questions.

Statistical analysis

Statistics were performed using analyses of variance for the comparison of continuous measures between the three groups (MSA-C, MSA-P and Parkinson's disease). Proportions were compared using the chi-square test. Results are reported as mean $\pm$ SD, unless otherwise noted.

Results

Clinical characteristics of the patients

Twenty-four of the patients with MSA had MSA-C, whereas 25 had MSA-P (Table 1). Mean Mini Mental State Examination was 27 ± 11. In the frontal evaluation, the mean Frontal Assessment Battery was 14 ± 7, and only 21% of the patients had no frontal

Table 1 Demographic and clinical characteristics of patients with MSA-P and MSA-C

	MSA-C	MSA-P	*P*-value
Number	24	25	
Age (years)	64 (9)	62 (8)	0.5
Sex (% male)	50	56	0.9
Body mass index (kg/m^2)	24 (4)	24 (4)	0.8
Disease course (years)	6 (3)	5 (3)	0.9
Historical (UMSARS1)	28 (8)	23 (10)	0.04
Motor disability (UMSARS2)	29 (9)	24 (10)	0.09
Use of levodopa (%)	37	76	0.01
Use of dopamine agonists (%)	4	20	0.2
Levodopa-equivalent dose (mg/day)	320 (479)	516 (531)	0.2
Use of benzodiazepine (% patients)	21	40	0.3
Use of selective serotonin reuptake inhibitors (% patients)	29	40	0.6
Use of midodrine (% patients)	54	36	0.2
Mini Mental State Examination (score/30)	27 (3)	28 (3)	0.5
Frontal Assessment Battery (score/18)	14 (2)	15 (5)	0.7
Beck Depression Inventory (depression if $\geqslant$13)	19 (10)	18 (9)	0.95
Epworth Sleepiness Scale (score/24)	7 (4)	7 (5)	0.96
Percentage of sleepy patients (score$>$10)	34	40	0.69
Clinical RBD (% patients)	91	84	0.7
Improvement of movement, speech or facial expression during sleep	78	85	1

Data are mean (SD) or percent. UMSARS = Unified Multiple System Atrophy Rating Scale.

signs (Frontal Assessment Battery = 18). According to the Beck Depression Inventory, 67% of the patients were depressed (score ⩾13). Ten patients reported excessive daytime sleepiness with an Epworth sleepiness score >10.

Clinical rapid eye movement sleep behaviour disorder

Based on the bed-partner interview, 43 of 49 patients (87.8%) had RBD. Patients were reported to have developed their RBD before (30%), at the same time (7%) or after (63%) the onset of MSA. When the RBD preceded the onset of MSA, it had occurred from a few months to 20 years before. When comparing patients whose RBD began before the MSA to patients whose RBD began at the same time or after the MSA, there were no significant differences in age, disease severity, cognitive evaluation, depression or sleep characteristics. RBD occurred less than once a month in 15% patients, between once a week and once a month in 38% patients and more than once a week in 47% patients. Dreams during RBD referred to fighting or running/fleeing in 57% patients. Approximately 19% of the patients had injured themselves and 24% had injured their bed partners during sleep.

Thirty-one bed partners were able to compare the quality of the movements, speech expressions, and facial expressions of their co-sleeper during RBD to similar awake behaviours. The remaining 12 bed partners said that they were asleep or that the room was too dark to evaluate these aspects. Twenty-five (81%) bed partners reported an improvement of at least one component of motor control during RBD. The level of movement improvement in comparison with the wakefulness state is shown in Fig. 1. The movements were improved in 73% of patients with MSA, including increased speed (67%), strength (52%) or smoothness (26%). Speech was improved in 59% of patients and was more intelligible (17%), better articulated (36%) or louder in volume (55%). Facial expressions were normal (with a disappearance of amimia, and expressions of smiling, frowning or fear) in 50% patients during the RBD. The percentage of patients who improved their movement (at least one item) according to their co-sleeper evaluation, was not different (78 versus 82%, $P = 0.8$) in patients with a disease duration <5 years ($n = 14$) versus ⩾5 years ($n = 17$). There was no significant difference in the percentage of patients who improved between the MSA-P and MSA-C groups for any behavioural aspect. These improvements were compared with those described by the 31 bed partners of patients with Parkinson's disease (Fig. 1). The percentage of patients with various RBD-associated motor improvements was higher in Parkinson's disease than in patients with MSA, except for facial expression. The movements deteriorated (in all items) in 16% of the patients with MSA, including decreased speed (10%), strength (16%) or smoothness (26%). Speech deteriorated in all items in 28% of patients and was less intelligible (59%), articulated worse (35%) or softer in volume (35%).

Sleep measures

All 22 of the patients who underwent sleep monitoring had RBD according to the interview, which was confirmed on the sleep recordings (American Academy of Sleep Medicine, 2005). There

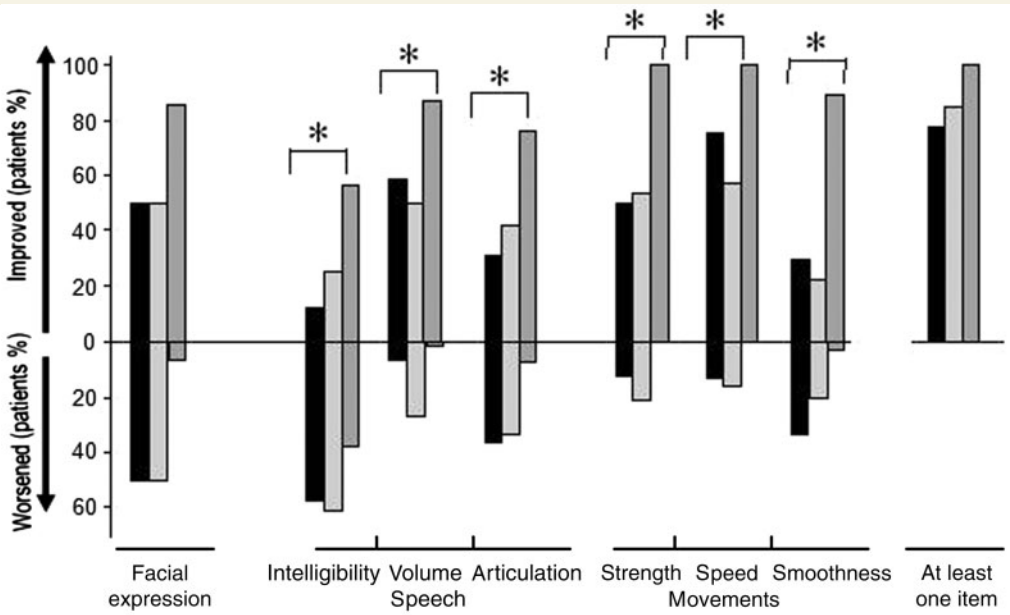

Figure 1 The level of improvement and worsening in movement (strength, speed and smoothness), speech (intelligibility, high volume and articulation) and facial expression during sleep in 31 patients with MSA (black columns: MSA-C, $n = 18$; light grey columns: MSA-P, $n = 13$) and 31 age- and gender-matched patients with Parkinson's disease (dark grey columns), as assessed by their bed partners. No significant differences were observed between MSA-C and MSA-P, but more patients with Parkinson's disease than with MSA showed improvement for all individual items except facial expression. *$P < 0.05$ for a difference between patients with MSA and Parkinson's disease.

Table 2 Sleep measures in patients with MSA-P, MSA-C and Parkinson's disease

Sleep measures	MSA-C	MSA-P	Parkinson's disease	MSA-P/C	*P*-value MSA/PD
Number	8	14	19		
Night-time sleep					
Total sleep time (min)	306 (58)	315 (98)	357 (80)	0.8	0.08
Sleep efficiency	62 (7)	62 (18)	70 (16)	1	0.1
Latency to (min)					
Sleep onset	48 (39)	47 (39)	56 (49)	0.9	0.6
REM sleep	281 (142)	105 (7)	145 (127)	**0.049**	0.2
Sleep duration (% total sleep time)					
Stage N1	10 (5)	7 (7)	5 (5)	0.2	**0.05**
Stage N2	52 (9)	63 (21)	54 (12)	0.1	0.3
Stage N3	24 (11)	20 (15)	20 (10)	0.4	0.8
REM sleep	14 (6)	11 (10)	21 (10)	0.3	**0.004**
Sleep fragmentation (*n*/h)					
Arousals	17 (8)	18 (14)	13 (10)	0.8	0.2
Periodic legs movements	23 (42)	24 (42)	11 (16)	1	0.1
Apnoea and hypopnoea	45 (28)	13 (10)	4 (6)	**0.02**	**0.001**

Data are mean (SD). PD = Parkinson's disease.

were no differences between patients with MSA-P and MSA-C with regard to sleep duration, efficiency, latency, fragmentation or structure; however, REM sleep latency and the apnoea/hypopnoea index were higher in patients with MSA-C than those with MSA-P (Table 2). Obstructive sleep apnoea was severe (apnoea/hypopnoea index >30/h) in six patients (five patients with MSA-C and one patient with MSA-P), moderate ($\leqslant 15$ apnoea/hypopnoea index <30/h) in five patients (two with MSA-C and three with MSA-P) and mild (apnoea/hypopnoea index <15) in five patients (two with MSA-C and three with MSA-P). One patient with MSA-C had central sleep apnoea syndrome. Stridor was recorded in four patients (three with MSA-C and one with MSA-P). The mean periodic leg movement index was 30 ± 44, and eight patients had more than 15 periodic leg movements per hour. Compared with patients with Parkinson's disease, patients with MSA had higher percentage of stage 1 sleep, lower percentage of REM sleep and a higher aponea/hypopnoea index.

Video monitoring of rapid eye movement sleep movements

A lack of REM sleep was observed in 3 of the 22 patients. Enhanced muscle tone during $>30\%$ of REM sleep time was observed in the remaining 19 patients. Only seven patients (five MSA-P and two MSA-C) had simple and complex motor behaviours on the video during REM sleep. One patient cried and looked terrified. Another one laughed. One kicked and another wrote on an invisible board. In all patients, the observed movements were surprisingly fast and lacked the characteristics of parkinsonism (bradykinesia, tremor, REM-sleep associated dystonia). Movements were performed with the same strength, amplitude and speed as those observed in healthy, awake subjects and sharply contrasted with the slow movements that are observed during wakefulness (example on Supplementary Video 1). Despite the fact that the movements were within the normal range, their aspect was jerky and broken (Supplementary Video 2). In addition, their faces were particularly expressive when they cried, seemed terrified or laughed, in contrast with their amimia in the awake state (Supplementary Videos 3, 4 and 5). None of the movements, speeches or facial expressions taken in REM sleep were deteriorated on the video clips, in contrast with those associated with arousals or awake states.

Discussion

Motor control was transiently improved during RBD in patients with MSA, as well as in patients with Parkinson's disease. Approximately 80% of patients exhibited improvements in their movements, speech expression, or facial expression during REM sleep in comparison with similar behaviours in the awake state. The improvement was present even in the most affected patients. There was no difference in the percentage of REM-related motor improvement between patients who were affected with MSA-P or MSA-C. An assessment of the video recordings revealed that REM sleep-associated movements are faster, smoother and stronger than awake movements but display broken and jerky aspects.

Parkinsonism disappeared in most patients with MSA during RBD, which is similar to the previous results for patients with Parkinson's disease; however, the rate of motor or vocal improvement during REM sleep is 30–60% greater in Parkinson's disease than in patients with MSA, except for amimia. Of interest, parkinsonism in MSA is less dopa-sensitive than that in Parkinson's disease due to the loss of post-synaptic dopamine receptors in MSA. This result suggests that the restoration of motor control during REM sleep is not secondary to a transient re-establishment of the dopamine nigro-striatal transmission, as suggested in the phenomena of sleep benefit or paradoxical kinesis in Parkinson's disease. The movements are complex and purposeful, as are the words and sentences that are pronounced

by the sleeping patients, suggesting they result, at least in part, from the same brain cortical area as those that drive the equivalent behaviours during wakefulness. Similarly, oscillatory activity was recently measured in the subthalamic nucleus (an output nucleus of the basal ganglia motor loop) during REM sleep with and without atonia in patients with Parkinson's disease. This activity fell within the same range as that present during bradykinesia in the awake state (Urrestarazu *et al.*, 2009). Taken together, these results suggest that the improvement of motor control during REM sleep is not secondary to a restoration of the dopaminergic loop. The minority of bed partners who reported a transient worsening of movements and speech during the night could have confounded movements associated to RBD and those associated to arousals, which are similar to the awake state. The absence of movement deterioration in the video clips, when the scorers are certain that they are taken in REM sleep, favours this explanation.

The presence or absence of cerebellar signs during RBD has not been previously assessed, even in patients with Huntington disease-associated RBD (Arnulf *et al.*, 2008); however, among the cerebellar signs, only dysarthria could be explored during sleep. Vocalizations during RBD were louder in 50% of patients with MSA, whereas articulation was improved in only one third of them. Language remained poorly intelligible with no further improvement in patients with MSA-C. Gait and balance cannot be explored because patients almost never stand up during RBD. Limb ataxia is difficult to assess because the movement goal is fictive (it belongs to the patients dreams) and is therefore invisible to the scorer. Therefore, the improvement of parkinsonism in both MSA groups could be exclusively responsible for motor improvement during RBD; however, the original model that has been proposed for Parkinson's disease-associated RBD could also apply to MSA because the RBD movements in MSA are as broken and jerky as those in Parkinson's disease. The sleep-induced loss of synaptic functional connections between the extrapyramidal and upper motor neuron pathway could allow for the rough expression of the primary motor cortex, which is relieved from the deleterious influence of the damaged basal ganglia. Whether the abnormal cerebellar control is also bypassed remains to be determined. Motor cortical stimulation in wakefulness has been unsuccessful in patients with MSA (Kleiner-Fisman *et al.*, 2003). The pyramidal tract is stimulated in this condition but the deleterious influence of the damaged basal ganglia remains active in these awake patients.

The main limit of our study is that it is based on the evaluation of the co-sleeper in most of the patients, because not all of them have been video recorded and because it is rare to record some complex movements during RBD in a laboratory. In fact, patients don't have RBD every night. However, we think that the co-sleeper is the best person to compare quality of movement during day and night. Even if we make a precise evaluation of the severity of parkinsonism, this syndrome fluctuates during the day and the co-sleeper that knows the all day long state of the patient seems to be the best evaluator of this improvement of movement.

The clinical observation that parkinsonism disappears during a condition such as RBD in MSA is all the more surprising since no treatment (even dopaminergic) provides a real benefit in this rare disabling disease. It shows that there are still functional pathways in these patients, but the means to free them from the deleterious influence of the basal ganglia (e.g. to specifically inactivate the thalamocortical final pathways issued from the basal ganglia) is unknown and requires work on the disjunction of functional synaptic connectivity during REM sleep.

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Supplementary material

Supplementary material is available at *Brain* online.

References

American Academy of Sleep Medicine. The international Classification of Sleep Disorders - Revised. Chicago, IL, 2005.

American Academy of Sleep Medicine. The international Classification of Sleep Disorders - Revised. Chicago, IL, 2007.

Arnulf I, Nielsen J, Lohmann E, Schiefer J, Wild E, Jennum P, et al. Rapid eye movement sleep disturbances in Huntington disease. Arch Neurol 2008; 65: 482–8.

Churchyard A, Donnan GA, Hughes A, Howells DW, Woodhouse D, Wong JY, et al. Dopa resistance in multiple-system atrophy: loss of postsynaptic D2 receptors. Ann Neurol 1993; 34: 219–26.

Comella C, Nardine T, Diederich N, Stebbins G. Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. Neurology 1998; 51: 526–9.

De Cock VC, Vidailhet M, Leu S, Texeira A, Apartis E, Elbaz A, et al. Restoration of normal motor control in Parkinson's disease during REM sleep. Brain 2007; 130: 450–6.

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology 2000; 55: 1621–6.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 2002; 59: 585–9.

Gilman S, Low P, Quinn N, Albanese A, Ben-Shlomo Y, Fowler C, et al. Consensus statement on the diagnosis of multiple system atrophy. American Autonomic Society and American Academy of Neurology. Clin Auton Res 1998; 8: 359–62.

Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999; 163: 94–8.

Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008; 71: 670–6.

Hobson D, Lang A, Wayne MW, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson Disease.

A survey by the Canadian Movement Disorder Group. JAMA 2002; 287: 455–63.

Iber C, Ancoli-Israel S, Chesson AL, Quan SF, Medicine AAoS. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. Westchester, IL, 2007.

Kleiner-Fisman G, Fisman DN, Kahn FI, Sime E, Lozano AM, Lang AE. Motor cortical stimulation for parkinsonism in multiple system atrophy. Arch Neurol 2003; 60: 1554–8.

Lu J, Sherman D, Devor M, Saper CB. A putative flip-flop switch for control of REM sleep. Nature 2006; 441: 589–94.

Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord 2010; 25: 2044–51.

Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 1989; 94: 79–100.

Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, et al. REM sleep behavior disorders in multiple system atrophy. Neurology 1997; 48: 1094–7.

Sastre JP, Jouvet M. Oneiric behavior in cats. Physiol Behav 1979; 22: 979–89.

Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep 1986; 9: 293–308.

Testa D, Monza D, Ferrarini M, Soliveri P, Girotti F, Filippini G. Comparison of natural histories of progressive supranuclear palsy and multiple system atrophy. Neurol Sci 2001; 22: 247–51.

Urrestarazu E, Iriarte J, Alegre M, Clavero P, Rodriguez-Oroz MC, Guridi J, et al. Beta activity in the subthalamic nucleus during sleep in patients with Parkinson's disease. Mov Disord 2009; 24: 254–60.

Vetrugno R, Provini F, Cortelli P, Plazzi G, Lotti EM, Pierangeli G, et al. Sleep disorders in multiple system atrophy: a correlative video-polysomnographic study. Sleep Med 2004; 5: 21–30.

Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002; 125: 1070–83.

Wenning GK, Ben-Shlomo Y, Magahaes. Clinical features and natural history of Multiple System Atrophy. Analysis of 100 cases. Brain 1994; 117: 835–45.

Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 2004; 19: 1391–402.