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P Zhuang, M Hallett, X Zhang, J Li, Y Zhang, Y Li

ABSTRACT

Objective: To explore the role of neuronal activity in the globus pallidus internus (GPI) in the generation of tic movements.

Methods: 8 patients with Tourette’s syndrome with medically intractable tics who underwent a unilateral pallidotomy for severe tics were studied. They ranged in age from 17 to 24 years; disease duration was 7–19 years. Microelectrode recording was performed in the GPI. The electromyogram (EMG) was simultaneously recorded in muscle groups appropriate for the patient’s tics. The relationship between neuronal firing pattern and the EMG was studied.

Results: 232 neurons were recorded during tics from eight trajectories. Of these neurons, in addition to decreased neuronal firing rate and irregular firing pattern, 105 (45%) were tic related showing either a burst of activity or a pause in ongoing tonic activity. They could be synchronous (n = 75), earlier than EMG onset (n = 27) or following EMG onset (n = 3). The GPI neuronal bursts preceded EMG onset with decreased (n = 6) or increased activity (n = 21). The initial change in neural activity occurred about 50 ms to 2 s before the EMG onset.

Conclusions: Although the data are descriptive and preliminary, the tic related neuronal activity observed in GPI appears to indicate that the basal ganglia motor circuit is involved in tic movements. The early neuronal activity seen in GPI may reflect premonitory sensations that precede a tic.

Tics, components of Tourette’s syndrome (TS), are characterised by brief, sudden, repetitive stereotype movements (motor tics) or sounds (vocal tics), either simple or complex. Tics are often preceded by a premonitory urge or sensation. Several aspects of TS pathophysiology remain unclear. According to the pathophysiology of movement disorders related basal ganglia dysfunction, tics have been viewed as hyperkinetic movement disorders due to a presumed reduction in the normal inhibitory basal ganglia output. In this model, tics would be caused by abnormal activity of striatal neurons, leading to unwanted inhibition in basal ganglia output neurons, which in turn disinhibit motor areas, resulting in unwanted movement. In TS, reduced volumes and abnormal asymmetries of the caudate, putamen and globus pallidus have been described adding evidence to the idea that the basal ganglia are relevant.

A post-mortem study of TS brains found an imbalance in striatal and globus pallidus internus (GPI) inhibitory neuron distribution, suggesting that the cortico-striato-pallido-thalamic circuitry is fundamentally altered in TS. In deep brain stimulation (DBS) case reports, patients with severe TS were treated with high frequency DBS of the centromedian–parafascicular complex (CM-Pf) in the thalamus or of the GPI. In these patients, tic severity was significantly reduced. The CM-Pf is reciprocally connected with the basal ganglia, giving rise to a projection to the striatum and receiving inputs from the GPI. These connections support a link of the limbic striato-pallido-thalamo-cortical neuronal circuit dysfunction to this disorder and have implications for the mechanisms underlying DBS in tics.

METHODS

Patients

Eight patients with TS (six men, two women) with medically intractable motor or vocal tics were investigated. Of these, six patients had tics mainly involving one side whereas two patients had both sites affected, including regions of the neck, shoulder, trunk and limbs. Their ages were 17–24 years (mean age 20.8 (2.1) years) and disease duration was 7–19 years (mean disease duration 10.5 (4.5) years) at the time of their operation. Diagnoses were based on clinical criteria for TS, including multiple motor tics, at least one vocal tic involving any sound, symptoms beginning before the age of 18 years and symptoms for more than 1 year. All had received medical therapy, including trials with haloperidol at doses of 1.5–6 mg for at least 3 months or benzodiazepines. Some patients stopped due to side effects whereas others stopped because there was little or no improvement in their tics. No patient had taken haloperidol in the 3 months prior to surgery. Lack of effective medical therapy led them to seek surgical intervention.

The primary objective of patient selection was to identify those individuals for whom the expected benefit would exceed the inherent risks of the surgical procedure. Inclusion criteria were: age ≥ 18 years (except for one patient who was 17 years old); severity of the disease adversely affecting social integration; failure of medical treatment after trial of at least 6 months; no cognitive deficits or psychosis; and ability to give informed consent. Pallidotomy was done on the side opposite the more severe symptoms or, if the disorders was symmetric, on the right side. The pallidal target was the posteroverentral portion. The protocol was performed according to the Declaration of Helsinki and was approved by the Institutional Review Board at Xuanwu Hospital of...
the Capital Medical University. Informed consent was obtained from all patients.

**Stereotactic surgery and neurophysiology**

Medications were withheld on the evening prior to surgery for all patients. The detailed surgical procedures for stereotactic, microelectrode guided GPi localisation electrophysiological recording techniques were similar to previous reports.21–23

Briefly, after having applied local anaesthetic agents at the pin sites, a stereotactic frame (CRW-FN; Radionics, Burlington, Massachusetts, USA) was affixed to the patient’s head. Sagittal MRI (Siemens 1.5 T, Sonata, Germany) sequences for whole brain were obtained. A Software Syno Leonardo WorkStation (Syngo VE 26A; Siemens) was used for three-dimensional reconstructions and target calculation was based on the stereotactic atlas of Schaltenbrand and Wahren.24 The coordinates of the anterior and posterior commissures (AC and PC, respectively) in relation to the centre of the stereotactic frame were adjusted, making them coincide with the length of the intercommisural line of the patient. In the present study, the coordinates to the target of GPi were defined as 0 mm anterior to the midpoint of ACPC line, 4–6 mm below the ACPC line and 18–22 mm lateral to the midline.

Physiological confirmation of the GPi was achieved using microelectrode recording. The presence of “border cells”21, 22, 25 marking the boundaries of the nuclear segments, the characteristic discharge patterns of neurons in the globus pallidus externus (GPe), GPi (including the external division (GPe) and internal division (GPii) of GPi) and the surrounding regions, and location of cell dense versus cell sparse zones allowed discrimination of the different pallidal segments.21, 22, 25 The final target landmark was the location of the border of the optic tract (OT), as confirmed by using strobe light and microelectrode stimulation. Microelectrode recording started at a distance of 10 mm from the final target in an anterosuperior position. Extracellular action potential signals were amplified (×20000), filtered (with bandpass of 100–5 kHz) and fed to an audio monitor with an AC Amplifier (FHC Inc, Bowdoinham, Maine, USA). Four channel recording was done using the PolyView program (A Data Acquisition and Analysis System, Astro-Med Inc, Rhode Island, USA). The signal was sampled at 7.5 kHz, and displayed on a computer screen and on an oscilloscope (Hitachi, V-1560, Japan).

Simultaneously with one channel of microelectrode recording, three channels of EMG were recorded using surface electrodes on contralateral muscle groups relevant for the tics involved, including the extensor carpi radialis (ECR), flexor carpi radialis, tibialis anterior, sternocleidomastoid (SCM) and trapezius (TP). A recording site was established when the microelectrode stopped in one place for at least 10 s. Only well isolated and stable single units recorded between 20 s to several minutes were analysed. Data were stored for offline analysis. Radiofrequency lesions were made with electrodes having a diameter of 1.1 mm and an exposed length of 5 mm (TM electrodes; Radionics, Burlington, Massachusetts, USA). When we were satisfied with the position, heating the tissue surrounding the tip of the electrode to 45°C for 30 s made a reversible test lesion. This allows for assessment of side effects and efficiency. Permanent lesions were produced at 70–85°C for 60 s. Generally, the electrode was withdrawn 2–5 mm to make a second lesion. The final lesion was typically 3–4 mm in diameter and 5–6 mm long. Lesions were made at least 2 or 3 mm away from any point at which stimulation evoked a visual or motor response.21, 22

Throughout the surgical procedure, all patients were required to be awake and conscious to cooperate with the neurosurgeon. They were assessed with physical monitoring (eg, speech assessed by verbal task such as sentence repetition; tone monitored by passively moving the limbs; performing a simple movement or holding a certain posture) to avoid complications and to evaluate the effect of target lesioning on limbs. During the surgical procedure, propofol (50 μg/kg/min) was often used to help sedate difficult patients who sometimes had severe tics. In order to avoid the lingering effect of propofol, microelectrode and EMG recordings were made no earlier than 10 min after the end of the propofol infusion while the patients were completely awake and conscious.

**Data analysis**

Postoperatively, visual assessment of EMG activity was first used to determine the onset of tics. EMG activity had to be preceded by a gap of at least 1 s in order to determine the onset of a new tic. Since many of the recorded neurons had very irregular discharge patterns, identification of tic related neuronal activities was based on the following criterion: neuronal activity related to tic movement with the presence of reproducible, visible changes in the firing rate—either augmentation or suppression—that were time locked to the tic movement of specific muscles. For data analysis, only spikes (negative upward) having a signal to noise ratio greater than 2:1 were used. Action potentials were confirmed to arise from a single cell by amplitude and shape criteria. The confirmation method included examining whether the shape of the action potential was constant, as verified by displaying the shape on the screen at a time window for at least 20 s.26 The interspike intervals (ISIs) were measured and ISI histograms were constructed to evaluate the pattern of neuronal discharges. The mean (SD) firing rate was calculated. The degree of regularity of neuronal discharge was determined by calculating the coefficient of variation (CV) of ISIs; for example, $CV = SD/\mu$. The PolyView Program (Astro-Med Inc) was used for the analyses.

Further quantitative analyses of neuronal and EMG signals were conducted to confirm their relationship. EMG signals and identified tic related neuronal activities were digitised and implemented in a custom program (Origin 7.0; OriginLab Corporation, USA). Raster displays of neuronal activity during tic movement were constructed relative to the onset of EMG activity.25, 26 Neuronal activity was full wave rectified, and only activity at least three times the level of the background noise was displayed. Changes in neuronal firing rate related to tic movement were compared with the baseline period. In order to prove whether this activity came from a single neuron, we superimposed the shape at fast sweep speed and found that it remained unchanged. Raster displays were prepared only with neurons of constant shape and similar timing with respect to the tics on at least three occasions.

**Clinical assessment**

The Yale Global Tic Severity Scale was used to evaluate the clinical outcome of surgery. Evaluations were done at 7 days preoperation and 7 days, 6 months and 12 months postoperation. The clinical outcome of obsessive–compulsive disorder (OCD) was assessed with patients’ self reports pre- and postoperation. The percentage value of clinical improvement was calculated by (presurgery – posturgery/presurgery) ×100.
Clinical outcome was statistically analysed for the four periods of evaluation using one way ANOVA and t test with Bonferroni correction, with a level of significance at 0.05. Values are expressed as means (SD).

RESULTS

Neuronal discharge pattern and firing rate in GPi in tics

In the present study, 232 neurons were identified from eight trajectories of GPi (1 per patient). The mean discharge frequency of GPi neurons in tic patients was 42.7 (23.5) Hz (n = 216), similar to the mean discharge frequency of GPi neurons in dystonia reported by Vitek’s and our group, 23 28 indicating that neuronal firing rate is reduced in GPi in patients with tics.

Mean ISI was 33.1 (46.3) ms (2–1170 ms) and mean CV of the ISIs of neuronal firing (n = 121) was 1.44 (0.29) (1.04–2.17), suggesting that the neuronal firing showed some irregularity, similar to that in GPi in patients with dystonia. 23 28 The pattern was often characterised by intermittent grouped discharges separated by periodic pauses (see figs 3, 4), and more repetitive and stereotyped than in dystonia. 7

Figure 1 shows the patterns of discharge representative for most of the neurons. Only a few neurons exhibited a more regular tonic pattern (7%), as represented in fig 1C. The two neurons in fig 1A and B were recorded 7 mm and 8 mm from the final target in GPi of two patients. ISI histograms verified that cells (A) and (B) had a broad range of ISIs (mean ISI 92.1 (136.8) ms with a frequency of 10.9 (7.3) Hz and CV of 1.49; and mean ISI 21.7 (29.5) ms with a frequency of 46.0 (33.8) Hz and CV of 1.36) compared with cell (C) which had relative even times of ISI (mean ISI 20.9 (12.0) ms with a frequency of 47.8 (12.0) Hz and CV of 0.40). Similar irregular patterns were distributed almost along the entire trajectory in all patients.

Tic related neuronal activity in GPi

All patients had tic movements during surgery, allowing correlation of GPi neuronal activity and EMG signals. A total of 105 neurons with changes in firing in relation to the EMG signals were identified. Values are expressed as means (SD).

Table 1 Characteristics of neuronal activity in the globus pallidus internus in patients with tics

<table>
<thead>
<tr>
<th>Patient No</th>
<th>No of recording sites</th>
<th>No of tic related neurons/total neurons recorded</th>
<th>ECR</th>
<th>ECR/FCR</th>
<th>ECR/FCR/TA</th>
<th>SCM</th>
<th>TP</th>
<th>SCM/TP</th>
<th>SCM/TP/TA</th>
<th>Neuronal discharge patterns of tic related neurons (pause/burst)</th>
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<th>After* (pause/burst) (s)</th>
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<td>2</td>
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<td>5</td>
<td>1</td>
<td>2</td>
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<td>1</td>
<td>2</td>
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<td>50/75</td>
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<td></td>
<td></td>
<td>46/59</td>
<td>75/27</td>
<td>10/27</td>
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</tbody>
</table>

Recording sites are stable electrode positions where neurons were recorded.

*Indication in relationship to EMG onset.

ECR, extensor carpi radialis; FCR, flexor carpi radialis; SCM, sternocleidomastoid; Syn, synchronous; TA, tibialis anterior; TP, trapezius.
Neuronal activity correlated with tics was either a burst or a pause in ongoing activity. The change in activity could be synchronous with EMG onset (n = 75), earlier than EMG onset (n = 27) or following EMG onset (n = 3). For the neurons that changed prior to EMG onset, the interval was broad, from 50 ms to 2 s (table 1).

An example of tic related neuronal activity from one trajectory of a patient is shown in fig 2. The figure demonstrates that GPI neuronal activity corresponded to SCM and TP muscle activity in a patient with dystonic tics. The first and third neurons showed pauses in ongoing activity that followed tic onset in the SCM and TP. The second neuron showed a preceding burst that began prior to tic onset, about 1 s, whereas the fourth neuron showed a burst that was approximately synchronous with tic onset.

To confirm the stereotypy of the relation of neuronal activity to EMG activity, raster displays were constructed (figs 3, 4). Figure 3 shows two cells from two patients. In fig 3A, neuronal firing during tic movement showed a burst that began simultaneously with increased SCM and TP activity whereas in fig 3B, neuronal firing showed a pause that began before ECR activity. Figure 4A–C shows the activity of three neurons in relation to tics that were recorded from different places in one patient’s trajectory. These three neurons were obtained at 8, 6 and 4 mm to the border of the OT. Activity in all three neurons showed bursts preceding the tic by about 500 ms.

Localisation of tic related neuronal activity in GPI
Figure 5 illustrates the distributions of GPI neuronal activity related to muscle activity of tics. Figure 5A shows localisation of tic related neuronal activity with a burst whereas figure 5B shows localisation of tic related neuronal activity with a pause. Most neurons were located 6–6.5 mm from the final target of the OT (fig 5A, 5B).

Clinical outcome
The patients’ tics decreased and this was sustained for the 12 months of follow-up (table 2). ANOVA demonstrated a significant effect of time (F:49, p<0.0001). Post hoc t tests with Bonferroni correction indicated that there were significant differences between mean motor tic score at 7 days, 6 months and 12 months postoperation compared with mean score

Figure 2 Globus pallidus internus (GPI) neuronal activity related to EMG during tic movements. A sagittal map 20 mm from the midline of the human globus pallidus is on the left of the figure. The example shows simultaneous recording in GPI neuronal activity and EMG along the trajectory to the target of GPI in a patient with severe dystonic tics. The activity of GPI neuron 1 has a prolonged pause and neuron 3 has a very brief pause that follows sternocleidomastoid (SCM) and trapezius (TP) muscles during tic movements. Neuron 2 shows preceding bursts that begin prior to tic onset whereas neuron 4 shows a burst that is approximately synchronised with SCM and TP activities. Location of a typical trajectory plotted on a sagittal map 20 mm from the midline of the human globus pallidus from the Schaltenbrand and Wahren atlas.24 Arrows indicate localisation and zero. ACPC, anterior comissure and posterior comissure; GPe, globus pallidus externus; GPi, the external division of GPI; GPii, the internal division of GPI; IC, internal capsule; OT, optic tract.

Figure 3 Raster and superimposed data from two representative tic related globus pallidus internus (GPI) neurons and EMG signals. In (A), the first row presents four superimposed traces of rectified raw data of GPI, sternocleidomastoid (SCM) and trapezius (TP) that correspond to each trace of raster of GPI, SCM and TP. The first trace of TP was used as the marker to align all other traces. In (B), the first row presents three superimposed traces of rectified raw data of GPI and extensor carpi radialis (ECR) that correspond to each trace of raster of GPI and ECR. The first trace of ECR was used as the marker to align all other traces. In the raster, each dot represents a “spike” in electrical activity that exceeds a specified threshold. The arrow and vertical line indicate movement onset.

Figure 4 A–C shows the activity of three neurons in relation to tics that were recorded from different places in one patient’s trajectory. These three neurons were obtained at 8, 6 and 4 mm to the border of the OT. Activity in all three neurons showed bursts preceding the tic by about 500 ms.

Clinical outcome
The patients’ tics decreased and this was sustained for the 12 months of follow-up (table 2). ANOVA demonstrated a significant effect of time (F:49, p<0.0001). Post hoc t tests with Bonferroni correction indicated that there were significant differences between mean motor tic score at 7 days, 6 months and 12 months postoperation compared with mean score.
preoperation. Although patients with vocal tics felt their symptoms improved, there was no significant change.

Two patients who had OCD were assessed with patients’ self report comparing pre- and postoperation, and they felt their OCD was reduced by 10% and 50%, respectively.

DISCUSSION

In all eight patients with medically intractable tics, a significant improvement in the severity of motor tics was found after pallidotomy. Several patients felt that their vocal tics and obsessions were also reduced. These beneficial effects have been maintained in all patients. No significant side effects were noted. The results are consistent with reports of improvement in tics after high frequency stimulation of Gpi\(^{16-18}\) suggesting that interference at the level of Gpi can result in clinical improvement of tics.

This study demonstrates that Gpi is probably a component in the neural network involved in tic generation. In addition to decreased neuronal firing rate and irregular firing pattern, 105 tic related neurons were identified from eight patients. Raster displays showed that Gpi neuronal bursts preceded, followed or were synchronised with EMG onset and demonstrated decreased or increased activity in relation to tics. The changes in neuronal activity appeared at a broad range of times from 50 ms to 2 s prior to tics. Some neuronal activity was related to tic involved muscles whereas others showed no relationship.

![Figure 4](image)

**Figure 4** Raster and superimposed data from three representative tic related globus pallidus internus (Gpi) neurons and EMG signals recorded along one trajectory during tics. In (A)–(C), the first row presents the superimposed three traces of rectified raw data of Gpi, sternocleidomastoid (SCM) and trapezius (TP) that correspond to each trace of raster of Gpi, SCM and TP. In (A) and (B), the first trace of TP was used as the marker to align all other traces. In (C), the second trace of TP was used as the marker to align all other traces. In the raster, each dot represents a “spike” in electrical activity that exceeds a specified threshold. The arrow and vertical line indicate movement onset. Neurons (A), (B) and (C) were obtained from 8 mm, 6 mm and 4 mm to the final target, the border of the optic tract, respectively.

![Figure 5](image)

**Figure 5** Localisation of tic related neuronal activity in the globus pallidus internus (Gpi). A sagittal map of the human globus pallidus from the Schaltenbrand and Wahren atlas\(^24\) (same atlas as in fig 2). Each small division on the scale is 1 mm. Arrow indicates final target. (A) Distribution of tic related neuronal activity with a burst in relation to muscle activity (n = 59) in eight patients with tics (black square). The histogram illustrates the cells mainly localised at 6.4 (1.9) mm from the final target (arrow indicates trajectory direction). (B) Distribution of tic related neuronal activity with a pause in relation to muscle activity (n = 46) in eight patients (black triangle). Histogram shows the cells mainly localised at about 6.5 (2.1) mm from the final target (arrow indicates trajectory direction). ACPC, anterior commissure and posterior commissure; GPe, globus pallidus externus; Gpi, the external division of Gpi; Gpii, the internal division of Gpi; IC, internal capsule; OT, optic tract.
The variable relationship may relate to the somatotopic arrangement within the GPi.\textsuperscript{25} The tic related cells are likely specific to those body parts involved in the tics. Those cells with no apparent relationship may relate to body parts that were not being recorded.

The involvement of the GPi in patients with tics is supported by imaging studies that showed reduced volumes of basal ganglia nuclei,\textsuperscript{10–12} and tic suppression was associated with decreased activity in the GPi and related cortical regions.\textsuperscript{13} The reduced neuronal activity observed in GPi is in keeping with models of pathophysiology of TS\textsuperscript{10} that propose increased activity of the inhibitory direct pathway and decreased activity in the indirect pathway. The net effect of these changes is to reduce the firing rate of inhibitory neurons in GPi that leads to a lessened inhibitory influence on the thalamus. Subsequently, the emergence of an unwanted stereotyped movement, such as tics, result from disinhibition of motor areas.\textsuperscript{8} Based on this model, each tic corresponds to the activity of a discrete set of striatal neurons.\textsuperscript{8} \textsuperscript{9} \textsuperscript{29}

In addition to reduced mean frequency in GPi, there was also a significant change in the pattern of neuronal activity with neurons firing in irregular grouped discharges and with neuronal firing increasing or decreasing correlated with tics. These phenomena might occur as a direct result of transmission of such activity from the subthalamic nucleus, the GPe, the CM nucleus of the thalamus and striatum, or as a result of increased inhibitory and excitatory activity from the striatum and subthalamic nucleus, respectively, to the GPi.\textsuperscript{25} Another hypothesis suggests that irregularity in pallidal activity interferes with thalamocortical signal transmission and disrupts the normal spatiotemporal pattern of cortical neuronal activity, leading to errors in cortical output and disordered motor control. Eventually, the ability of cortical neurons to respond appropriately to changes in rate and pattern of afferent activity will likely be altered; increased at times, decreased at others.\textsuperscript{9}

The current study found that the irregular discharge patterns, occurring in intermittent grouped discharges separated by periodic pauses in tics, are similar to those seen in GPi in dystonia.\textsuperscript{27} \textsuperscript{28} However, the patterns observed in dystonia were not as stereotyped as those in dystonic tics.\textsuperscript{2}

The present data showed that the timing of GPi neuronal activity associated with tics was not the same for all neurons. Neurons with synchronous activity are similar to those seen in primate studies of voluntary movement where modulation of activity in the GPi occurred at about the same time as EMG.\textsuperscript{31–33} Changes in neuron firing following EMG onset during tics might be due to somatosensory feedback from the tics. A number of GPi neurons showed a burst of activity that began about 0.5–2.0 s prior to the tics, similar to the timing of premovement activity recorded in various parts of the brain, including the basal ganglia.\textsuperscript{34} \textsuperscript{35} The observation of the 0.5–2.0 s delay between GPi activity and EMG onset is consistent with a human study using a self-paced movement paradigm that a Bereitschaftspotential/readiness potential at 500–1500 ms preceded the onset of movement seen in the caudate, GPi and putamen.\textsuperscript{34} Similar results have been obtained from the primate striatum in self-initiated movement showing premovement activity that began 0.5–5.0 s before movement onset.\textsuperscript{36} An event related functional MRJ study in patients with tics showed that activation occurred in a paralimbic network before tic onset.\textsuperscript{37} EEG studies, however, reflecting activity in the supplementary motor area and premotor cortex, do not show normal premotor potentials in spontaneous tics.\textsuperscripts{38} Thus the early neuronal activity seen in GPi might reflect limbic and/or subcortical generated motor commands (possibly associated with sensations of urges) that precede unwanted repetitive movements, rather than via the premotor cortical route.

This is a descriptive paper with preliminary conclusions which will have to be substantiated to prove significance.

**REFERENCES**