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RESEARCH ARTICLE

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Effects of pallidal deep brain stimulation and levodopa treatment on reaction-time performance in Parkinson's disease

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Abstract Basal ganglia-thalamocortical circuits play an important role in movement preparation and execution. Tracer, single-cell, and lesion studies in monkeys suggest the existence of topologically segregated motor and nonmotor basal ganglia cortical circuits. In this study we used deep brain stimulation (DBS) of the posteroventrolateral globus pallidus internus (GPi) in patients with Parkinson's disease to elucidate the function of the GPi in human sensorimotor behavior. This question was investigated by comparing the influence of DBS on patients' performance in various reaction-time tasks that differed with respect to cognitive but not motor requirements. As a main result, DBS improved performance on the different tasks independently of the complexity of the involved cognitive processing functions. Furthermore, the observed effects did not depend on the modality of the processed information. These results suggest that the functional state of the posteroventrolateral GPi selectively affects the motor stage in simple sensorimotor acts, because this stage was the only stage involved in all investigated tasks. In addition to DBS, we manipulated the levodopa medication state of the PD patients. In contrast to DBS, levodopa effects on reaction times were less consistent. Levodopa improved reaction times in choice reaction tasks significantly, while affecting reaction times in a simple reaction task to a lesser extent. Error analysis revealed that the medication-dependent reaction-time improvement in the choice reaction tasks was accompanied by an increase in errors, suggesting a shift of the speed-accuracy criteria of the patients. A similar pattern of results was not observed for the DBS effects. Taken together, our data are in agreement with recent findings in monkeys that indicate a topological organization of the GPi in which motor functions are localized in posterolateral regions apart from cognitive regions. Furthermore, our data show a way to uncover the subcortical-cortical circuitry serving human sensorimotor behavior.

Keywords Deep brain stimulation · Sensorimotor functions · Motor responses · Basal ganglia-thalamocortical circuits · Globus pallidus internus · Human

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Introduction

Basal ganglia-thalamocortical circuits play an important role in the generation of simple behavioral acts. Recent studies in monkeys have revealed the existence of segregated (Alexander et al. 1986) motor, limbic, and cognitive circuits originating from distinct cortical areas and projecting back to these areas via basal ganglia and thalamus (Parent and Hazrati 1995). The corresponding topological organization of the basal ganglia includes a subdivision of the globus pallidus internus (GPi), with posterolateral segments conveying their information to motor cortex and mediodorsal segments to prefrontal cortex (Hoover and Strick 1993, 1999; Middleton and Strick 1994). While the former segments are assumed to be part of the motor circuits, the latter are assumed to be part of the cognitive basal ganglia-thalamocortical circuits.

We used deep brain stimulation (DBS), a neurosurgical therapy for advanced Parkinson's disease (PD), to elucidate the functions of motor basal ganglia-thalamo-

cortical circuits in humans. Patients with PD suffer from a degeneration of dopaminergic neurons and dopamine depletion within the basal ganglia, resulting in an impairment of the basal ganglia-thalamocortical connections. Presumably, this impairment is caused by hyperactive inhibitory influence of the GPi on thalamic nuclei and via this path on cortical motor areas linked with the corresponding thalamic areas.

As a result, PD symptoms like akinesia, bradykinesia, and rigidity emerge. Via permanent electrodes in the posteroventrolateral GPi or in the subthalamic nucleus (STN; Siegfried and Lippitz 1994; Limousin et al. 1995), DBS improves motor symptoms in PD and reduces side-effects of long-term levodopa treatment such as dyskinesias and motor fluctuations (Bejjani et al. 1997; Troester et al. 1997; Krack et al. 1998a, 1998b). Although the exact physiological mechanisms of DBS for the treatment of advanced PD are not yet clear (Marsden and Obeso 1994), it is assumed that electrical high-frequency pulses lead to a functional blockade of pathologically increased neuronal activity within the target structure and release the cortical and brainstem motor system from abnormal inhibition (Davies et al. 1997). Consequently, the effects of DBS are comparable with a lesion of the GPi or STN, with the advantages of reversibility and adaptability.

Using DBS we tested whether the human posteroventrolateral GPi is selectively involved in motor functioning during the generation of sensorimotor actions (Ardouin et al. 1999; Pillon et al. 2000). For that purpose, we examined the influence of DBS on the performance of PD patients in various reaction time (RT) tasks, which allow us to distinguish between perceptual (e.g., stimulus detection), cognitive (e.g., response selection), and motor (Donders 1969; Sternberg 1969) stages of simple sensorimotor actions. By comparing the influence of DBS on the performance of patients in simple and choice RT tasks, one can test whether the posteroventrolateral GPi is selectively involved in the motor stages or in the cognitive processes related to response selection. This approach is based on the assumption that simple and choice RT tasks differ in the extent to which a response-selection stage is involved. While a complete response-selection stage is involved in choice RT tasks, simple RT tasks do not involve the response-selection stage (Donders 1969; Frith and Done 1986; see also: Gottsdanker and Shragg 1985; and Gottsdanker 1992 for support of this assumption). Instead, simple RT tasks involve the possibility of anticipatory response preparation, because in these tasks the stimuli and the motor responses remain the same in all trials (Frith and Done 1986; Goodrich et al. 1989).

We reasoned that the different involvements of the response-selection stage in simple and choice RT tasks allow formulation of different predictions concerning which processing stages are affected by the DBS of the posteroventrolateral GPi. Thus, an exclusive effect of the DBS on the simple RT task would imply an involvement of the GPi in the mechanism of anticipatory response preparation, since this stage is especially involved in simple and not in choice RT tasks. On the other hand, an exclusive influence of the DBS on the choice RT task would imply an involvement of the GPi in the response-selection mechanism. Third, similar quantitative effects of the DBS on simple and choice RT tasks would imply a selective influence of DBS on the motor stages, because the motor stage is the only stage that is similarly involved in both types of tasks.

In addition to DBS, we manipulated the dopaminergic state of the PD patients by administering a levodopa challenge after overnight drug withdrawal. While the anatomical target of the DBS is a rather focused one, levodopa effects are not restricted to a single structure within the basal ganglia. Instead, dopamine-dependent neural projections diffusely influence the whole striatal system. Studies in PD which investigated the influence of levodopa on performance in RT tasks do not reveal a systematic pattern of results. While some studies indicate no effect of levodopa on RT (for a review, see Harrison et al. 1995; Gauntlett-Gilbert and Brown 1998), other studies reveal selective effects solely on the choice RT (see Pullman et al. 1988; Rafal et al. 1984). The causes of this rather contradictory pattern of results remain unknown.

The different topography of DBS and levodopa effects might be predictive for differential effects of DBS and levodopa dose on RT paradigms. Thus, a further aim of the present study was to compare the effects of DBS and levodopa on the RTs in the abovementioned tasks.

Materials and methods

Behavioral tasks

Subjects were asked to carry out three RT tasks in the following order:

1. Visual simple RT task. After the presentation of a visual warning signal, an imperative visual stimulus was shown for 300 ms at the center of the computer screen. The duration of the delay between offset of the warning signal and onset of the imperative visual stimulus was varied randomly between 200 ms, 500 ms, 1,000 ms, or 2,000 ms. Imperative stimuli were a square in the first trial block and a circle in the second trial block. Each block consisted of 48 trials. Subjects responded to the presentation of the stimulus by pressing a button on a key box. In the first trial block (squares), subjects responded with the right middle finger and, in the second trial block (circles), with the left middle finger
2. Visual choice RT task. The experimental situation was identical to that of the visual simple RT task, with the exception that now circles and squares were presented randomly. Subjects responded with the corresponding fingers to the randomly presented stimuli
3. Auditory choice RT task. After the presentation of a visual warning signal, either a low-pitched (300 Hz) or a high-pitched (900 Hz) tone was presented randomly as the imperative auditory stimulus via loudspeakers. The time interval between the warning signal and onset of the auditory signal was set to 1,000 ms. Subjects responded with the left index finger to the low-pitched tone and with the right index finger to the high-pitched tone.

Table 1 Characteristics (mean values) of the patients with Parkinson's disease (*Med* levodopa medication, *DBS* deep brain stimulation, *UPDRS* Unified Parkinson's Disease Rating Scale)

	Hoehn and Yahr Med		UPDRS motor score Med	
	Off	On	Off	On
Before surgery	3.60	2.90	48.20	27.70
After surgery				
DBS on	2.70	2.10	16.10	10.10
DBS off	3.37	2.32	42.00	15.37

Following the third auditory choice RT task, subjects conducted a fourth task that is, however, not relevant to the present study and will therefore not be described.

The sequence of three tasks was carried out by PD patients under each of the four treatment conditions described in the next section. This led to four experimental sessions of about 1–1.5 h duration each. One complete treatment condition was tested in each session. To reduce maximal time of experimentation, patients did not practice the RT tasks before the experiment. Due to randomization of conditions, there was an equal amount of practice in each of the four treatment conditions.

Patients and design of the treatment conditions

Six female and two male PD patients (mean age ± SD, 55.3± 10.70 years; disease duration 11.1±2.64 years) were investigated after written informed consent had been obtained according to the 1964 declaration of Helsinki and according to the guidelines of the ethics committee of the Heinrich-Heine-University, Duesseldorf. All patients suffered from advanced idiopathic PD and had undergone surgery for bilateral DBS of the GPi 12–24 months (mean 8.6±5.13 months) prior to the experiment. Before surgery, patients were taking a mean levodopa equivalent daily dose (LEDD) of 402.8±168.56 mg, which did not change significantly after surgery. For a summary of further clinical patient characteristics, see Table 1.

We used a 2×2 factorial design according to which the medication, and DBS states were manipulated "on" and "off" in all possible combinations for therapeutic purposes. The combination of all on and off states yielded four different treatment conditions (medication) on/(DBS) on, on/off, off/on, off/off. In the medication-on state, patients took an equivalent of their regular dopaminergic morning dose as shortacting levodopa formulation. Dopamine agonists were converted to LEDDs given the conversion formula provided by Volkmann et al. (1998). Before starting the test, we waited for the patient and the examiner to agree upon the best medication-on condition. The medication-off state was realized by an overnight withdrawal of antiparkinsonian drugs. Medication-on and -off conditions were investigated on separate days with half of the patients beginning in the off state. Manipulation of the DBS state was realized by switching on or off the bilaterally implanted pulse generators (ITREL II; Medtronic, Minneapolis, Minn.). Order of on- and off-DBS states was permutated across patients. After each change of the DBS state, patients waited until a stable clinical condition had been achieved (minimum of 15 min) before beginning to work on the RT tasks. The decision when to start testing was made by a neurologist (J.V.), who knew the individual symptomatology in all four treatment conditions from prior clinical testing.

Normal control subjects

Eight normal control subjects, who also gave informed consent, performed all three RT tasks mentioned above consecutively in four sessions in order to equate for the amount of practice the PD patients received. The control subjects were individually matched to the PD patients concerning age (52±10.36 years), sex (six female and two male control subjects), and education (the highest degree of education was equal in each matched pair of PD patients and control subjects).

Neurosurgery and parameters of the DBS

The details of the stereotactic procedure for placement of the GPi electrodes have been described elsewhere (Volkmann et al. 1998). The target for the stereotactic insertion of the stimulation electrodes was the posteroventrolateral aspect of the GPi. The initial target coordinates were those reported by Laitinen et al. (1992). The target was determined by using stereotactic contrast ventriculography with reference to intraoperatively performed computer tomography. Final electrode positions were adjusted according to effects of macrostimulation on contralateral bradykinesia and rigidity and side effects during neurosurgery. Once the optimal target point resulting in best clinical improvement at lowest stimulation intensities had been defined, a permanent quadripolar stimulating electrode was fixed (model DBS 3387; Medtronic, Minneapolis). From intraoperative ventriculography and stereotactic plane X-rays, the final coordinates of each contact of the quadripolar stimulating electrode were determined for each patient and referenced to standard stereotactic space. Mean ventriculographic coordinates of the distal electrode pole were 20.95 mm lateral to the midline of the third ventricle, 6.11 mm below the intercommissural line (ICL), and 2.13 mm anterior to the midcommissural point (MCP). The mean coordinates of the contact that was finally chosen for chronic stimulation after the testing period were 21.5 mm lateral to the midline of the third ventricle, 1.34 mm below the ICL, and 3.76 mm anterior to the MCP. The optimal stimulation parameters were adjusted during the postoperative course according to the patient's need. Mean stimulation parameters at the time of the experiment were: amplitude 3.29±0.8 V, frequency 178±16.37 Hz, and pulse width 160.7±85.34 μs. None of the patients experienced side effects during chronic stimulation from current spread to internal capsule or optic tract.

Data analysis

As a first step in the data analysis, an overall ANOVA with the within-subjects factors (repeated measures) Medication, DBS, and Task was conducted on the mean RTs of the PD patients in all three RT tasks. As a second step, we assessed the effects of medication and DBS for each task separately. Therefore, we conducted ANOVAs with the within-factors Medication and DBS on the RTs of the PD patients for each task. To compare the performance of PD patients with that of the control group, we conducted subsequent ANOVAs with the between-subjects factor Group, and the within-subjects factors DBS and Medication.

In addition, a distributional analysis was conducted on the RTs in the three tasks. The aim of this analysis was to obtain more detailed information about the influence of medication and DBS on the RTs of the PD patients (for more details about the purpose of this analysis see the Results section). In order to draw inferences about the group RT distributions, we analyzed Vincentized cumulative probabilities of the RTs. To form the group distributions, we organized the RTs of each individual subject in ascending order and computed the percentiles. Then, we averaged the percentiles over the subjects to get group percentiles (Ratcliff 1979). From these group percentiles, group RT distributions were constructed that retain the shape of subjects' individual RT distributions. The RT distributions of the PD patients were analyzed with appropriate ANOVAs, with the within-subjects factors Medication, DBS, and Percentiles, separately for each RT task. The lower-bound procedure was used to adjust degrees of freedom for avoiding an increase in type I error due to possible linear dependencies between different percentile levels.

All pair-wise comparisons were conducted with a corresponding Bonferroni correction, which adjusted the level of significance at $P<0.05$.

Results

Analysis of the mean RTs

To test whether the manipulation of the functional state of the GPi affects the motor stages or the cognitive stages (response selection), an overall ANOVA with the factors medication, DBS, and task was conducted on the RTs of the PD patients. DBS affected RTs in all three tasks to a similar extent, thus indicating an effect on the motor stages (see Fig. 1). This was shown by a significant main effect of DBS on RTs ($F_{1,7}$=34.92, $P<0.01$), which did not vary across tasks. The interaction between DBS and task was not significant ($F_{2,14}$=0.63, $P>0.5$). Medication affected RTs of the PD patients, too ($F_{1,7}$=6.56, $P<0.05$). However, this effect tended to be unequal across tasks, as is indicated by the interaction between task and medication ($F_{2,14}$=2.79, $P<0.10$), which approached significance. A subsequent analysis revealed that the Task by Medication interaction did not reach the significance level of P=0.05, because of high data variability in the simple RT task compared with the other two tasks. Thus, when the data from the simple RT task were excluded from the ANOVA then the Task by Medication interaction was significant ($F_{1,7}$=7.45, $P<0.05$). All other effects remained unaffected by the exclusion of the simple RT data.

Importantly, DBS and medication affected the RTs in these tasks independently of each other, as indicated by the nonsignificant DBS by Medication interaction ($F_{1,7}$=0.95, $P>0.35$).

Visual simple RT task

The separate analysis of the data in the visual simple RT task showed that DBS led to an improvement of the RTs by 71 ms ($F_{1,7}$=17.25, $P<0.01$). Medication did not affect the RTs ($F_{1,7}$=2.12, $P>0.19$). The effect of DBS did not depend on the medication condition, as shown by a nonsignificant interaction between DBS and medication ($F_{1,7}$=1.38, $P>0.2$).

To test the validity of the observed DBS and medication effects, we compared the performance of PD patients with that of the normal control subjects. For comparison purposes, the data of the control group were matched with the data of the PD group with respect to the order of experimental sessions and the corresponding medication and DBS states of the PD group in each session. Thus, for example, if a PD patient performed the medication and DBS conditions in the following order: 1st session, medication on/DBS on; 2nd session, on/off; 3rd session, off/on; 4th session, off/off, then the data of the corresponding control subject were treated as follows: 1st session corresponds to on/on condition; 2nd session to on/off; 3rd to off/on; and 4th to off/off (Fig. 1). To compare the RTs between both groups, an ANOVA with the factors group, DBS, and medication was conducted. It yielded significant effects of the factors group ($F_{1,14}$=12.75, $P<0.01$) and DBS ($F_{1,14}$=12.89, $P<0.01$). The significant interaction between group and DBS ($F_{1,14}$=12.72, $P<0.01$) on the RTs shows the validity of our results. It reveals that DBS affected RTs only in the PD group and not in the control group as can be expected, since the normal control subjects were only hypothetically “treated” by medication or DBS. All other effects did not approach significance.

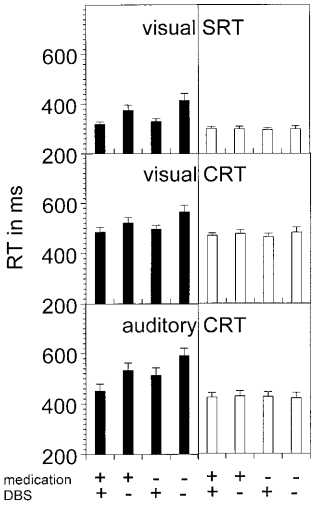

Fig. 1 Influence of medication and high-frequency stimulation (*DBS*) on mean reaction times (*RT*). Visual simple (*SRT*), visual choice (*CRT*), and auditory choice reaction tasks (*CRT*). *Left panel*: PD patients; *right panel*: normal controls that performed the tasks in the same order as the PD patients, but without DBS and medication manipulation. *Plus signs: upper row,* with medication; *lower row* with DBS; *minus signs*: respectively, without medication or DBS. Note, normal controls did not perceive medication or DBS treatments. *Plus* and *minus signs* in normal controls denote the medication and DBS states of the corresponding age-, sex-, and education-matched PD patient according to the corresponding task order

Visual choice RT task

In the visual choice RT task, DBS led to an improvement of RTs by 54 ms, ($F_{1,7}$=17.28, $P<0.01$). The effect of medication on RTs approached significance ($F_{1,7}$=3.54, P=0.10). As was true for the simple reaction task, the effect of the DBS on RTs did not depend on the medication condition ($F_{1,7}$=1.84, $P>0.2$). The subsequent comparison of the RTs of PD patients with those of the control group yielded an effect of the DBS ($F_{1,14}$=16.6, $P<0.01$) and a tendency toward a group effect ($F_{1,14}$=3.99, $P<0.07$). The significant DBS by Group interaction ($F_{1,14}$=6.03, $P<0.05$) indicates that DBS affected only the RTs of PD patients, revealing the validity of the results. No other effects were significant.

Auditory choice RT task

In the auditory choice RT task, DBS improved RTs by 80 ms ($F_{1, 7}$=11.30, P<0.05). Medication improved RTs independently of the DBS condition ($F_{1, 7}$=9.21, P<0.05). Similar to the two previous tasks, the DBS by Medication interaction was not significant ($F_{1, 7}$=0.00, P>0.9). A comparison of the RTs of PD patients and control subjects yielded significant effects of DBS ($F_{1, 14}$=9.00, P<0.01), medication ($F_{1, 14}$=6.34, P<0.05), and group ($F_{1, 14}$=12.33, P<0.01). However, the significant interactions between group and DBS ($F_{1, 14}$=6.34, P<0.05), as well as between group and medication ($F_{1, 14}$=9.08, P<0.05) indicated that DBS and medication affected RTs selectively in the PD patients group and not in the control group. The selective effects of DBS and medication on PD patients are to be expected, because normal control subjects were not treated by medication or DBS. This result emphasizes the validity of the observed selective effects.

One major result of the previous analysis is that DBS affected the RTs similarly in all three tasks. This finding is consistent with the assumption that DBS affected the motor stages of the tasks, because this stage was the only one that was involved in all three RT tasks. An alternative explanation would be an increased arousal level of the PD patients during the DBS-on state. This increased arousal level could have led to the observed improvement of RTs just as well.

To test whether DBS actually affected the motor stage during task performance or whether it had a nonspecific effect on the arousal level of PD patients, we analyzed the RT distributions of the subjects in the three tasks (Fig. 2). If DBS affected the arousal level of patients, then it should primarily influence the slower (right tail) part of the RT distribution, because slow RTs are most severely affected by arousal fluctuations, as has been shown by different authors (Sanders 1983; Miller 1988). On the other hand, if DBS affected one processing stage, i.e., the motor stage, then it should have affected all parts of the RT distributions, i.e., the fast, middle, and slow RTs (Ratcliff 1979; Meyer et al. 1988; Schubert 1999).

Figure 2 shows that DBS led to a leftward shift of all RTs in all three tasks. This finding is supported by the results of separate ANOVAs with the factors medication, DBS, and percentiles conducted on the RT distributions in all three tasks.

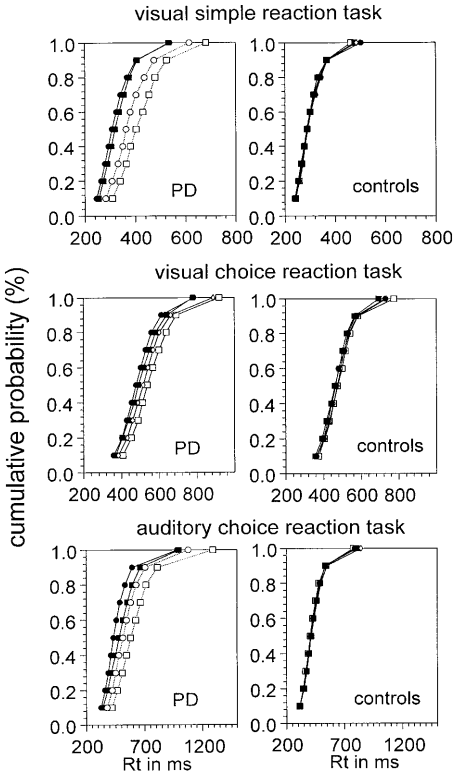

Fig. 2 Analysis of reaction time (*RT*) distributions. Vincentized cumulative probabilities of RT in the visual simple and choice as well as in the auditory choice reaction tasks. The curves were obtained by averaging across patients' individual probability curves. *Filled circles* denote medication-on/deep brain stimulation (DBS)-on. *Open circles*, on/off; *filled squares*, off/on; and *open squares*, off/off. Note, normal controls did not perceive medication or DBS treatments. On and off conditions in normal controls denote the medication and DBS states of the corresponding age-, sex-, and education-matched PD patient according to the corresponding order

Analysis of RT distributions

Visual simple RT task

For the simple visual RT task, the ANOVA yielded significant effects of DBS ($F_{1, 7}$=16. 2, P<0.01) and percentiles ($F_{1, 7}$=178.97, P<0.00). There was a slight tendency for a larger effect of DBS on the slower compared with the faster RT (see Fig. 2). However, the DBS by Percentile interaction was not significant ($F_{1, 7}$=3.51, P>0.10). This indicates that DBS affected all parts of the RT distribution to a comparable extent. The corresponding RT distributions of the control group are presented on the right panel of Fig. 2 for comparison purposes. The data were matched to the data of the PD group according to the procedure described above. As can be seen in the right upper panel, RT distributions in the different conditions did not differ for the control group. This is also indicated by nonsignificant effects of medication ($F_{1, 7}$=0.69), and DBS ($F_{1, 7}$=0.00) on the RT distributions of the control subjects.

Visual choice RT task

Similar results were obtained for the visual choice RT task. Here the ANOVA also yielded significant effects of DBS ($F_{1, 7}$=10.36, P<0.05) and percentiles ($F_{1, 7}$=165.27, P<0.00). There was also a slight tendency for a larger effect of the DBS on the slower part compared with the faster part of the RT distribution, as is revealed by the DBS by Percentile interaction, which approached signifi-

cance ($F_{1,7}$=4.88, P<0.10). However, separate ANOVAs showed that DBS improved RTs on each percentile (all P<0.05), revealing that DBS affected all parts of the RT distribution. For comparison purposes, RT distributions of the normal controls are presented in the right middle panel of Fig. 2. Similar to the data for the visual simple RT task, RT distributions in the different conditions did not differ for the control group. This is indicated by nonsignificant effects of medication ($F_{1,7}$=0.00) and DBS ($F_{1,7}$=1.18) on the RT distributions of the control subjects.

Auditory choice RT task

For the auditory choice RT task the ANOVA yielded significant effects of DBS ($F_{1,7}$=25.52, P<0.01), medication ($F_{1,7}$=9.01, P<0.02), and percentiles ($F_{1,7}$=41.98, P<0.00). There was a significant DBS by Percentiles interaction ($F_{1,7}$=8.69, P<0.05), demonstrating a larger influence of DBS on the slower compared with the faster part of the RT distribution. However, separate ANOVAs showed that DBS improved RTs on each percentile (all P<0.05) revealing that DBS affected all parts of the RT distribution. The interaction between medication and percentiles was not significant ($F_{1,7}$=2.48, P>0.15), indicating that medication affected all parts of the RT distribution to a similar extent. The RT distributions of the control group in the auditory choice RT task are presented in the right lower panel of Fig. 2. Similar to the data for the two visual RT tasks, RT distributions in the different conditions did not differ for the control group. This is indicated by nonsignificant effects of medication ($F_{1,7}$=0.00) and DBS ($F_{1,7}$=0.12) on the RT distributions of the control subjects.

Error analysis

The mean number of errors as a function of group, task, medication, and DBS state is presented in Table 2. Separate ANOVAs were conducted to analyze the influence of medication and DBS state in the PD group.

In the visual simple RT task, medication and DBS did not affect the mean number of errors ($F_{1,7}$=3.03, P>0.10) and ($F_{1,7}$=0.66, P>0.4), respectively. There was no significant Medication by DBS interaction ($F_{1,7}$=3.72, P=0.10).

In contrast, in the visual choice RT task, medication tended to affect the mean number of errors for the PD patients ($F_{1,7}$=4.23, P<0.08). As can be seen in Table 2, patients made more errors in the medication-on (mean number=3.94±1.06) compared with the -off state (mean number 2.19±0.70). The effect of DBS did not reach significance ($F_{1,7}$=0.03, P>0.86), nor did the Medication by DBS interaction ($F_{1,7}$=0.2, P>0.66).

In the auditory choice RT task, the effect of medication on the mean number of errors was highly significant ($F_{1,7}$=10.65, P<0.01). As in the visual choice RT task, patients made more errors when medicated-on (mean number 3.82±0.89) compared with -off (mean number 2.13±0.89). It is important to note that, together with the results of the RT analysis, these results show that the medication-on state led to a shift of the speed-accuracy criteria of the patients. With levodopa medication, patients used a riskier strategy such that faster RTs were accompanied by more errors. The same but slightly milder speed-accuracy tradeoff could be observed for the visual choice RT task. As previously, DBS did not affect the error number ($F_{1,7}$=0.15, P>0.7). The important Medication by DBS interaction was also far from significant ($F_{1,7}$=0.05, P>0.83), suggesting that the increase in errors with levodopa was equivalent during DBS-on and -off states.

The observed increase in errors was therefore not related to interference of involuntary movements with completion of the motor tasks during drug-induced dyskinesias, which were present in most patients to a variable degree in the medication-on and DBS-off condition, but were suppressed in the DBS-on condition (compare the clinical data of the parkinsonian symptoms presented in Table 1).

Table 2 Mean number of errors as a function of group, task, medication (*Med*), and deep brain stimulation (*DBS*). (*VSRT* Visual simple reaction task, *VCRT* visual choice reaction task, *ACRT* auditory choice reaction task, *SEM* standard error of mean)

	PD patients				Control subjects			
Med	Off	Off	On	On	Off	Off	On	On
DBS	Off	On	Off	On	Off	On	Off	On
VSRT	0.63	0.13	1.25	1.37	0.13	0.25	0.25	0.25
SEM	0.26	0.13	0.56	0.56	0.13	0.25	0.16	0.16
VCRT	2.13	2.25	4.13	3.75	2.75	2.38	2.38	2.38
SEM	0.74	0.65	1.38	0.75	0.75	0.92	0.46	0.50
ACRT	2.38	1.88	3.88	3.75	1.63	1.88	1.25	1.63
SEM	1.05	0.72	0.48	1.31	0.60	0.48	0.37	0.46

Discussion

In this study we explored whether the human posteroventrolateral GPi is selectively involved in motor processing stages during the generation and execution of sensorimotor behavior. We used DBS to modulate the functional state of the posteroventrolateral GPi in patients with PD. In concert with a careful manipulation of the perceptual, cognitive, and motor requirements of the behavioral paradigms, DBS allows us to determine the particular involvement of the GPi in different information processing functions.

DBS effects on RT-task performance

The results showed that DBS of the posteroventrolateral GPi improved RTs of PD patients in different RT tasks.

Specifically, DBS improved RTs in a simple RT task that did not require the selection of responses but involved the possibility of anticipatory motor preparation (Donders 1969). In addition, DBS improved, to a similar extent as in simple RT tasks, the performance in choice RT tasks that involved the selection of responses. Clearly, these findings are not in accord with the assumption that the posteroventrolateral GPi is exclusively involved in cognitive processes related to response selection. In this case a selective effect of DBS on the choice RTs would be expected. The results also do not comply with the assumption that the GPi is exclusively involved in anticipatory response preparation. In this case DBS should have selectively influenced simple RTs. Furthermore, similar effects of DBS on RTs in visual and auditory choice RT tasks revealed that the observed improvement of RTs was independent of the sensory modality of the processed information. Taken together, these findings are in support of the assumption that DBS of the posteroventrolateral GPi affects the motor stage in simple behavioral acts, because this stage was the only stage involved in all three RT tasks used.[1]

An alternative explanation of the data, namely that DBS may not have affected one information processing stage but rather the general arousal level of PD patients, was approached by an extended RT distribution analysis. According to the arousal assumption, DBS should have affected the slowest RTs, because these are most severely affected by an unstable arousal level (Sanders 1983; Miller 1988). In contrast, when affecting a particular processing stage, DBS should influence the RTs in all trials irrespective of their speed (Ratcliff 1979; Meyer et al. 1988). The results of our RT distribution analysis primarily indicated an influence on one particular processing stage, i.e., the motor stage, although an additional influence of DBS on the general arousal level cannot be ruled out.

Our results are supported by a recent study of Brown et al. (1999), also finding an effect of DBS on the motor stage in different RT tasks. Interestingly, the amount of the improvement in our study (mean improvement in all three tasks of 69 ms) was similar to the RT improvement in the study by Brown et al. (mean improvement across all tasks of 71 ms), suggesting reliable RT improvements due to DBS in PD patients. However, the RT distributions of the PD patients were not systematically analyzed by Brown et al. (1999) Furthermore, in their study, PD patients were investigated in the medication-off state only. This experimental design does not allow comparison of the anatomically focused effects of DBS on sensorimotor behavior from the more global effects of changes in the whole striatal dopaminergic system by a levodopa challenge.

[1] DBS could theoretically be influencing the anticipatory maintenance of response sets in the simple RT tasks, as well as the response-selection processes in the choice RT tasks, without affecting the motor stage in both types of tasks. This assumption seems implausible because of the empirical data obtained. For example, if the RT improvement in the simple RT tasks were due to a DBS-induced increase in anticipatory responding, then an increased number of anticipatory responses should have been found in that condition. However, the results of the RT distribution analysis indicate that this was not the case. In the simple RT task, DBS affected the fastest RTs, which cover most of the anticipatory responses, to a similar extent as the slowest RTs. This rules out the possibility that DBS affected response speed in the simple RT tasks simply by inducing anticipatory responding.

Levodopa effects on RT-task performance

In general, the levodopa effects on RT task performance are less clear than those of DBS. Levodopa medication led to a significant reduction of RTs only in the auditory choice RT task. In the visual choice RT task, the effect of levodopa still approached significance, while there was a nonsignificant reduction of the RTs in the simple RT task. This pattern of results was paralleled by the results of the error analysis. Levodopa led to an increase in the error rate in both choice RT tasks, while its effect on error rate in the simple RT task was not significant. This indicates that the levodopa-related reduction of RTs in the choice RT tasks may have been caused by a shift in the speed-accuracy criteria of patients. This pattern of results was not observed for the DBS manipulation.

It must be noted that these differential effects of levodopa and DBS on RT-task performance were not capitalized by significant interactions between medication and DBS on RTs, as well as on the error results in the ANOVA. However, one should be cautious in interpreting this lack of interaction because of the low statistical power (less than 0.8 for the medication effects on visual simple and choice RTs, as well as for the interaction effects) due to a small sample size.

Importantly, the observed differences in the effects of levodopa on simple and choice RTs are in accord with results of other studies. For example, Pullman et al. (1988) and Rafal et al. (1984) have demonstrated a significant improvement of RTs in choice RT tasks, while performance in simple RT tasks was only nonsignificantly improved by levodopa manipulation. For an overview of studies revealing different effects of levodopa on performance in simple and choice RT tasks, see also Gauntlett-Gilbert and Brown (1998), Harrison et al. (1995), and Robbins and Brown (1990).

Different explanations are proposed for this phenomenon. According to Pullman et al. (1988), cognitive computation in the more complex choice RT tasks requires the involvement of additional dopaminergic modulation, resulting in a stronger levodopa dependency of the performance in these tasks compared with simple RT tasks.

Alternatively, Robbins and Brown (1990) propose dopamine to affect performance in simple and choice RT tasks as a “limited resource” needed for the initiation of motor responses, with more dopamine needed for the faster RTs. Because choice RTs are usually slow and simple RTs are fast, smaller doses of levodopa are required for speeding choice relatively to simple RTs. Consequently, with the same levodopa dose, choice RTs should be more affected than simple RTs.

Our data allow the specification of a possible speed dependency of levodopa effects (Robbins and Brown 1990). The RT distribution analysis indicates that levodopa affects the slow, middle, and fast RTs to a similar extent in the simple as well as in the choice RT tasks. Therefore, the assumption of Robbins and Brown (1990) does not hold for fine differences in response speed. Rather, it may be correct only for gross RT-speed differences that emerge from fundamental processing differences between simple and choice RT tasks (Frith and Done 1986).

Although our and other results are not entirely conclusive, they suggest that levodopa effects on RT performance depend on the complexity of the required cognitive computation in the sensorimotor task. In sharp contrast, DBS of the posteroventrolateral GPi seems to affect the RT performance independently of the involved cognitive operation and of the perceptual modality.

One reason for the observed difference between levodopa and DBS effects could be that the specific doses of levodopa medication and electrical stimulation (DBS) in our experiment were not equally titrated. Thus, one could argue that relatively low doses of levodopa were accompanied by relatively high doses of electrical stimulation, which might have caused a different influence on behavior. However, if this were true, then the clinical effects of levodopa medication and DBS on patients' behavior should have been in the same direction, only differing in magnitude. Clinical scoring (Table 1), however, revealed no significant differences in the impact of DBS or levodopa challenge on motor symptoms as assessed by the unified PD rating scale (UPDRS) scale (postoperative state: medication-on/DBS-off, 15.37 points; and medication off/DBS on, 16.1 points; $P>0.2$) as well as by the Hoehn and Yahr scale (on/off 2.32, and off/on 2.7; $P>0.2$), respectively. Therefore, we do not believe that the observed inconsistency of levodopa and DBS effects on more fine-grained parameters of the sensorimotor behavior are solely an artifact of nontitrated doses for the two treatments.

Neuroanatomical interpretation

Our results are consistent with findings in monkeys that indicate a topological organization of the GPi (Hoover and Strick 1993, 1999; Middleton and Strick 1994). In these studies, the injection of tracers into the motor cortex of monkeys caused labeling of neurons in the posterolateral GPi. Injection into SMA labeled slightly more dorsal regions of the GPi, wheras an injection into the prefrontal area 46 labeled segregated neurons in the most dorsal aspect of the inner and outer segments of GPi, anterior to motor and premotor projections (see also a single-cell study by Yoshida et al. 1993). According to these studies, motor functions are localized in posterolateral portions of the GPi rather than in mediodorsal regions, which are thought to mediate cognitive processes (see also Alexander et al. 1986).

Indirect support for a similar functional subdivision within human GPi could come from studies on the behavioral effects of the location of DBS electrodes or pallidotomy lesions (Durrif et al. 1999; Gross et al. 1999). In a recent study of parkinsonian patients who had undergone pallidotomy, Lombardi et al. (2000) could indeed demonstrate a correlation between cognitive outcome and lesion location along the anteromedial-to-posterolateral axis in GPi. Anteromedially placed pallidotomy lesions were likely to induce cognitive deficits, whereas neuropsychological motor functions such as finger-tapping speed or manual dexterity were not affected by these lesions.

Additionally, our data support the notion that the posterolateral GPi is primarily a motor region. The findings are in agreement with the concept of multiple, segregated circuits connecting frontal cortex, basal ganglia, and thalamus derived from tracer studies in nonhuman primates (Alexander et al. 1986). The behavioral implications of the parallel circuits, however, had been difficult to study so far. The use of DBS for research purposes now opens up the possibility of manipulating the state of a selective human brain structure and investigating the behavioral consequences with elaborated methods and paradigms from experimental psychology. Future studies, by carefully manipulating cognitive and motor requirements of the investigated tasks and relating them to the exact topography of the stimulated brain area, may uncover the involvement of subcortical structures in a variety of other cognitive and motor operations.

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