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Short Communication

Increased beta activity in dystonia patients after drug-induced dopamine deficiency

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ABSTRACT

Several studies have confirmed that subthalamic and pallidal *local field potential* activity in the beta frequency band (13–30 Hz) is exaggerated in untreated patients with Parkinson's disease (PD) and is suppressed by dopaminergic treatment. This particular spectral pattern differs from that in patients with dystonia in whom pallidal activity is prominent at low frequencies (<12 Hz). Here we demonstrate that tetrabenazine induced monoamine depletion and dopamine blockade is associated with increased activity in the low beta band (13–20 Hz) in the internal pallidum of patients with dystonia. Beta activity was elevated in six patients treated with tetrabenazine compared to six patients in whom this drug was not used. Our findings suggest that beta activity is enhanced in the chronically dopamine-depleted and blocked state irrespective of the underlying pathology, consistent with the idea that excessive synchrony in the beta band is directly related to dopaminergic hypofunction, rather than some degenerative disease-specific attribute of Parkinson's disease.

Dopamine is a key neurotransmitter for corticostriatal circuit function related to voluntary movement. According to the classical model of cortex–basal ganglia interaction, dopamine depletion should lead to increased neuronal discharge of the internal pallidum and attenuation of the usual thalamic facilitation of the motor cortex and thereby reduced movement (Albin et al., 1989; DeLong, 1990). Recent observations from deep brain recordings in patients undergoing functional neurosurgery for movement disorders have suggested that not only changes in neuronal discharge rate but also the nature of synchronisation within neuronal populations of the basal ganglia may contribute to the motor deficits (Marsden and Obeso, 1994; Bevan et al., 2002; Brown, 2003; Hammond et al., 2007). In patients with Parkinson's disease off medication this synchronisation tends to be oscillatory and predominate in the beta band (13–30 Hz; Brown et al., 2003). Such synchronisation is suppressed after levodopa administration (Brown et al., 2001; Levy et al., 2002; Priori et al., 2004). The reduction in beta power correlates with clinical improvement of motor symptoms (Kühn et al., 2006; Weinberger et al., 2006). Beta activity is also suppressed during and after high frequency stimulation of the subthalamic nucleus (STN) in PD patients (Brown et al., 2004; Wingeier et al., 2006) and the degree of deep brain simulation (DBS)-induced beta power suppression correlates with improvement in bradykinesia (Kühn et al., 2008). Therefore, it has been suggested that excessive synchronisation in the beta band may be antikinetic in nature and contribute to parkinsonism (Brown, 2003; Hammond et al., 2007). Implicit in this has been the notion that chronic dopaminergic hypofunction leads to the pathological beta activity in Parkinson's disease. However, this need not necessarily be the case as PD is associated with a variety of degenerative changes and neurochemical disturbances (Scatton et al., 1983), and both dopaminergic and anticholinergic medication can influence levels of beta activity (Priori et al., 2004).

We hypothesised that if loss of dopamine leads to pathological beta synchrony then beta activity should also be elevated in patients without PD following chronic treatment with a drug that leads to dopaminergic underactivity. The opportunities for depth recordings in patients on such drugs are limited but tetrabenazine is often used to treat hyperkinesias in patients with dystonia, some of whom undergo surgery for deep brain stimulation. Tetrabenazine depletes vesicular monoamines like dopamine and directly blocks dopamine (DeJesus et al., 2002), providing a practical, if not totally specific test of our hypothesis. Accordingly, we recorded pallidal local field potentials (LFP) in six patients undergoing DBS for severe dystonia during chronic treatment with tetrabenazine for hyperkinetic movements (3 idiopathic generalized, 1 idiopathic multifocal, 2 tardive dystonia, mean age 52.2±8.1 years [mean±SEM]) and compared the pattern of synchronised oscillatory activity to that in six dystonia patients

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without medication (3 idiopathic generalized, 3 idiopathic segmental dystonia, mean age 39.5±5.1 years; no significant difference in age between groups, Mann–Whitney *U* test, $p=0.132$). Preoperatively, patients in the tetrabenazine group had a higher mean score for dystonic symptoms but the difference was not significant between groups (Burke–Fahn–Marsden dystonia rating scale (BFMDRS): tetrabenazine 42.3±9.1; no medication 26.0±4.1, $p=0.177$, Mann–Whitney *U* test). Patients were selected for bilateral implantation of deep brain electrodes in the globus pallidus internus (GPi) at the Departments of Neurology and Neurosurgery of the University Hospital Charité, Campus Virchow in Berlin (10 patients) and the Department of Neurosurgery of the University Hospital of the Medical School Hannover and Mannheim (2 patients). In case 2 additional bilateral thalamic electrodes were implanted for severe dystonic tremor. All patients participated in the study with informed consent and the permission of the local ethics committees. Their clinical details are summarized in the table (Supplementary material).

The operative procedure and beneficial clinical effects of stimulation have been described previously (Krauss et al., 2004; Coubes et al., 2004; Kupsch et al., 2006). The macroelectrode used was model 3387 (Medtronic Neurological Division, Mineapolis, USA) with four platinum–iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and contact to contact separations of 1.5 mm (except for case 7, where model 3389 was used with contact to contact separations of 0.5 mm). Contact 0 was the lowermost contact. Pallidal electrode trajectories were aimed at the postero-ventral portion of the *GPi* and the posterior ansa lenticularis. The intended coordinates at the tip of contact 0 were 2–3 mm in front of the mid-commissural point, 20–22 mm lateral to the midline of the third ventricle and 4–6 mm below the anterior commissure (AC)-posterior commissure (PC) line. Adjustments to the intended coordinates were made in accordance with the direct visualization of GPi on high resolution T2-weighted magnetic resonance imaging (MRI). Furthermore, correct electrode localization was supported by intra-operative microelectrode recordings (cases 1–10) and intra-operative macrostimulation in all patients. In particular, the location of the lowest contact was established by the intra-operative induction of visual phosphenes by high frequency stimulation. Correct placement of the DBS electrodes in GPi was further supported by: [1] post-operative T2 weighted MRI compatible with the placement of at least two electrode contacts in GPi (a representative example of a post-operative MRI is given in Supplementary Figure 1); [2] significant improvement in dystonic symptoms during chronic DBS compared to preoperative state (as measured by BFMDRS; mean improvement 45.7±11.1%, $p=0.006$ paired Student's *t*-test; cases 1–10, and 12).

Patients were studied 2–6 days postoperatively, during the period of externalisation of DBS electrodes prior to their connection to the subcutaneous stimulator device. In all patients LFP recordings were performed at rest with the patient sitting comfortably in an armchair. Patients were on their usual medication (cases 1–6 on tetrabenazine treatment, case 7–12 without medication except for propranolol in case 9; see Supplementary Table 1). The mean duration of LFP recordings was 430.2±41.6 s. Deep brain activity was recorded from the 4 contacts (0, 1, 2 and 3) of each DBS electrode. With the exception of one case, signals were amplified (×50,000) and filtered at 1–250 Hz using a custom-made, 9 V battery-operated portable high impedance amplifier (which had as its front end input stage the INA128 instrumentation amplifier, Texas Instruments Incorporated 12500 TI Boulevard Dallas Texas, USA) and recorded through a 1401 A–D converter (Cambridge Electronic Design, Cambridge, UK) onto a computer using Spike2 software (Cambridge Electronic Design). Signals were sampled either at 625 Hz ($n=4$) or 1 kHz ($n=7$) and monitored on-line. For case 9, signals were amplified and band pass filtered between 1.5–200 Hz (sampling rate 1200 Hz; Biopotential Analyzer Diana, St Petersburg, Russia).

Data were interpolated to a common sampling rate of 1024 Hz. The principal statistical tool used for data analysis was the discrete Fourier transform. Autospectra of the LFP were estimated by dividing the records into a number of disjoint sections of equal duration (1024 points), and estimating spectra by averaging across these discrete sections affording a frequency resolution of 1 Hz (Halliday et al., 1995). LFP power recorded from bipolar contact pairs (01, 12, 23) was determined and expressed as percentage of total power in the 5–95 Hz range. Frequencies below 5 Hz and in the 44–56 Hz band were excluded since these are prone to movement artefacts and mains noise, respectively. In addition, a subsidiary power analysis was performed using the mean power value of the 105–145 Hz frequency band to normalize data across subjects. Three frequency bands of interest were selected for further analysis: sub-beta band (5–12 Hz), low beta band (13–20 Hz) and upper beta band (21–30 Hz), in line with a previous study (Priori et al., 2004). We picked the contact pair of each side that displayed the maximum 13–30 Hz activity for further analysis. In 12 out of 22 DBS electrodes (55%) both contacts of the selected bipolar pair lay within GPi and all remaining cases (45%) included one contact that, according to the blinded evaluation of post-operative MRI, lay within GPi. The mean power values for each frequency band were compared between the two patient groups using Mann–Whitney U test for non-parametric data (SPSS for Windows version 11, SSPS Inc, Chicago, Illinois, USA). P-values were Bonferroni corrected for multiple comparisons.

The power spectrum of all patients showed the characteristic dominant low frequency activity (5–12 Hz) previously described in dystonia (Silberstein et al., 2003) and no difference was revealed for 5–12 Hz power between groups (tetrabenazine: 45.7±5.1%, no medication: 46.1±2.9%, $p>0.7$, Fig. 1). In contrast, low beta power was

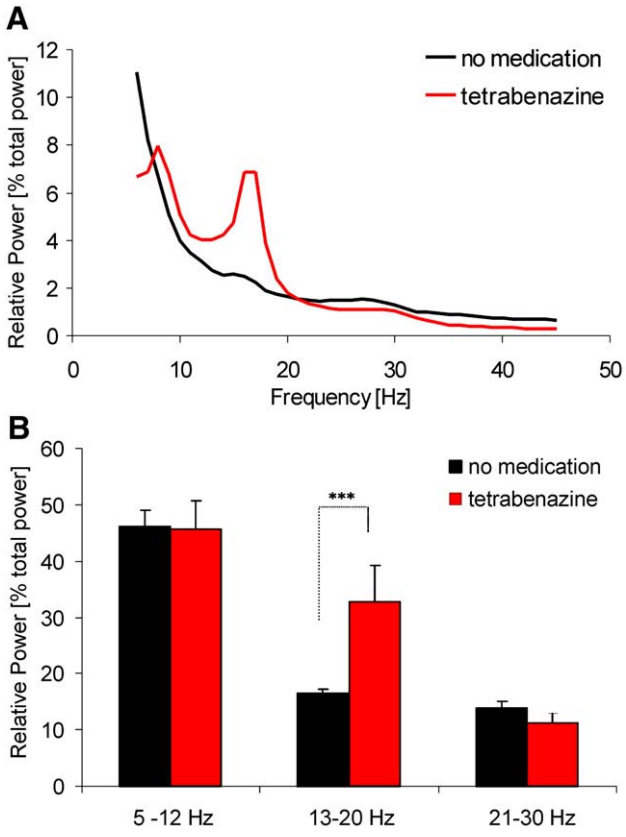

Fig. 1. (A) Mean power spectrum from pallidal rest recordings in patients treated with tetrabenazine ($n=6$, red line) and without medication ($n=6$, black line). (B) Mean percentage power in the three frequency bands of interest. Low beta activity is significantly larger in patients treated with tetrabenazine (red columns) compared to patients without drugs (black columns) ***$p<0.001$.