Neuroscience 132 (2005) 659–664

COHERENT SPIKE-WAVE OSCILLATIONS IN THE CORTEX AND SUBTHALAMIC NUCLEUS OF THE FREELY MOVING RAT

P. J. MAGILL,[a]* A. SHAROTT,[b] D. HARNACK,[c] A. KUPSCH,[c] W. MEISSNER[c,d] AND P. BROWN[b]

[a]*Medical Research Council Anatomical Neuropharmacology Unit, University of Oxford, Oxford OX1 3TH, UK*

[b]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, UK*

[c]*Department of Neurology, Charité Virchow-Klinikum, Humboldt University, Berlin, Germany*

[d]*Basal Gang, Laboratoire de Neurophysiologie, Université Victor Segalen, CNRS UMR 5543, Bordeaux, France*

Abstract—The basal ganglia play a critical role in controlling seizures in animal models of idiopathic non-convulsive (absence) epilepsy. Inappropriate output from the substantia nigra pars reticulata (SNr) is known to exacerbate seizures, but the precise neuronal mechanisms underlying abnormal activity in SNr remain unclear. To test the hypothesis that cortical spike-wave oscillations, often considered indicative of absence seizures, propagate to the subthalamic nucleus, an important afferent of SNr, we simultaneously recorded local field potentials from the frontal cortex and subthalamic nucleus of freely moving rats. Spontaneous spike-wave oscillations in cortex (mean dominant frequency of 7.4 Hz) were associated with similar oscillations in the subthalamic nucleus (mean of 7.9 Hz). The power of oscillations at 5–9 Hz was significantly higher during spike-wave activity as compared with rest periods without this activity. Importantly, spike-wave oscillations in cortex and subthalamic nucleus were significantly coherent across a range of frequencies (3–40 Hz), and the dominant (7–8 Hz) oscillatory activity in the subthalamic nucleus typically followed that in cortex with a small time lag (mean of 2.7 ms).

In conclusion, these data suggest that ensembles of subthalamic nucleus neurons are rapidly recruited into oscillations during cortical spike-wave activity, thus adding further weight to the importance of the subthalamic nucleus in absence epilepsy. An increase in synchronous oscillatory input from the subthalamic nucleus could thus partly underlie the expression of pathological activity in SNr that could, in turn, aggravate seizures. Finally, these findings also reiterate the importance of oscillations in these circuits in normal behaviour. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: basal ganglia, absence epilepsy, substantia nigra, corticosubthalamic.

Idiopathic non-convulsive (absence) epileptic seizures in humans are characterised by a sudden, brief impairment of consciousness that is accompanied by a generalised, synchronous, slow (2.5–4 Hz) 'spike-wave' oscillation in the electroencephalogram (for review, see Crunelli and Leresche, 2002). Recent studies on animal models of absence epilepsy have stressed that although these spike-wave oscillations, which are usually faster in animals (5–11 Hz), are generated within corticothalamic 'loop' networks, other forebrain systems may still exert strong influences over seizure activity (for review, see Danober et al., 1998). Indeed, the basal ganglia, particularly the GABAergic projection neurons of the substantia nigra pars reticulata (SNr), are thought to play a critical role in the expression of epileptic activity (Proctor and Gale, 1998; Deransart and Depaulis, 2002). In support of this, spike-wave oscillations have been reported to occur in the SNr during absence seizures (Vergnes et al., 1990; Deransart et al., 2003), and suppressing nigral activity has wide-ranging antiepileptic effects (McNamara et al., 1984; Sperber et al., 1989; for review, see Deransart and Depaulis, 2002).

Whilst these correlations are clear, the precise neuronal mechanisms underlying seizure-related activity in SNr are unknown. Studies in rats that are genetically susceptible to absence epilepsy suggest that at least three nigral afferents, provided by the GABAergic projection neurons of the striatum and globus pallidus (GP), and the glutamatergic neurons of the subthalamic nucleus (STN), exert powerful influences over the SNr during seizures (Deransart and Depaulis, 2002). Electrophysiological studies in anaesthetised (Slaght et al., 2002) and unanaesthetised rats (Vergnes et al., 1990; Berke et al., 2004) have shown that spike-wave oscillations (or 'high-voltage spindles') in cortex are accompanied by similar activity patterns in the local field potentials (LFPs) recorded from striatum and GP. Seizures are also suppressed during GABA-mediated inhibition of SNr neurons, further implicating the participation of striatonigral and pallidonigral circuits in epilepsy control (Deransart and Depaulis, 2002).

Excitatory drive from STN is also an important determinant of SNr activity and thus, may influence the propagation of seizures. Indeed, inhibition or inactivation of STN by pharmacological or electrical means, which suppress SNr activity through a process of disfacilitation, has antiepileptic effects (Vercueil et al., 1998). The STN is in a prime position to be directly recruited during spike-wave activity in the cortex and thalamus because it receives monosynaptic excitatory projections from both of these structures (Smith et al., 1998). Studies in immobilised rats have shown that spike-wave oscillations are present in the 'subthalamic region' during seizures (Vergnes et al., 1990). However, the nature of population activity in STN during cortical spike-wave activity remains uncharacterised. To

*Corresponding author. Tel: +44-1865-271870; fax: +44-1865-271647.
E-mail address: peter.magill@pharm.ox.ac.uk (P. J. Magill).

Abbreviations: GP, globus pallidus; LFP, local field potential; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; 6-OHDA, 6-hydroxydopamine.

0306-4522/05$30.00+0.00 © 2005 Published by Elsevier Ltd on behalf of IBRO.
doi:10.1016/j.neuroscience.2005.01.006

test the hypothesis that cortical spike-wave oscillations propagate to STN, we simultaneously recorded LFPs from the cerebral cortex and STN of freely moving rats during spontaneous behaviour.

Propagating epileptic activity likely exploits normal patterns of connectivity and some forms of epilepsy involve exaggerations of physiological phenomena, such as the exaggerated corticospinal 'drive' seen in myoclonic epilepsy (Guerrini et al., 2001). Likewise, the high-voltage spindles at 7–12 Hz in the cortex of animals may not, in fact, be solely indicative of absence epilepsy, but may instead be shared by a natural activity state that is analogous to the μ rhythm in humans (Wiest and Nicolelis, 2003; also see Berke et al., 2004). Oscillatory activity in cortico-basal ganglia circuits may be important for normal behaviour (Brown, 2003). Thus, the characterisation and correlation of oscillatory activity in cortex and STN may also aid in the elucidation of the neuronal substrates underlying normal behaviour.

EXPERIMENTAL PROCEDURES

This study was carried out in accordance with the European Communities Council Directive (86/609/EEC) for care of laboratory animals. All experiments conformed to local guidelines on the ethical use of animals. In addition, care was taken to minimise the number of animals used and their suffering. Electrophysiological recordings were made in 30 adult male rats (250–350 g; HsdCpb:WU [Wistar-Unilever] strain; Harlan Winkelmann, Borschen, Germany), 17 of which received a unilateral injection of 6-hydroxydopamine (6-OHDA; hydrochloride salt; Sigma, Germany) into the median forebrain bundle (A: −4.2 mm; L: 1.1 mm; V: −7.6 mm; Paxinos and Watson, 1997) as part of a study of oscillatory activity in STN in the 6-OHDA lesion model of parkinsonism, which is to be reported separately. Of the 30 rats, 14 rats (five of which were successfully lesioned with 6-OHDA; assessed by apomorphine rotation test; see Magill et al., 2001) incidentally exhibited the typical behavioural characteristics of spontaneous absence seizures together with spike-wave neuronal activity in the cortex (Jandó et al., 1995; also see below). Animals of the HsdCpb:WU strain used in this study, which are outbred, have not previously been shown to exhibit spontaneous spike-wave activity or, indeed, absence seizures. However, it is known that many similarly bred strains are particularly susceptible to absence epilepsy and thus, this finding is not surprising (Jandó et al., 1995; Gralewicz, 1999). The fact that less than half of the rats that underwent surgery (see below) displayed spike-wave activity suggests that the experimental procedures themselves did not induce these oscillations, which is in agreement with previous findings indicating that absence epilepsy is due to a genetically determined trait (Danober et al., 1998).

Rats were anaesthetised with chloral hydrate (400 mg/kg; i.p., Sigma) and placed in a stereotaxic frame (David Kopf Instruments, Tujunga, USA). A concentric, bipolar 'semi-microelectrode' (customised SNE-100; Rhodes Medical Instruments, USA) was implanted in the left STN under stereotaxic conditions (A: −3.8 mm; L: 2.5 mm; V: −7.6 mm), as previously described (Brown et al., 2002). Semi-microelectrodes were constructed from stainless steel cannulae and wires, which were insulated with epoxylite (except at the two electrode contacts). The outer contact was 100 μm in length and had a diameter of 150 μm. The inner contact had a diameter of 25 μm (only the tip of the inner wire was exposed). The two recording contacts were separated by 100 μm. Stainless steel screws (1 mm diameter) were positioned above each frontal cortex (A: 2.7 mm; L: 2.0 mm), each cerebellar hemisphere (A: −12.0 mm; L: 2.0 mm) and centrally over an area of thickened bone rostral to the cerebral cortex (A: 5.7 mm; L: 0.0 mm). Thereafter, the microelectrode and screws were fixed to the skull with dental cement (Technovit; Heraeus-Kulzer GmbH, Wehrheim, Germany). Animals were allowed at least 72 h to recover from the surgery before recording began.

During recording, animals were placed in a plexiglas bowl within a Faraday cage. Residual mains artefact (50 Hz) was eliminated by the use of 'Humbugs' (Quest Scientific, North Vancouver, Canada). Cortical LFPs (i.e. electrocorticograms) were recorded from the screw above the left frontal cortex. Screws above the cerebellum and in the bone rostral to the cerebral cortex were used as the indifferent/reference and ground, respectively. Subthalamic LFPs were recorded from the concentric bipolar microelectrode in both bipolar and monopolar modes. Raw signals were AC-coupled, amplified (×1000–2000), band-pass filtered (0.1–100 Hz; Neurolog 100AK and 104A modules; Digitimer Ltd., Welwyn Garden City, UK), and sampled on-line at 512 Hz (Spike2 software; Cambridge Electronic Design Ltd., Cambridge, UK). Data traces were digitally high-pass filtered offline (cutoff at 0.5 Hz; Spike2) before analysis (see below). After the experiments, animals were transcardially perfused under deep anesthesia with 30 ml 0.1 M phosphate-buffered saline, followed by 100 ml 4% paraformaldehyde in 0.1 M phosphate buffer. Brains were removed, post-fixed in 4% paraformaldehyde for at least 24 h, and then processed for Nissl staining on coronal sections (20 μm thick). All recording sites were verified by light microscopy, as shown in the example in Fig. 1. Histological analysis confirmed that the recording electrode was not in the STN of six of these 14 epileptic animals, further suggesting that electrode placement in STN per se does not precipitate spike-wave activity or indeed, epileptic seizures. The targets of the clearly 'misplaced' electrodes included the thalamus, entopeduncular nucleus and substantia nigra. The spike-wave activity in each of these areas has previously been described in detail (Vergnes et al., 1990; Danober et al., 1998), and thus, will not be considered further here. Macroscopic examination of the cortical recording sites did not reveal any extensive damage of the underlying tissue, reiterating that the basis of spike-wave activity and absence epilepsy is mostly likely genetic, rather than surgical or mechanical.

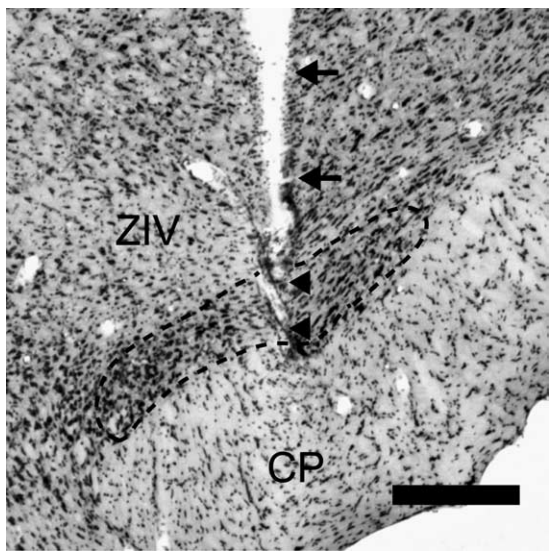

Fig. 1. Histological confirmation of electrode placement. Electrode track above STN (arrows) and recording sites in STN (arrowheads), an oval structure containing densely-packed cells (within dashed line). CP, cerebral peduncle; ZIV, ventral division of zona incerta. Scale bar=300 μm.

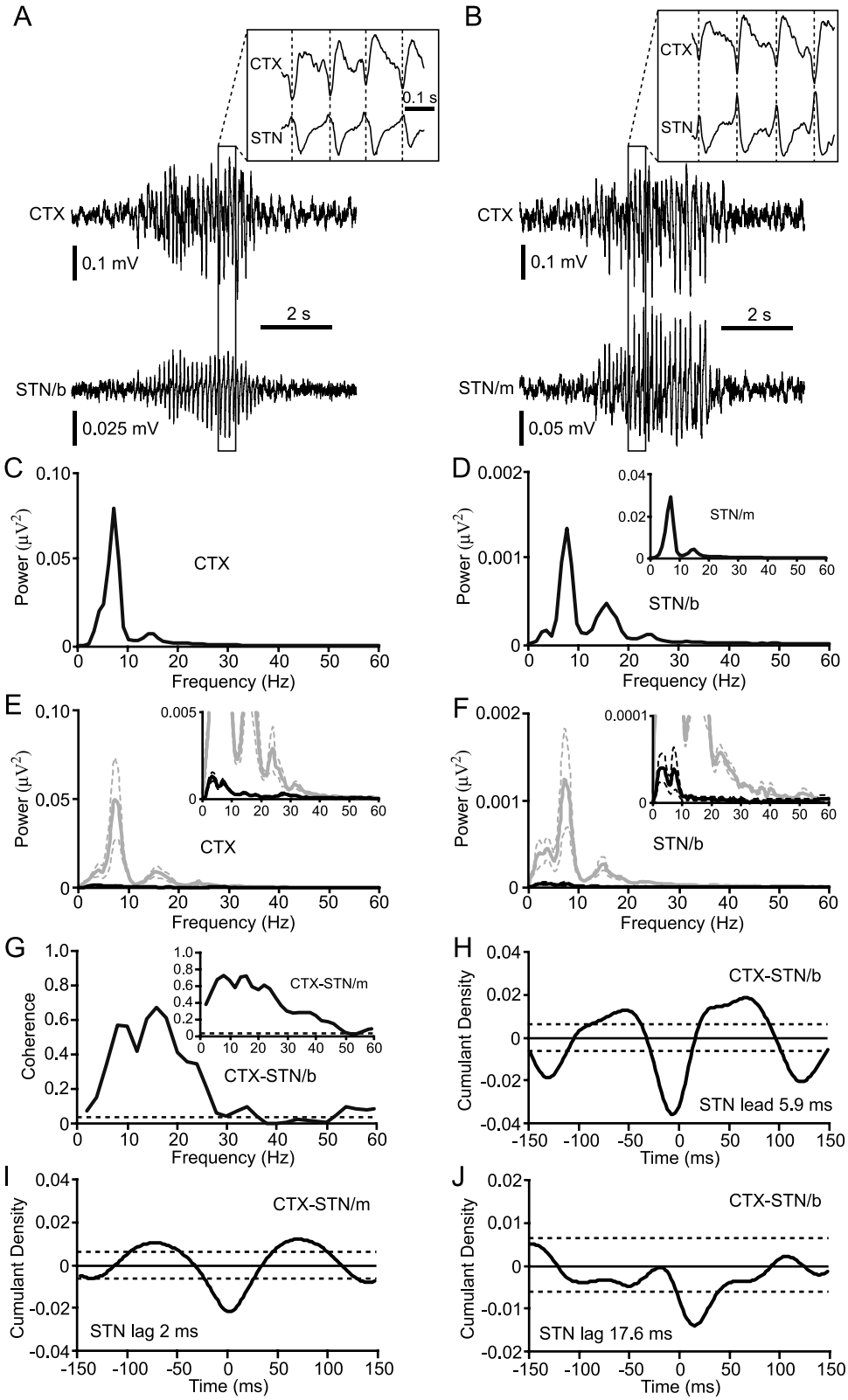

Fig. 2. (*Caption overleaf*).

Spike-wave oscillations were readily identified for analysis upon visual inspection of the data because this neuronal activity, as recorded in LFPs, was stereotyped (Danober et al., 1998; and see below). The onset of spike-wave activity was identified as a sharp increase in the amplitude of LFPs i.e. the first spike-wave complex with an amplitude more than double the 'base-line' activity of low-amplitude, high-frequency LFP fluctuations, which are characteristic of the 'alert' brain state. The offset was identified as a subsequent decrease in LFP amplitude i.e. last spike with amplitude at least double the base line. Neuronal activity was characterised in the frequency domain by deriving autospectra of power and frequency (Hanning window function; block size of 512 data points, giving 1.0 Hz resolution) using Spike2 software. The frequency relationships between activity in cortex and STN were further defined by coherence analysis (Halliday et al., 1995). Coherence is a measure of the linear association between two signals; waveforms must be phase-locked (temporally coupled) and their amplitudes must have a constant ratio to be coherent over a frequency range. Episodes of spike-wave activity were brief (see below) and thus, to enable high-resolution analysis in the frequency domain, data from individual episodes were concatenated. Temporal relationships were characterised using cumulant density estimates, which are similar to cross-correlograms and provide a general measure of statistical dependence between random processes that assumes the value zero when the processes are independent (Halliday et al., 1995). A lag/lead was defined as the time between zero and the peak of the (significant) deflection with the largest amplitude. Electrophysiological recordings and analyses of neuronal activity were performed blind to the results of histology. Data are expressed as mean±standard deviation unless noted otherwise.

RESULTS

Episodes previously attributed to non-convulsive epileptic seizures (Jandó et al., 1995; Gralewicz, 1999) were stereotyped and identified as brief periods of quiet immobility (occasionally with mild head and neck tremor and/or orofacial twitching) that were associated with high-voltage oscillations of a characteristic spike-wave shape in the cortical LFP (Fig. 2A, B). The incidence of spike-wave episodes differed between animals (mean of 1.0±0.9 episodes per minute), but were never seen when the animals were moving or engaged in grooming. The mean duration of the episodes of spike-wave activity in cortex was 4.1±2.3 s (mean of 107 episodes from the eight animals displaying spike-wave activity and in which STN activity was recorded, three of which were incidentally lesioned with 6-OHDA). The mean fundamental frequency of the cortical spike-wave oscillation was 7.4±0.9 Hz (mean of 13.4 s of spike-wave activity analysed from each animal; Fig. 2C, E).

Spike-wave oscillations in the cortex were closely associated with similar oscillations in the STN, albeit of smaller amplitude, as evinced in bipolar (Fig. 2A, D, F) and monopolar (Fig. 2B, D inset) recordings of LFPs in this nucleus. The fundamental frequency of spike-wave activity in STN was similar to that in cortex at 7.9±1.2 Hz (Fig. 2D). Spike-wave oscillations did not occur in STN independently or in the absence of similar activity in cortex. The mean power of activity at 1–60 Hz recorded in cortex and STN across animals during defined episodes of immobility with spike-wave oscillations was significantly higher ($P<0.005$, paired *t*-test) than the mean power of activity recorded during rest periods that were not associated with spike-wave oscillations (Fig. 2E, F). This was also the case for the mean power of oscillatory activity at 5–9 Hz ($P<0.01$, paired *t*-test). Importantly, simultaneously recorded cortical and STN activities were significantly coherent over a range of frequencies, including the fundamental frequency and harmonics of the spike-wave oscillation, and the β- and (low) γ-bands, i.e. 20–40 Hz (Fig. 2G).

Cumulant density estimates showed that although the delays between spike-wave oscillatory activity in cortex and STN were variable (Fig. 2H–J), STN activity lagged behind the 'spike' component of cortical activity by a mean of 2.7 ms (range of lags was −5.9 ms to +17.6 ms; Fig. 2I, J). In particular, the spike component of cortical activity led STN activity in all but one of the recordings. In the latter exceptional record, STN activity led the spike component of cortical activity by 5.9 ms (Fig. 2H). There was no apparent difference in the spike-wave oscillations exhibited by non-lesioned animals as compared with 6-OHDA-lesioned animals (also see Depaulis et al., 1990), although the small numbers involved precluded a meaningful statistical comparison of the two groups.

DISCUSSION

This study provides the first characterisation of the activity present in STN during spontaneous cortical spike-wave

Fig. 2. Coherent oscillations are present in the cortex and STN during spontaneous spike-wave activity. (A) Raw data trace showing the characteristic spike-wave activity present in the cerebral cortex (CTX). The high-voltage spike-wave oscillations in cortex were also consistently expressed in bipolar LFPs that were simultaneously recorded from the STN (STN/b). Inset shows the spike-wave activity in CTX and STN at greater resolution. (B) Another seizure recorded in CTX and STN (monopolar recording of LFP; STN/m). Inset shows the spike-wave activity at greater resolution. Scale bar in inset of A applies to inset of B. (C) Power spectrum showing the dominant frequencies of the cortical oscillations present during spike-wave activity. The fundamental frequency (approximately 7.5 Hz) and first harmonic (approximately 15 Hz) of the spike-wave activity are clearly distinguished. (D) Power spectrum showing the dominant frequencies of the oscillations present in the bipolar LFP from STN. Inset is power spectrum of monopolar LFP from STN. Note the similar frequency contents of the cortical and STN power spectra. (E) Summary plot of power in cortex for all animals during immobility with spike-wave oscillations (grey) and during rest periods with no spike-wave oscillations (black). Inset shows power distribution at greater resolution. Solid lines represent means and dashed lines represent ±2 SDs. (F) Summary plot of power in bipolar recordings from STN for all animals. Labelling as in E. Inset shows power distribution at greater resolution. (G) Coherence plot showing significantly coherent activity in cortex and STN (bipolar recording) at frequencies associated with spike-wave oscillations, and at frequencies associated with β and γ (20–40 Hz) activity. Plot was derived from data shown in C and D. Inset shows a similar plot between cortical and monopolar STN recordings (plot was derived from data shown in C and D inset). Dashed lines are 95% confidence intervals. (H) Cumulant density plot showing the exceptional record where activity in STN (bipolar recording) led the approximately 7 Hz 'spike' component of the cortical oscillation (by 5.9 ms). Plot derived from data shown in G. Dashed lines are 95% confidence intervals. Units are arbitrary. (I, J) In the remaining records, the spike component of the cortical oscillation led activity in STN, as recorded in monopolar (I) or bipolar (J) configurations. Panels A–D and G–I are derived from spike-wave activity in the same animal. Panel J is from another animal.

oscillations. The data show that the stereotypical spike-wave oscillations that occur in the cortex are also consistently expressed in LFPs recorded from the STN. The novel application of analyses in the time and frequency domains demonstrated that spike-wave oscillations in cortex and STN were significantly coherent, with a small temporal difference, thereby arguing against volume conduction and suggesting that these oscillations in STN are robustly and rapidly propagated from corticothalamic networks, the pacemakers of spike-wave activity.

The predominant generators of current flow underlying LFPs are the synchronised, subthreshold and suprathreshold activities of local neural ensembles (for reviews, see Hubbard et al., 1969; Mitzdorf, 1985). In these respects, it seems likely that the spike-wave oscillations in STN, as evinced in the LFPs, are due to synchronous and periodic firing of local ensembles of neurons. Studies of the single-cell responses and LFPs evoked in STN by cortical stimulation certainly support this idea (Magill et al., 2004). Whilst the contribution of volume-conducted potentials to LFPs recorded in STN remains controversial (Dinner et al., 2002; Wennberg and Lozano, 2003), the fact that spike-wave oscillations could be recorded in STN using either bipolar or monopolar recording configurations, with a mean time lag behind cortical activity of 2.7 ms, suggests that these oscillations were not simply due to the volume conduction of cortical activity (in agreement with Dinner et al., 2002). Further support for localised recruitment of neurons during spike-wave activity can be found in recordings from striatum, thalamus, and cortex where, in each case, the discharges of single cells or small groups of neurons have been shown to be phase-locked to ongoing spike-wave oscillations in the respective LFP (Kandel and Buzsáki, 1997; Slaght et al., 2002; Berke et al., 2004).

The present data suggest that populations of STN neurons are actively and synchronously recruited to spike-wave oscillations. During spike-wave activity and epileptic seizures, large ensembles of cortical neurons are activated in unison (Kandel and Buzsáki, 1997). Rhythmic, synchronised output from cortex will be first integrated in the basal ganglia at the level of the two input structures, the striatum and STN. Direct excitatory input from the cortex is known to have powerful effects on STN neurons (Fujimoto and Kita, 1993; Magill et al., 2004) and therefore, the corticosubthalamic projection is a good candidate pathway through which the cortex could drive, recruit or otherwise modulate the activity of STN neurons during seizures. Activity in STN lagged behind the dominant (7–8 Hz) spike component of the cortical oscillation by a mean of 2.7 ms, which is comparable to the latency of the first response of most STN neurons to electrical stimulation of the cortex (Fujimoto and Kita, 1993). Moreover, corticosubthalamic input can synchronise the oscillatory activity of groups of STN neurons at both slow (approximately 1 Hz) and spindle (7–12 Hz) frequencies (Magill et al., 2000, 2001). In further support, corticofugal and corticostriatal neurons, a proportion of which also project to STN (Smith et al., 1998), are recruited to the spike-wave oscillation during seizures (Slaght et al., 2002). Thus, synchronous and rhythmic corticosubthalamic volleys could produce the input necessary to widely synchronise neuronal responses and produce oscillations in the LFP (also see Magill et al., 2004). The tight association between cortical and STN activities was supported by our finding that the two signals were significantly coherent at frequencies associated with spike-wave oscillations and β/γ activity. Although coherent activity in cortex and STN indicates a linear frequency relationship between activities in these two structures, we cannot exclude the possibility that there is also a non-linear component to the relationship. Indeed, the one case in which STN led cortex may have been due to the non-linear and/or highly dynamic nature of this relationship (Meeren et al., 2002). Alternatively, the variation in temporal relationships may have been due to slightly different topographical relationships between recording sites (Meeren et al., 2002).

It is unlikely that other excitatory inputs to STN, namely those from the parafascicular nucleus, play the lead role in the propagation or recruitment of STN activity because spike-wave oscillations are thought to be weak or nonexistent in the medial thalamus (Vergnes et al., 1990; Danober et al., 1998). However, other indirect pathways to STN e.g. feed-forward connections through GP, may be involved in the recruitment of STN neurons. Indeed, corticostriatal and striatal neurons are engaged by cortical spike-wave oscillations (Slaght et al., 2002; Berke et al., 2004). Furthermore, spike-wave activity has been reported in GP (Vergnes et al., 1990). Thus, it seems possible that GABAergic mechanisms might orchestrate or modify oscillatory activity in STN to at least some degree.

The finding that STN activity appears to be synchronised and oscillatory during cortical spike-wave activity reiterates the potentially important contribution of STN oscillations to the inappropriate oscillatory activity of SNr neurons in absence epileptic seizures (Proctor and Gale, 1998; Deransart and Depaulis, 2002; Deransart et al., 2003) or, indeed, to appropriate oscillatory activity in the basal ganglia during normal behaviour (Wiest and Nicolelis, 2003; Berke et al., 2004). The presence of oscillations suggests that the critical influence of STN over SNr during spike-wave activity is probably not monotonic, but is likely phasic and periodic. Whilst our data support the importance of STN in absence epilepsy (Vercueil et al., 1998), it should also be noted that other (GABAergic) inputs to SNr are still crucial (Deransart and Depaulis, 2002).

Acknowledgments—This work was supported by the Medical Research Council UK and Brain Research Trust. P.J.M. holds a Fellowship by Examination at Magdalen College, Oxford, and W.M. was a Marie Curie Fellow of the European Community (HPMF-CT-2001-01300).

REFERENCES

Berke JD, Okatan M, Skurski J, Eichenbaum HB (2004) Oscillatory entrainment of striatal neurons in freely moving rats. Neuron 43:883–896.

Brown P (2003) Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. Mov Disord 18:357–363.

Brown P, Kupsch A, Magill PJ, Sharott A, Harnack D, Meissner W (2002) Oscillatory local field potentials recorded from the subthalamic nucleus of the alert rat. Exp Neurol 177:581–585.

Crunelli V, Leresche N (2002) Childhood absence epilepsy: genes, channels, neurons and networks. Nat Rev Neurosci 3:371–382.

Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C (1998) Pathophysiological mechanisms of genetic absence epilepsy in the rat. Prog Neurobiol 55:27–57.

Depaulis A, Vergnes M, Liu Z, Kempf E, Marescaux C (1990) Involvement of the nigral output pathways in the inhibitory control of the substantia nigra over generalized non-convulsive seizures in the rat. Neuroscience 39:339–349.

Deransart C, Depaulis A (2002) The control of seizures by the basal ganglia? A review of experimental data. Epilepsy Disord. 4(Suppl 3):S61–S72.

Deransart C, Hellwig B, Heupel-Reuter M, Léger JF, Heck D, Lücking CH (2003) Single-unit analysis of substantia nigra pars reticulata neurons in freely behaving rats with genetic absence epilepsy. Epilepsia 44:1513–1520.

Dinner DS, Neme S, Nair D, Montgomery EB, Baker KB, Rezai A, Lüders HO (2002) EEG and evoked potential recording from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. Clin Neurophysiol 113:1391–1402.

Fujimoto K, Kita H (1993) Response characteristics of subthalamic neurons to the stimulation of the sensorimotor cortex in the rat. Brain Res 609:185–192.

Gralewicz S (1999) Behavioural research and nonconvulsive spontaneous electrocortical seizures in laboratory rats: a note of concern. Int J Occup Med Environ Health 12:201–208.

Guerrini R, Bonanni P, Patrignani A, Brown P, Parmeggiani L, Grosse P, Brovedani P, Moro F, Aridon P, Carrozzo R, Casari G (2001) Autosomal dominant cortical myoclonus and epilepsy (ADCME) with complex partial and generalized seizures: a newly recognized epilepsy syndrome with linkage to chromosome 2p11.1-q12.2. Brain 124:2459–2475.

Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farner SF (1995) A framework for the analysis of mixed time series/point process data: theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. Prog Biophys Mol Biol 64:237–278.

Hubbard JI, Llinás R, Quastel DMJ (1969) Extracellular field potentials in the central nervous system. In: Electrophysiological analysis of synaptic transmission, pp 265–293. London: Edward Arnold Ltd.

Jandó G, Carpi D, Kandel A, Urioste R, Horvath Z, Pierre E, Vadi D, Vadasz C, Buzsáki G (1995) Spike-and-wave epilepsy in rats: sex differences and inheritance of physiological traits. Neuroscience 64:301–317.

Kandel A, Buzsáki G (1997) Cellular-synaptic generation of sleep spindles, spike-and-wave discharges, and evoked thalamocortical responses in the neocortex of the rat. J Neurosci 17:6783–6797.

Magill PJ, Bolam JP, Bevan MD (2000) Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. J Neurosci 20:820–833.

Magill PJ, Bolam JP, Bevan MD (2001) Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. Neuroscience 106:313–330.

Magill PJ, Sharott A, Bevan MD, Brown P, Bolam JP (2004) Synchronous unit activity and local field potentials evoked in the subthalamic nucleus by cortical stimulation. J Neurophysiol 92:700–714.

McNamara JO, Galloway MT, Rigsbee LC, Shin C (1984) Evidence implicating substantia nigra in regulation of kindled seizure threshold. J Neurosci 9:2410–2417.

Meeren HK, Pijn JP, Van Luijtelaar EL, Coenen AM, Lopes da Silva FH (2002) Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. J Neurosci 22:1480–1495.

Mitzdorf U (1985) Current-source density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. Physiol Rev 65:37–100.

Paxinos G, Watson C (1997) The rat brain in stereotaxic coordinates, 4th ed. San Diego: Academic Press.

Proctor M, Gale K (1998) Basal ganglia and brainstem anatomy and physiology. In: Epilepsy: a comprehensive textbook (Engel J, Pedley TA, eds), pp 353–368. Philadelphia: Lippincott-Raven.

Slaght SJ, Paz T, Mahon S, Maurice N, Charpier S, Deniau JM (2002) Functional organization of the circuits connecting the cerebral cortex and the basal ganglia: implications for the role of the basal ganglia in epilepsy. Epilepsy Disord 4(Suppl 3):S9–S21.

Smith Y, Bevan MD, Shink E, Bolam JP (1998) Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 86:353–387.

Sperber EF, Wurpel JN, Zhao DY, Moshe SL (1989) Evidence for the involvement of nigral GABAA receptors in seizures of adult rats. Brain Res 480:378–382.

Vercueil L, Benazzouz A, Deransart C, Bressand K, Marescaux C, Depaulis A, Benabid AL (1998) High-frequency stimulation of the sub-thalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. Epilepsy Res 31:39–46.

Vergnes M, Marescaux C, Depaulis A (1990) Mapping of spontaneous spike and wave discharges in Wistar rats with genetic generalized non-convulsive epilepsy. Brain Res 523:87–91.

Wennberg RA, Lozano AM (2003) Intracranial volume conduction of cortical spikes and sleep potentials recorded with deep brain stimulating electrodes. Clin Neurophysiol 114:1403–1418.

Wiest MC, Nicolelis MAL (2003) Behavioral detection of tactile stimuli during 7–12 Hz cortical oscillations in awake rats. Nat Neurosci 6:913–914.

(Accepted 7 January 2005)
(Available online 16 March 2005)