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Pallidotomy and bradykinesia
Implications for basal ganglia function

Kerstin D. Pfann, PhD; Richard D. Penn, MD; Kathleen M. Shannon, MD; and Daniel M. Corcos, PhD

Article abstract—Background and Objective: The scientific rationale for pallidotomy as a treatment for PD is that the lesion will reduce excessive tonic inhibition of the thalamus, thereby allowing movement to proceed more normally. If true, then PD patients who move slowly while on medication should increase movement speed following pallidotomy. To test this we used a simple motor task to determine if pallidotomy leads to an improvement in "on" motor performance when those movements are impaired before surgery. Methods: Nine patients with PD performed elbow flexion movements "as fast as possible" while they were "on" before and 1 month after pallidotomy. Patients with mild PD and healthy control subjects were also tested. Results: The clinical effects of pallidotomy were typical of those found in other studies. "Off" Unified Parkinson's Disease Rating Scale scores improved and dyskinesias were reduced. Although before surgery the patients were far slower while they were "on" than the groups of mild PD patients and healthy control subjects, there was no change in mean peak velocity while they were "on" after pallidotomy. There was no change in other mean "on" motor performance measures such as peak acceleration, peak deceleration, initiation time, and symmetry. There was a decrease in the variability of peak acceleration, symmetry, and initiation time. Conclusion: Despite the clinical efficacy of pallidotomy while patients were "off," bradykinesia of elbow flexion movements while patients were "on" is not affected by pallidotomy. Therefore, we conclude that the bradykinesia observed in this experiment is due to a mechanism other than excessive tonic inhibition of the motor thalamus. Our results are consistent with the idea that pallidotomy reduces the noise from the abnormally functioning basal ganglia.

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The resurgence of posteroventral pallidotomy in the 1990s has been based on both research on the brain circuits thought to be involved in generating the symptoms of PD and clinical research. Animal research has led to insights providing a scientific framework from which to interpret and predict the effects of pallidotomy. We sought to examine the primary hypothesis providing the rationale for the use of pallidotomy—that excessive tonic inhibition of the thalamus from the overactive internal segment of the globus pallidus (GPI) is the primary mechanism of bradykinesia.

This hypothesis is based on research, primarily on monkeys rendered parkinsonian by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), that has led to the development of motor circuit representations of the imbalance in neural activity associated with PD (see DeLong, figure 1, p. 282). The basic motor circuit of a properly functioning basal ganglia consists of excitatory activation of the putamen by the cerebral cortex. The putamen inhibits the output structure directly, the internal segment of the GPI, and the substantia nigra pars reticulata (SNr). In contrast, the putamen increases
activity indirectly in the output structure (GPi/SNr) via the indirect pathway by inhibiting the external segment of the globus pallidus (GPe), which in turn inhibits the subthalamic nucleus, which excites the GPi and the SNr. The GPi and the SNr have an inhibitory effect on the thalamus, whereas the thalamus excites the motor areas of the cerebral cortex. In addition, output projections from the basal ganglia are sent to other motor-related areas such as the superior colliculus and the pedunculopontine nucleus.\(^1\) In monkeys who received MPTP, the loss of dopamine from the substantia nigra pars compacta (SNC) is associated with a decrease in the putamen activity of the direct pathway and an increase in the putamen activity in the indirect pathway. Therefore, dopamine loss in both pathways is associated with an increase in GPi and SNr activity.\(^4\) The resulting increased inhibition of the thalamus is thought to make movement difficult, accounting—at least in part—for bradykinesia.\(^1\) It is this hypothesis that underlies the scientific rationale for performing pallidotomies, because a GPI lesion silences a portion of the overactive output, which then reduces the excessive inhibition.

Many recent clinical studies have shown that the main benefits from pallidotomy are 1) an improvement in the “off” state Unified Parkinson’s Disease Rating Scale (UPDRS) score\(^8,14\) and 2) a reduction in drug-induced dyskinesias.\(^8,17\) Prelevodopa era clinical studies documented improvement primarily in rigidity and tremor, with an occasional statement suggesting an improvement in bradykinesia proportional to changes in rigidity.\(^18,19\) The effect of pallidotomy on basic motor function when the patient is in the “on” state is less clear. Some authors report no improvement in the “on” state UPDRS scores\(^8,15,16\) and some report slight improvement,\(^18\) and some report clear improvement.\(^17,20\) Moreover, several studies have shown an improvement in bradykinesia with the patient in the “on” state in such tasks as writing,\(^13,16\) tapping,\(^8,11\) and the Purdue pegboard task.\(^21\) In their paper entitled “Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms,” Laitinen et al.\(^22\) report: “Our study confirmed the findings of Svennilson et al.\(^18\) that parkinsonian tremor, rigor and hypokinesia can be effectively abolished by VPL pallidotomy” (p. 18).\(^22\)

To date, few if any studies on the efficacy of pallidotomy have used laboratory-based objective measures of motor performance. In this study we use objective measures to determine whether pallidotomy will result in improved performance of elbow flexion movements on the side contralateral to surgery when patients are “on.” Specifically, we tested the prediction that mean peak movement speed on the side contralateral to the surgery will increase following pallidotomy and should approach those speeds achieved in patients with mild parkinsonian symptoms. We also tested for improvement in other measures of motor performance including initiation time, peak acceleration, peak deceleration, and symmetry. Elbow flexion movements were studied because they are known to be impaired in PD\(^23-26\); they are simple, well-studied movements; and they can be studied efficiently in a population with severe motor disabilities and motor fluctuations. We chose to test medicated patients to maximize the reduction in inhibition by combining drug therapy and pallidotomy. A lesion should silence a portion of the GPi output better than dopamine replacement therapy alone. Consequently, if the hypothesis is true, then a patient who is still bradykinetic when in the “on” state should move faster while in the “on” state after pallidotomy.

**Methods.** Patients. A subset of nine of the 26 patients (seven men and two women) enrolled in a clinical efficacy study of pallidotomy\(^13,26\) agreed to participate in this motor control study. No patients with surgical complications were included. (Note: The protocol for this study was developed after the clinical study began. Consequently, only a subset of the patients from the clinical study are included in this study.) Eligibility requirements for the clinical study included patients with idiopathic PD whose disease was no longer controlled adequately by medical therapy due to disabling motor fluctuations or dyskinesias. Patients were required to be Hoehn and Yahr stage III or better when in the “on” state and stage IV or V when in the “off” state. Patients with a history of stereotactic neurosurgery for PD or with significant dementia or psychosis were excluded. Every attempt was made to hold antiparkinsonian medication doses constant. Changes in drug dose were allowed only in response to adverse events. Explicit informed consent was obtained from all subjects for the motor control study according to medical center-approved protocols. In addition, we identified seven age-matched men from our laboratory database of neurologically healthy subjects (age, 61.6 ± 13 years; age range, 42 to 78 years) and the same from our database of patients with mild PD (Hoehn and Yahr stages I and II; age, 60 ± 11 years; age range, 44 to 72 years) who had undergone the same motor control paradigm. Our database did not contain appropriate age-matched control subjects for the two female pallidotomy patients, so they were excluded from the analysis associated with figure 2 (seven male pallidotomy patients; age, 58 ± 10.7 years; age range, 44 to 68 years) in which the mean peak velocity of the pallidotomy patients before and after surgery while they were “on” was compared with healthy and mild parkinsonian control groups.

**Neurosurgical methods.** MRI and microelectrode techniques were used to target the ventral posterior portion of the internal segment of the Gpi. A unilateral radiofrequency lesion was placed at the target site. The day after surgery, standard MRI was performed to identify the lesion and its location. The scans showed the lesion to be placed properly in the Gpi in all nine patients. Preoperative medications were reinstated immediately after surgery and the patients were discharged the first or second day after surgery. For a detailed description of the neurosurgical methodology see Shannon et al.\(^14\)

**Experimental protocol.** Clinical evaluations were performed 1 month before and 1 month after surgery. They were performed in the “practically defined off” state in the
The evaluation included the motor (part III) and complications of therapy (part IV) subclasses of the UPDRS as well as timed motor tests as described in the Core Assessment Program for Intracerebral Transplantation (CAPIT). For a detailed description of the clinical methodology see Shannon et al. The patients were tested in the motor control laboratory 1 month before and 1 month after pallidotomy. Patients came to the laboratory immediately after their clinical evaluation in the "on" state and began motor testing.

We did not test patients who were in the "off" state for two reasons. The primary reason was based on the scientific question we wanted to address. We were interested in whether bradykinesia in PD can be explained predominantly by excessive tonic inhibition of the thalamus. Because there is already evidence from changes in "off" motor performance that excessive tonic inhibition is one contributing factor to bradykinesia, we chose to minimize tonic inhibition of thalamus with drug therapy first, then test whether patients who are slow even with drug therapy are further improved by pallidotomy. A secondary reason was that pilot experiments suggested that many patients were not able to perform the task as a single movement when they were in the "off" state. Consequently, the overall movement time was the only measure that might be compared with the "on" data. We did not believe that this would give us information that was any more insightful than the timed motor tests that were already part of the clinical study, as well as clinical studies reported in the literature.

Motor control experiment setup. The subject viewed a computer monitor that displayed a cursor, positioned along the horizontal axis by the joint angle. A small, stationary marker corresponded to the initial position. A broad band, 6 deg in width, was centered at the desired angular distance.

The subject was seated with the arm abducted 90 deg (the two limbs were tested sequentially). The forearm was strapped to a rigid, lightweight manipulandum that could rotate freely only in the horizontal plane. The axis of rotation was aligned with the elbow. Full extension of the right limb was defined as 90 deg (left limb, −90 deg). Elbow flexion of the right limb was in the negative direction (left limb, positive direction). The initial position of the right limb was 35 deg (left limb, −35 deg). The joint angle was measured by a capacitive transducer mounted on a shaft at the axis of rotation. This angle was differentiated digitally to generate joint velocity. Joint acceleration was measured by a piezoresistive accelerometer mounted 47.6 cm from the center of rotation. Surface electrodes were used to record electromyograms from the biceps and triceps (lateral head) muscles. The electromyographic (EMG) signals were amplified (gain, 1,600) and bandpass filtered (60 to 300 Hz). All signals were digitized at 1,000/sec with 12-bit resolution. The EMG signals were full-wave rectified and filtered with a 25-msec moving average window off-line.

Task. Subjects were asked to perform elbow flexion movements with both limbs over three distances (36, 54, and 72 deg) "as fast as possible to the target." A tone signaled the subject to initiate the movement. A second tone, delivered 3 seconds later, signaled the end of the trial, at which time the subject was asked to return to the initial position. Fifteen consecutive trials were performed at each distance.

Data analysis. A total of 2,250 trials were analyzed, including those of the control group. The following parameters were derived to characterize the data in each trial: peak velocity, maximum acceleration (peak acceleration during the acceleration phase), minimum acceleration (peak acceleration during the deceleration phase), symmetry (ratio of time in acceleration phase [i.e., time of peak velocity minus time of movement onset] to time in deceleration phase [i.e., time of movement offset minus time of peak velocity]), and initiation time (i.e., time at which the velocity first reaches 5% of peak velocity minus time of "go" tone).

Note that although initiation time was calculated, the instructions to the subjects did not emphasize reacting to the tone as quickly as possible, so this was not a reaction-time experiment.

Statistical analysis. The data were analyzed using paired t-tests, the sign test, and three-way repeated measures of ANOVAs. A preliminary study that we conducted during which nine patients were tested on the limb contralateral to the planned side of surgery two times at 1-month intervals before surgery showed no change in mean or variability of the motor control parameters from one session to the next. Consequently, in the current study we performed only one baseline test before surgery.

Results. The upper panel of figure 1 shows the "off" UPDRS motor scores. Seven of nine patients had a lower off-state UPDRS score after pallidotomy, which resulted in a statistically significant improvement in the group mean (p < 0.05, sign test). The lower panel of figure 1 shows the "on" UPDRS motor score before and after pallidotomy. There was no statistically significant improvement in the "on" motor UPDRS score. The group showed a statistically significant decrease in dyskinesia duration (p = 0.0312, sign test; see figure 1).

Pallidotomy did not affect group mean peak movement velocity for elbow flexion movement. There was no effect of the surgery (F[1,8] = 1.68, p = 0.231) and no effect of the side tested (contralateral versus ipsilateral; F[1,8] = 0.08, p = 0.785), but there was a significant effect of movement distance (F[2,7] = 38.53, p = 0.0001). Higher peak velocities were achieved during longer movements than were achieved during shorter movements both pre- and postsurgery. These data show no evidence that pallidotomy improved the speed with which elbow flexion movements are performed when patients are "on." In addition, three-way ANOVAs (surgery by side by distance) were performed on peak movement acceleration, peak movement deceleration, symmetry, and initiation time. None of the variables showed a statistically significant effect of pallidotomy.

Moreover, when compared with age- and gender-matched neurologically healthy subjects and age- and gender-matched patients with mild PD, the pallidotomy patients were markedly slow both before and after surgery. Figure 2 shows the mean and standard error of peak movement velocity for both control groups and for seven of the pallidotomy patients (see Methods) before and after surgery. The pallidotomy patients moved at nearly half the speed of the mild PD patients, who in turn moved more slowly than the neurologically healthy subjects (see figure 2).
Discussion. In contrast to the hypothesis that pallidotomy should lead to an increase in movement speed, our study shows that pallidotomy does not restore movement speed of elbow flexion movements performed while the patient is “on” compared with healthy subjects or mildly impaired parkinsonian subjects. Pallidotomy was efficacious clinically for the patients in our study. They showed improved clinically tested motor function when they were “off” (see figure 1) and decreased dyskinesias when they were “on.” Although we did not have subjects perform this experiment while they were “off” (see Methods), we predict that “off” motor performance would have improved after pallidotomy. Preliminary results of motor testing experiments have suggested that “off” movement speed increases after pallidotomy, with greater increases for tasks at proximal joints compared with tasks performed at distal joints. In addition, reports of off-state, timed motor tests as part of clinical examinations have suggested improvement in bradykinesia, as well as with those reported in the literature (e.g., Lozano et al.). However, even though the pallidotomy patients were clearly slower than the mild PD patients and healthy control subjects (see figure 2), pallidotomy did not result in any increase in mean peak velocity of elbow flexion movement made as fast as possible while the patients were “on.” In addition, there was no change.
in the patient’s ability to scale peak velocity with distance while they were “on” after pallidotomy.

The other finding from this study is that the variability of some motor performance measures was reduced after pallidotomy. However, we do not know what component of the reduced variability is due to the reduction in dyskinesias and what component is due directly to a reduction in the variability of the motor commands associated with the intended movement. The reduction in variability of the motor performance measures reflecting events that occur later in the time series (peak velocity and peak deceleration) did not reach significance. Nevertheless, the reduction in the variability of peak acceleration is particularly important because it does imply that the forces required to initiate the movements are produced more consistently.

Excessive tonic inhibition of the thalamus is not the only factor contributing to bradykinesia. The failure to increase movement speed while the patient is “on” after pallidotomy is somewhat surprising in light of the popular interpretation of the basal ganglia circuit model, which has motivated the resurgence of pallidotomy in treating the symptoms of PD.1,2,7,29

Dopamine replacement and enhancement therapy in monkeys who received MPTP has been shown to reduce the tonic firing rates of the overactive parkinsonian GPi.30 The subsequent disinhibition of the thalamus presumably facilitates movement in medicated PD patients. Because a pallidotomy completely silences a portion of the GPi output, it should disinhibit the thalamus similarly. Consequently, pallidotomy should further improve motor performance beyond that of drug therapy alone in those patients who are slow before surgery.

Our results show that pallidotomy does not result in the expected increase in speed of simple elbow flexion movements in spite of presurgery “best on” performances that are far slower than patients with mild PD. This suggests that excessive tonic inhibition is not the only major factor contributing to bradykinesia.

Note, however, that this result is not entirely surprising. The efficacy of lesions in the motor thalamus in treating some symptoms of PD show limitations of the idea that excessive tonic inhibition of the thalamus produces parkinsonian symptoms.

Loss of tuned, phasic activity may contribute to bradykinesia. Loss of normal phasic activity may also contribute to bradykinesia in PD,1,7 and pallidotomy clearly cannot facilitate this. It has been suggested that in a healthy basal ganglia, phasic activity may facilitate movement by selectively disinhibiting the thalamus (e.g., Chevalier and Deniau31) or that it may prevent unwanted movement during a movement task while turning off selected postural muscle activity to allow a voluntary movement to occur.20–34 The interaction of tuned excitatory and inhibitory inputs to the GPi may create a tuned movement field that leads to normal movements.

Filion et al.5 showed that cells in the GPi of monkeys who received MPTP exhibit an increase in magnitude of response and a loss of specificity in response to passive movement stimuli. Consequently, they suggest that movement leads to abnormal responses in the GPi of monkeys who received MPTP, and that dopamine regulates both gain and selectivity within the basal ganglia. Moreover, striatal stimulation studies have shown that both spatial and temporal patterns of inhibition and excitation of GPi are abnormal in monkeys who received MPTP.35,36 The net effect is to increase dramatically the noise in the system. We believe it is the interference caused by this noise that is relieved by pallidotomy.37 However, the loss of the specific, well-
controlled phasic responses of a healthy basal ganglia is likely to limit the maximal level of motor performance that is possible.

Studies of parkinsonian subjects have shown that PD patients generate large movements at low velocity, have a reduced ability to scale peak speed with movement amplitude, and exhibit a reduced range of scaling of the initial agonist EMG burst for movements of different distances. It is possible that the decrease in specificity and the decrease in the range of phasic activity in the GPi correlate with the reduced ability to scale the agonist burst and to scale speed with movement amplitude. However, it is interesting that there was no change in the ability to scale speed with distance following pallidotomy even though all phasic activity is eliminated in the lesioned portion of the pathway.

Even though dopamine replacement and enhancement therapy has been shown to reduce the tonic overactivity in the GPi of monkeys who received MPTP, it is not clear that drug therapy can restore the function of the motor circuit to the extent achieved by an intact SNc in which dopamine release is more controlled. Percheron and Filion, have suggested that the role of the intact dopaminergic system in the basal ganglia is precisely to increase the specificity and selectivity of the system. If the motor circuit has been degraded severely, it may no longer have the capability of controlling specificity adequately. If the benefits of drug therapy in patients at this stage are predominantly a result of reducing the tonic pallidal discharge (without regaining the normal specificity and tuning), then pallidotomy would be expected to have the same type of effect as medication. Of course, parkinsonian medication is also operating on the unlesioned portion of the GPi and other pathways within the system. This is consistent with clinical data in which pallidotomy leads to improvement in “off” UPDRS motor scores, but pallidotomy alone does not result in the “on” UPDRS scores achieved before or after pallidotomy (e.g., see figure 1, Lozano et al., and Baron et al.).

In fact, it would be surprising if creating a lesion in the GPi in a parkinsonian brain could restore function beyond that achieved when a lesion is made in the GPi in an otherwise healthy brain. Because pallidal inactivation in an otherwise healthy monkey is most associated with slow movement speeds, it would be surprising if there was no evidence of bradykinesia after placing a lesion in the GPi in these subjects, whether they were “on” or “off.” (Note that one study showed slowing of movements with small GPe lesions but not small GPi lesions.) It is possible that bradykinesia as a result of a lesion is due to the loss of phasic activity of the lesioned pathway. In fact, we believe that the hypothesis of Marsden and Obeso that there is a deficit in some aspect of motor control after pallidotomy, will be extremely difficult to document because it is likely that the motor system in advanced-stage PD patients no longer relies on this circuit for its normal role in motor control. In contrast we believe such deficits would become identifiable if pallidotomy were performed on patients with very mild PD in whom a partially functioning basal ganglia motor circuit is lesioned.

**No contradiction with reports of improvement of bradykinesia.** It is important to note that our finding that “on” movement speed does not increase in single-degree-of-freedom elbow flexion movements does not conflict necessarily with the finding that bradykinesia may improve in a repetitive or sequential task such as tapping or with off-state improvement. Individual movements may still be slow, but switching the time between movements may be improved, presumably due to a reduction in the interference with movement caused by presurgical abnormal GPi firing. Moreover, excessive tonic inhibition appears to be an important mechanism of bradykinesia in the “off” state, thus pallidotomy should improve off-state bradykinesia. However, drug therapy appears to minimize its contribution to the remaining bradykinesia in the “on” state.

**Effect of pallidotomy on dyskinesia.** Finally, we discuss briefly how the effect of pallidotomy on dyskinesias fits into our understanding of this motor circuit. With a simple gain control interpretation of the effect of dopamine, the reduction in dyskinesias after pallidotomy would be surprising because dyskinesias would result from too little activity of the GPi/SNr. Lesions would result in a more complete silencing than expected from dopamine therapy and thereby, if anything, would increase the dyskinesias. However, a more common interpretation, still consistent with the model, is that drug-induced dyskinesias fit into our understanding of this motor circuit. With a simple gain control interpretation of the effect of dopamine, the reduction in dyskinesias after pallidotomy would be surprising because dyskinesias would result from too little activity of the GPi/SNr. Lesions would result in a more complete silencing than expected from dopamine therapy and thereby, if anything, would increase the dyskinesias. However, a more common interpretation, still consistent with the model, is that drug-induced dyskinesias result from a differential effect of drug therapy on the direct and indirect pathways, possibly via different effects on D1 and D2 receptors. The resulting imbalance in interactions between the pathways, then, induces dyskinesias. Consequently, a pallidotomy blocks the outputs of the pathways through which dyskinesias are induced. This is consistent with the circuit model and the clinical results. Note, however, the fact that two opposing predictions about the effect of pallidotomy on dyskinesias are consistent with the same model emphasizes the need for development of more detailed basal ganglia motor circuit models.

The results that we have presented suggest that excessive tonic inhibition of the thalamus is not the only significant mechanism of bradykinesia in PD. Moreover, our results are consistent with the interpretation that pallidotomy reduces the interference in movement caused by the abnormal GPi firing but that deficits associated with the loss of the basal ganglia motor circuit remain. Consequently, having a lesioned basal ganglia motor circuit in patients with more advanced PD may be preferable to having a complete but malfunctioning motor circuit.
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The metabolic anatomy of tremor in Parkinson’s disease

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Article abstract—Objective: To identify regional metabolic brain networks related specifically to the presence of tremor in PD. Background: The pathophysiology of parkinsonian tremor is unknown. Because tremor in PD occurs mainly in repose, we used resting state PET with 18F-fluorodeoxyglucose (FDG) to identify specific metabolic brain networks associated with this clinical manifestation. Methods: We studied two discrete groups of eight PD patients with and without tremor using FDG/PET. Both patient groups were matched for gender, age, and Unified Parkinson Disease Rating Scale ratings for akinesia and rigidity. Ten normal volunteer subjects served as controls. Results: Network analysis with the Scaled Subprofile Model was performed in two steps. 1) We computed the expression of the PD-related pattern (PDRP) identified by us previously in each of the PD patients and control subjects. Although PDRP subject scores were abnormally elevated in the combined PD cohort (p < 0.005), these values did not differ in the PD patient groups with and without tremor (p = 0.36). 2) We used SSM to analyze the data from the combined PD cohort comprising both patient groups. We found that PD patients with tremor were characterized by increased expression of a metabolic network comprising the thalamus,pons, and premotor cortical regions. Subject scores for this pattern were elevated in the tremor group compared with the atremulous patient group and the normal control group (p < 0.005). Conclusions: The findings suggest that PD patients with tremor are characterized by distinct increases in the functional activity of thalamo-motor cortical projections. Modulation of this functional anatomic pathway is likely to be the mechanism for successful interventions for the relief of parkinsonian tremor.

Along with rigidity and bradykinesia, resting tremor constitutes one of the cardinal clinical features of PD. Nonetheless, the functional substrate of parkinsonian tremor is not understood. Because tremor in PD occurs primarily in repose, we used resting state PET with 18F-fluorodeoxyglucose (FDG) to identify abnormal motor pathway activity that is tremor specific. In earlier studies we utilized FDG/PET and network analysis (Scaled Subprofile Model [SSM]) to identify a specific pattern of regional metabolic covariation associated with PD. This PD-related pattern (PDRP) was characterized by relative hypermetabolism of the lentiform nucleus and the thalamus associated with metabolic decreases in the primary and association motor cortices.

We also developed a technique of quantifying network expression in individual subjects on a prospective basis (Topographic Profile Rating [TPR]). This approach was used to quantify PDRP expression (pattern subject scores) in individual subjects from their FDG/PET scans. PDRP subject scores have been found to discriminate PD patients from normal controls and atypical parkinsonian patients in multiple study populations. These measures of patho-
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