Dopamine dependent functional connectivity of Subthalamic and Pedunculopontine rhythms in a Parkinsonian patient

Yi-Ting Hsu, Hsin-Yi Lai, Shang-Ming Chiou
Ming-Kuei Lu, Yu-Chin Lin, You-Yin Chen, and Chon-Haw Tsai

YT Hsu, MK Lu, YC Lin and CH Tsai are with the Department of Neurology, China Medical University Hospital, Taichung, Taiwan.

SM Chiou is with the Department of Neurosurgery, China Medical University Hospital, Taichung, Taiwan.

HY Lai is with the Department of Electrical Engineering, National Chiao Tung University, Hsinchu, Taiwan

YY Chen is with Department of Biomedical Engineering, National Yang-Ming University, Taipei

Abstract—The interplay of local field potentials (LFP) between subthalamic nucleus (STN) and pedunculopontine nucleus (PPN) in patients with Parkinson's disease (PD) is not known in any detail. To this end, we recorded LFPs from electrodes implanted for deep brain stimulation (DBS) in the STN and PPN of a parkinsonian patient during ON and OFF dopaminergic agents. We investigate the existence of possible linear and nonlinear interactions between LFP rhythms of PPN and STN respectively by coherence and biphase-locking analysis. Coherence in the alpha frequency between the PPN and STN LFP was higher in ON than OFF medication but reversal pattern existed in beta frequency. Using bi-phase locking calculation we find out that the dopamine stimulation induce cross-frequency bands interactions in reciprocal direction. This intimate reciprocal connection of PPN and STN has implications relating to our understanding, and possibly the treatment, of Parkinson's disease.

I. Introduction

The Pedunculopontine nucleus (PPN) was connected with STN confirming by the results of numerous anatomical and electrophysiological studies previously conducted in animals.[1-4]. In human study, some reports determined the anatomical connections of STN and PPN in health people by probabilistic diffusion tractography [5, 6]. Low frequency peripeduncular nucleus-stimulation changed the firing activity of almost every subthalamic nucleus cell was recently reported in a microelectrode single-unit study in parkinsonian patients [7].

However, the interplay of local field potentials (LFP) within and between STN and PPN in patients with Parkinson's disease (PD) is not known in any detail. Recent studies with LFP recordings from electrodes implanted for deep brain stimulation (DBS) in patients with PD are providing a new complementary scenario of information processing in the human basal ganglia, PPN and motor cortex [8-10]. Here we look for functional connectivity between the human STN and ipsilateral PPN in the presence and relative absence of dopaminergic stimulation, by recording LFP of these two areas in a patient undergoing functional neurosurgery for PD. The connectivity between STN and PPN was checked by coherence and biphase-locking analysis to further elucidate the synchronization network.

II. Materials and Methods

A. Patient details, Test conditions and data recording

The patient's symptoms began in 2005 at age of 53 with symptoms of insomnia and depressive mood. In 2006, she experienced left hand clumsiness, tremor and dragging the left leg. During off periods, the Unified Parkinson's Disease Rating Scale (UPDRS) scored 116 and UPDRS III 62 and after levodopa challenge test, the UPDRS III 44 (29% improvement). Implantation of bilateral STN and left PPN stimulators were performed at age of 58 for severe motor complication, dyskinesia, gait and postural instability.

Depth electrode recordings were performed 1 day after electrode implantations and in the resting, awake state with the patient in a supine position. OFF-medication recordings were performed following withdrawal of all anti-parkinsonian medication in the preceding 12 h. ON-medication recordings were performed at least 30 min after administration of usual dopaminergic medication dosage and improvement of clinical symptoms. LFP recordings were taken from contacts of the stimulating electrodes (Medtronic3389, Medtronic Inc., Minneapolis, Minnesota, USA) implanted in the left STN and PPN. LFPs were recorded biploarly from the four adjacent contacts of each DBS electrode (contact pairs 01, 12 and 23) simultaneously. LFPs were sampled at a rate of 1 KHz per channel and amplified (×100,000) (Digitimer 360, Welwyn Garden City, Hertfordshire, England) with a bandpass filter of 1–250 Hz, digitized by an analog-digital convert (CED power 1401, Cambridge Electronic Design Ltd., UK). Then the signals were recorded and monitored online using Spike2 software (Cambridge Electronic Design Ltd., UK).

B. Analysis

300 seconds LFP recording at on and off medication in left STN and PPN was digitally converted offline to contiguous bipolar derivations (e.g. 01, 12, 23) and was taken for synchronization estimation with the coherence [11] and the

bi-phase locking (BPL) analysis [12] by using the numerical computing software (MATLAB R2009b, Mathworks Inc., USA). For the BPL value analysis, frequencies below 40Hz were divided into four bands [13]: very-low frequencies (2–7Hz), alpha (8–12Hz), low-beta (13–20Hz) and high-beta (20-35Hz). Accordingly, we defined six regions of interest (ROIs) in the BPLV frequency map that represent all the possible intersections of the spectral bands (Fig. 2A): ROIs corresponding to the high-beta rhythm were not considered, because the generated harmonics would be within the range of the line noise (50 Hz).

III. RESULTS

Off medication, there is coherence between the PPN and STN LFP at alpha frequency (8-12 Hz), low beta (13-20 Hz) and high beta (20-35 Hz) activity, while the power in the alpha frequency was lower than in the total beta band (Fig. 1 solid line). The beta frequency activity is reduced on treatment when increased activity over alpha frequency after treatment with levodopa is observed (Fig. 1 dashed line).

In the analysis seeking non-linear correlations between LFP rhythms of PPN and STN, the resulting BPLV produce a frequency-by-frequency map in Fig 2B. This map shows the BPLV increase at ROI 1,2,4,6 and decrease at ROI 5 after levodpa in the direction of STN to PPN. In the direction of PPN to STN, the BPLV increase at ROI 2,4,6 and decrease at ROI 5 after levodopa (Fig 2C).

IV. DISCUSSION AND CONCLUSIONS

The current case study substantiates the previous evidences from animal and human study that the existence of functional connectivity between PPN and STN in parkinsonian patients by synchronous neuronal activity and reciprocal interactions in LFP.

Previous study demonstrates that alpha frequency oscillations in PPN are augmented by the administration of levodopa in PD [9]. Contrast with those in subthalamic nucleus, excessive synchronization in the beta band has been suppressed after treated with levodopa [14]. In the coherence between these nuclei, it estimates the signal linear relationship between STN and PPN LFP at specific frequency band. Oscillatory linear interactions between STN and PPN were dominated by activity at alpha frequency with dopamine stimulation whereas those at low beta or high beta frequency were greatly diminished. However, coherence values doesn't provide the causality information and would be affect by amplitude covariance [15].

Bi-phase locking value is a method to research pure phase-phase cross-frequency band interaction between signals without amplitude interference. Using the high-order spectral analysis with bi-phase locking calculation we find out that PD produces non-linear correlations between STN and PPN LFP rhythms oscillating at different frequencies. After levodopa administration these non-linear correlations increase whether in the direction of STN to PPN or vice versa. The dopamine stimulation not only affects the rhythmic-specific oscillation in identical frequency band interaction in brain circuit but also induce cross-frequency bands interactions in particular direction. These dramatic effects of levodopa on STN-PPN oscillations may have been exerted through the projection of the substantia nigra pars compacta to the putamen and thence to STN or directly via a dopaminergic substantia nigra pars compacta–STN projection. The STN then provides glutamatergic innervation of the PPN which, in turn, sends cholinergic, glutamatergic and GABAergic projections back to the STN.[16]. Disruption of the circuit could alter normal activity of PPN neurons and consequently motor functions. The increased non-linear correlations after dopaminergic stimulation (i.e. toward more normal condition) between these nuclei might be crucial in the normal function of STN and PPN

In conclusions, synchronization of activity does occur between STN and PPN, and its pattern is critically dependent on dopaminergic stimulation The fact that the STN have reciprocal connections with the PPN has implications relating to our understanding, and possibly the treatment, of Parkinson's disease.

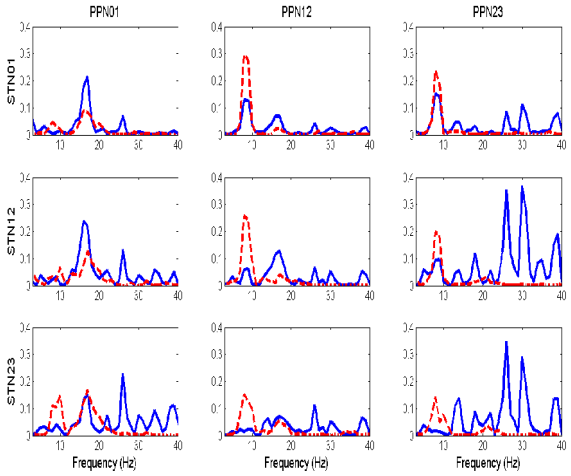

Figure 1. Coherence spectra between each STN and PPN contact pairs after withdrawal (solid line) or reinstitution (dashed line) of levodopa.

REFERENCES

[1] [1] T. Florio, E. Scarnati, G. Confalone, D. Minchella, S. Galati, P. Stanzione, A. Stefani, and P. Mazzone, "High-frequency stimulation of the subthalamic nucleus modulates the activity of pedunculopontine neurons through direct activation of excitatory fibres as well as through indirect activation of inhibitory pallidal fibres in the rat," *Eur J Neurosci,* vol. 25, pp. 1174-86, Feb 2007.

[2] [2] C. Hammond, B. Rouzaire-Dubois, J. Feger, A. Jackson, and A. R. Crossman, "Anatomical and electrophysiological studies on the reciprocal projections between the subthalamic nucleus and nucleus tegmenti pedunculopontinus in the rat," *Neuroscience,* vol. 9, pp. 41-52, May 1983.

[3] [3] B. Lavoie and A. Parent, "Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by

anterograde tract-tracing methods," *J Comp Neurol,* vol. 344, pp. 210-31, Jun 8 1994.

[4] [4] A. Capozzo, T. Florio, G. Confalone, D. Minchella, P. Mazzone, and E. Scarnati, "Low frequency stimulation of the pedunculopontine nucleus modulates electrical activity of subthalamic neurons in the rat," *J Neural Transm,* vol. 116, pp. 51-6, Jan 2009.

[5] [5] K. A. Muthusamy, B. R. Aravamuthan, M. L. Kringelbach, N. Jenkinson, N. L. Voets, H. Johansen-Berg, J. F. Stein, and T. Z. Aziz, "Connectivity of the human pedunculopontine nucleus region and diffusion tensor imaging in surgical targeting," *J Neurosurg,* vol. 107, pp. 814-20, Oct 2007.

[6] [6] B. R. Aravamuthan, K. A. Muthusamy, J. F. Stein, T. Z. Aziz, and H. Johansen-Berg, "Topography of cortical and subcortical connections of the human pedunculopontine and subthalamic nuclei," *Neuroimage,* vol. 37, pp. 694-705, Sep 1 2007.

[7] [7] S. Galati, E. Scarnati, P. Mazzone, P. Stanzione, and A. Stefani, "Deep brain stimulation promotes excitation and inhibition in subthalamic nucleus in Parkinson's disease," *Neuroreport,* vol. 19, pp. 661-6, Apr 16 2008.

[8] [8] P. Brown and D. Williams, "Basal ganglia local field potential activity: character and functional significance in the human," *Clin Neurophysiol,* vol. 116, pp. 2510-9, Nov 2005.

[9] [9] A. G. Androulidakis, S. Khan, V. Litvak, C. W. Pleydell-Pearce, P. Brown, and S. S. Gill, "Local field potential recordings from the pedunculopontine nucleus in a Parkinsonian patient," *Neuroreport,* vol. 19, pp. 59-62, Jan 8 2008.

[10] [10] A. G. Androulidakis, P. Mazzone, V. Litvak, W. Penny, M. Dileone, L. M. Gaynor, S. Tisch, V. Di Lazzaro, and P. Brown, "Oscillatory activity in the pedunculopontine area of patients with Parkinson's disease," *Exp Neurol,* vol. 211, pp. 59-66, May 2008.

[11] [11] D. Williams, M. Tijssen, G. Van Bruggen, A. Bosch, A. Insola, V. Di Lazzaro, P. Mazzone, A. Oliviero, A. Quartarone, H. Speelman, and P. Brown, "Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans," *Brain,* vol. 125, pp. 1558-69, Jul 2002.

[12] [12] F. Darvas, J. G. Ojemann, and L. B. Sorensen, "Bi-phase locking - a tool for probing non-linear interaction in the human brain," *Neuroimage,* vol. 46, pp. 123-32, May 15 2009.

[13] [13] S. Marceglia, G. Foffani, A. M. Bianchi, G. Baselli, F. Tamma, M. Egidi, and A. Priori, "Dopamine-dependent non-linear correlation between subthalamic rhythms in Parkinson's disease," *J Physiol,* vol. 571, pp. 579-91, Mar 15 2006.

[14] [14] P. Brown, A. Oliviero, P. Mazzone, A. Insola, P. Tonali, and V. Di Lazzaro, "Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease," *J Neurosci,* vol. 21, pp. 1033-8, Feb 1 2001.

[15] [15] J.-P. Lachaux, E. Rodriguez, J. Martinerie, and F. J. Varela, "Measuring phase synchrony in brain signals," *Human Brain Mapping,* vol. 8, pp. 194-208, 1999.

[16] [16] P. A. Pahapill and A. M. Lozano, "The pedunculopontine nucleus and Parkinson's disease," *Brain,* vol. 123 (Pt 9), pp. 1767-83, Sep 2000.

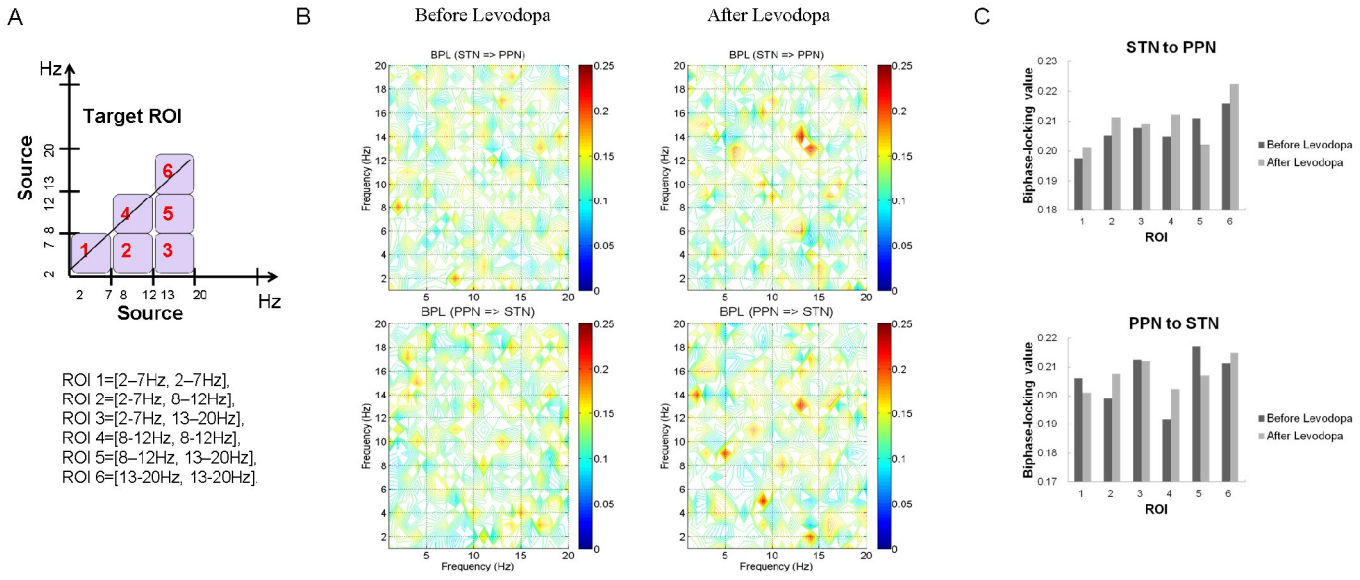

Figure 2. A. Regions of interest (ROIs) in the bispectral plane.The diagonal represents a symmetry axix) B. Biphase locking value frequency map: upper panel represents the direction from STN to PPN; lower panel represent the direction from PPN to STN C. BPLV in different ROI regions was showed