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Relationship between oscillatory activity in the cortico-basal ganglia network and parkinsonism in MPTP-treated monkeys ☆

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ABSTRACT

Parkinsonism is associated with changes in oscillatory activity patterns and increased synchronization of neurons in the basal ganglia and cortex in patients and animal models of Parkinson's disease, but the relationship between these changes and the severity of parkinsonian signs remains unclear. We examined this relationship by studying changes in local field potentials (LFPs) in the internal pallidal segment (GPi) and the subthalamic nucleus (STN), and in encephalographic signals (EEG) from the primary motor cortex (M1) in Rhesus monkeys which were rendered progressively parkinsonian by repeated systemic injections of small doses of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Observations during wakefulness and sleep (defined by EEG and video records) were analyzed separately. The severity of parkinsonism correlated with increases in spectral power at frequencies below 15.5 Hz in M1 and GPi and reductions in spectral power at frequencies above 15.6 Hz with little change in STN. The severity of parkinsonism also correlated with increases in the coherence between M1 EEG and basal ganglia LFPs in the low frequency band. Levodopa treatment reduced low-frequency activity and increased high-frequency activity in all three areas, but did not affect coherence. The state of arousal also affected LFP and EEG signals in all three structures, particularly in the STN. These results suggest that parkinsonism-associated changes in alpha and low-beta band oscillatory activity can be detected early in the parkinsonian state in M1 and GPi. Interestingly, oscillations detectable in STN LFP signals (including oscillations in the beta-band) do not appear to correlate strongly with the severity of mild-to-moderate parkinsonism in these animals. Levodopa-induced changes in oscillatory M1 EEG and basal ganglia LFP patterns do not necessarily represent a normalization of abnormalities caused by dopamine depletion.

Introduction

Prominent beta-band (13–35 Hz) oscillations in local field potentials (LFPs) in the basal ganglia (Brown et al., 2001; Gatev et al., 2006; Hammond et al., 2007) are seen as a key feature of the pathophysiology of Parkinson's disease (PD). This notion is supported by the finding that beta-band oscillations in the subthalamic nucleus (STN) of PD patients are reduced by antiparkinsonian treatments, such as dopaminergic medications or high-frequency stimulation of the STN (Bronte-Stewart et al., 2009; Kuhn et al., 2008; Levy et al., 2002; Priori et al., 2004; Wingeier et al., 2006). Beta-band LFP oscillations also increase in the internal pallidal segment (GPi) (Brown et al., 2001; Cassidy et al., 2002), and abnormal delta and theta band activities have been found in electroencephalographic recordings (EEGs) from the primary motor cortex (M1) of parkinsonian patients (Neufeld et al., 1994; Serizawa et al., 2008; Soikkeli et al., 1991; but see Sebban et al., 1999).

Studies in animal models of PD are consistent with these observations in patients. Thus, the power of beta-band oscillations was found to be increased in basal ganglia LFPs in 6-hydroxydopamine treated (dopamine-depleted) rats (Avila et al., 2009; Mallet et al., 2008; Sharott et al., 2005), and in single neuron recordings in monkeys treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Bergman et al., 1994; Meissner et al., 2005; Wichmann et al., 1994). More recently, oscillatory activity patterns were also demonstrated in M1 neuron recordings in MPTP-treated primates (Pasquereau and Turner, 2011).

Because M1, STN, and GPi are anatomically connected (Mathai and Smith, 2011), the hypothesis has emerged that parkinsonism-related oscillations in these structures are linked. According to this view, dopamine depletion in PD triggers pathologic oscillatory patterns throughout the basal ganglia-thalamocortical network, eventually leading to the behavioral signs of parkinsonism. However, while there is strong evidence that abnormal oscillations occur in this network in the dopamine-depleted state, it is not clear whether the oscillations

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cause parkinsonism. While some evidence in PD patients suggests that beta band activity in the STN contributes to akinesia (Kuhn et al., 2004; Williams et al., 2005), other studies failed to demonstrate a strong correlation between clinical impairments and STN beta-band activity at rest in these patients (Kuhn et al., 2009; Ray et al., 2008; Weinberger et al., 2006; Zaidel et al., 2010). Recordings in monkeys showed also that parkinsonism precedes changes in oscillatory single neuron activities in GPi (Leblois et al., 2007).

Because of this uncertainty, we examined the temporal relationship between the appearance of motor disabilities and the appearance of oscillatory LFP changes in STN and GPi, and M1 EEG in a progressive model of parkinsonism in primates. If increased low-frequency LFP or EEG oscillations truly *cause* parkinsonism, the onset of such changes would have to either coincide with or precede the appearance of parkinsonism. In order to avoid the confounding effects of parkinsonism-related changes of the state of arousal (Rye, 2006; Videnovic and Golombek, 2013), we focused our examination of parkinsonism-related oscillations on observations in the awake state. Finally, we examined the effect of antiparkinsonian levodopa treatment on oscillatory activity in STN, GPi and M1 in the fully developed parkinsonian state.

Materials and methods

General experimental strategy

We studied rhesus monkeys in the normal state, during the gradual development of parkinsonism induced by repeated small injections of MPTP, and again, when treated with antiparkinsonian doses of levodopa in the fully parkinsonian state. The animals were permanently implanted with EEG recording electrodes over the M1 cortex, as well as recording chambers that allowed us to record LFP signals in STN and GPi. Signals were recorded at weekly intervals, and then subjected to spectral analysis. The coherence between simultaneously recorded traces from different brain locations was also analyzed.

Animals, surgical procedures

Three adult rhesus monkeys (*Macaca mulatta*; 6–10 kg; monkeys A, B, and C; 1 male and 2 females) were used. The animals were pair-housed with other monkeys, and had ad libitum access to food and water. All experiments were performed in accordance with the United States Public Health Service Policy on the humane care and use of laboratory animals, including the provisions of the "Guide for the Care and Use of Laboratory Animals" (Garber et al., 2011). All studies were approved by the Institutional Biosafety and Animal Care and Use Committees of Emory University.

The animals were first conditioned to accustom them to handling by the experimenter and to sitting in a primate chair. They then underwent aseptic surgery under isoflurane anesthesia (1–3%) for placement of epidural bone screw electrodes and two stainless steel recording chambers (Crist Instruments, Hagerstown, MD; inner chamber diameter 16 mm), positioned stereotactically and embedded, along with a stainless steel head holder, into an acrylic 'cap'. Four epidural screw electrodes (diameter: 0.25 mm, length 0.4 mm) were inserted on each side of the skull bilaterally through small holes drilled in the skull over M1 for bipolar recordings. In this study, only recordings from the left side were used (ipsilateral to the basal ganglia recordings). Wires from the electrodes were soldered to a 9-pin connector that was also embedded in the acrylic. The chambers were directed at the pallidum and the STN on the animal's left side. The pallidal chamber was placed at a 40° angle from the vertical in the coronal plane (A = 11, L = 11, D = 2), and the STN chamber was positioned at a 36° angle anterior to the vertical in the sagittal plane (A = 10, L = 7, D = 2). The animals were allowed to recover for one week after the surgery before recording and other procedures begun.

MPTP treatment

After the recordings in the normal state were completed, the animals were rendered progressively parkinsonian by weekly administration of small doses of MPTP (0.2–0.6 mg/kg i.m.). Monkey A received 21 injections (9.4 mg/kg total), monkey B received 26 injections (10.2 mg/kg total) and monkey C received 19 injections (6.0 mg/kg total). All three animals eventually reached comparable states of stable moderate parkinsonism (defined below). To assess the degree and stability of the MPTP-induced motor disability, the severity of parkinsonism was assessed weekly while the monkey was in an observation cage equipped with infrared beams, allowing us to continuously observe the animal and to automatically measure its body movements. In these sessions we also scored the motor impairment in terms of ten aspects of motor function (bradykinesia, freezing, extremity posture, trunk posture, action tremor, the frequency of arm and leg movements, finger dexterity, home cage activity, and balance). Each was scored on a 0 to 3 scale (maximal score 30). The maximal severity of parkinsonism in any animal in this study was 15, corresponding to moderately severe parkinsonism. For statistical comparisons, we binned the range of scores into three groups: stage 1 (scores between 0 and 5), stage 2 (scores between 6 and 10), and stage 3 (scores between 11 and 15). For each monkey, several recordings in each of the 3 stages of parkinsonism were available (Table 1).

Electrophysiological mapping

All recordings were made while the animal sat in a primate chair with its head immobilized but its body and limbs free to move. The locations of STN and GPi were mapped by extracellular electrophysiological recording with tungsten microelectrodes (FHC, Bowdoinham, ME; Z = 0.5–1.0 MΩ at 1 kHz). The dura was pierced with a guide tube and the electrode lowered into the brain with a microdrive (MO-95B; Narishige, Tokyo, Japan). The locations and borders of STN and GPi (in chamber coordinates) were defined with single unit extracellular recordings. These signals were amplified (DAM-80 amplifier; WPI, Sarasota, FL), filtered (400–6000 Hz; model 3700 filter; Krohn-Hite, Brockton, MA), displayed on a digital oscilloscope (DL1540; Yokogawa, Tokyo, Japan), and made audible via an audio amplifier. Neurons in the STN were identifiable by their typical activity pattern, which differed from that of the more dorsal zona incerta (low neuronal activity), and that of the more ventrally located substantia nigra pars reticulata (Starr et al., 2000). GPi neurons were identified by their location ventromedial to the external pallidal segment, and by their continuous high frequency discharge (DeLong, 1971).

After delineating STN and GPi, the sensorimotor portion of each nucleus was targeted for LFP recordings. LFPs were recorded with bipolar concentric electrodes (SNEX-100 × 120 mm; outer diameter, 250 μm; inter-contact separation, 500 μm; impedance, 25–35 kΩ; Rhodes Medical Instruments Inc., Tujunga, CA). On each recording day, one of these electrodes was placed in the STN and one in the GPi for

Table 1
Total number of recording sessions across different stages of parkinsonism (as defined in the Methods), and numbers of 'wakefulness' or 'sleep' periods within these recordings (each period lasted 10 s).

Monkey		Baseline	Stage 1	Stage 2	Stage 3
A	Number of recording sessions	3	10	3	2
	Number of wakefulness periods	54	950	249	143
	Number of sleep periods	40	10	10	10
B	Number of recording sessions	12	6	13	17
	Number of wakefulness periods	627	389	769	994
	Number of sleep periods	109	44	31	68
C	Number of recording sessions	8	4	4	5
	Number of wakefulness periods	202	192	259	349
	Number of sleep periods	209	106	94	23

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