Hugues Duffau · Nathalie Tzourio
Dominique Caparros-Lefebvre · Fabrice Parker
Bernard Mazoyer

Tremor and voluntary repetitive movement in Parkinson’s disease: comparison before and after L-dopa with positron emission tomography

Received: 17 July 1994 / Accepted: 28 August 1995

Abstract Brain regions involved in tremor and voluntary movement were compared in seven subjects with hemiparkinsonian tremor using positron emission tomography and the [15O]water bolus activation method. Repeated measurements of the regional cerebral blood flow were performed both before and after tremor arrest induced by administration of L-dopa as well as during voluntary repetitive movements of the hand contralateral to tremor side. The normalized regional cerebral blood flow (NrCBF) was measured in regions of interest with anatomical boundaries that were defined for each subject by means of a three-dimensional reconstruction of magnetic resonance imaging data. Taking the rest after L-dopa as a control condition, NrCBF increased during tremor in a network of regions including the precentral (mean_±SD 5.36±4.6%, P=0.006) and paracentral (6.11±6%, P<0.01) gyri contralateral to tremor side, the supplementary motor area (SMA; 4.03±4%, P=0.02, n=8 pairs), and the cerebellar vermis (8.64±9.9%, P=0.01, n=12). During voluntary repetitive movement of the hand contralateral to tremor compared with rest after L-dopa, the same patients activated the precentral (8.25±2.6%, P=0.0006) and postcentral regions contralateral to movement (8.43±3.7%, P=0.002), and the cerebellar cortex (3.49±2.1%, P=0.03), precentral (3.58±3.1%, P=0.04), and paracentral (4.03±3.6%, P=0.04) regions ipsilateral to movement. The cerebellar vermis was activated (8.15±5.6%, P=0.02, n=8) as well as the SMA, but not significantly at the 0.05 level (5.16±5%, P=0.08, n=5). These results confirm the similarities of brain structures involved in parkinsonian tremor and voluntary movement and provide an anatomofunctional substrate for their clinical interactions.

Key words Parkinsonian tremor · Positron emission tomography · Regional cerebral blood flow · Voluntary movement · Cerebellum · Supplementary motor area · L-Dopa

Introduction

Interactions between tremor and voluntary movement in the parkinsonian patient are an often referred to notion in literature, although the basis of this relationship is not still clearly understood. On the one hand, it is a well-known clinical fact that the execution of a voluntary movement will result in the disappearance of the ipsilateral parkinsonian resting tremor (PRT), while the same movement will, contrarily, increase the PRT on the contralateral side (Cambier et al. 1994). On the other hand, it has been proved that the parkinsonian tremor can cause an acceleration of repetitive voluntary movements, the maximum frequency of the PRT being also the upper limit of frequency of these movements (Logigian et al. 1991).

Using positron emission tomography (PET) and the [15O]water brain activation paradigm, we previously studied PRT in parkinsonian patients bearing thalamic stimulators. Normalized regional cerebral blood flow (NrCBF) was compared during PRT and after PRT was stopped by thalamic electrical stimulation. NrCBF increases were observed during PRT in the precentral, postcentral, and paracentral gyri of the hemisphere contralateral to tremor side, as well as in the supplementary motor area (SMA), and bilaterally in the cerebellum. These results led us to postulate the existence of a common network of cerebral areas involved in tremor and voluntary repetitive movements and to consider the PRT
as an involuntary running of a program of motor behavior (Parker et al. 1992).

One could argue, however, that the activations of motor areas observed in our previous study were an epiphenomenon of the thalamic stimulation, the cerebellum being the main generator of parkinsonian tremor (Deiber et al. 1993). To document this issue further, we designed an experimental PET activation protocol in parkinsonian patients in which: (1) tremor was arrested using L-dopa instead of electrical thalamic stimulation, and (2) both tremor and voluntary repetitive movements were studied in the same subjects.

This work has been presented in part at the 45th Annual Meeting of the American Academy of Neurology (New York, April 1993).

**Materials and methods**

**Patients**

We selected seven right-handed patients suffering from idiopathic Parkinson's disease on the basis of the presence of a predominantly unilateral tremor, controlled by L-dopa therapy. Before the PET study, all patients had undergone an acute pharmacological test to assess the response of tremor to drugs. We used the L-dopa test described by Esteguy (Esteguy et al. 1985). It is comparable with the acute apomorphine test, but induces fewer adverse effects (Gauthier and Nutt 1987). After 12 h of L-dopa withdrawal, the patients received 200 mg of L-dopa in the early morning. Tremor and other parkinsonian symptoms were rated every 30 min. If tremor disappeared completely during the L-dopa test, for a period of 90 min at least, the patient was selected for the PET study. The examinations were conducted after patients had given their informed written consent.

Clinical characteristics of the patients are given in Table 1. The Parkinson's disease diagnosis was based on the clinical criteria defined by the UKPD Society Brain Bank (Hughes et al. 1992). Tremor was evaluated according to the unified Parkinson's disease rating scale (UPDRS) before and after L-dopa administration, using the clinical score of Fahn (Fahn et al. 1987). The patients' mean age was 66 years (range 60–77 years), and mean disease duration was 9 years (range 2–14 years). Their Hoehn and Yahr score (Hoehn and Yahr 1967) is given in Table 1. All patients were under L-dopa therapy, with a daily dose varying from 325 to 750 mg. Two patients showed a unilateral tremor of the superior and inferior limbs, two patients presented a unilateral tremor affecting the superior limb only, the last three showing a bilateral but predominantly unilateral tremor. Four out of the seven patients exhibited an akinetic-rigid syndrome. None of the patients had clinical signs of dementia and their magnetic resonance imaging (MRI) tomogram confirmed the absence of cortical or subcortical atrophy. One patient's MRI tomogram (patient 4) showed bilateral thalamic infarcts.

**Experimental protocol**

All antiparkinsonian treatments were stopped 24 h before the PET study. PET measures were split into two sessions: before L-dopa and 1 h after administration of one 300-mg dose of L-dopa that induced tremor arrest. Patients' tremor was evaluated using the Hoehn and Yahr score during each NrfCBF measurement (see Table 2).

Four NrfCBF measures were obtained during each session, replicating a series of two conditions: tremor and voluntary repetitive movement (first session before L-dopa), rest and voluntary repetitive movement (second session after L-dopa; see Fig. 1). The rest condition consisted in lying quietly and no instruction was given except to avoid head movements. The movement condition consisted of repetitive opening and closing of the hand contralateral to the side of the tremor at a frequency of 1 Hz. The task performance was controlled by a physician, without any quantitative recording such as electromyography (EMG) or accelerometry. The task was started 45 s before the [15O]water-bolus injection and pursued during the data acquisition period. All examinations were completed in darkness.

Table 2 gives tremor scores and their time course during each of the NrfCBF PET acquisitions, for each patient. Tremor was stopped in all cases by a single dose of L-dopa and reappeared, although less intense during the movement condition, in the superior and inferior limbs or limited to the superior limb contralateral to the movement in three out of the six subjects.

**Imaging protocol**

For each of the seven subjects, MR and PET images were acquired on the same day. MR images were obtained using a 0.5-T MR imager (MRMAX; General Electric, USA). A dataset of about forty 3-mm-thick, contiguous axial slices was acquired. NrfCBF

---

**Table 1 Patients' clinical characteristics (Sup superior, Inf inferior, UPDRS unified Parkinson's disease rating scale)**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Hoehn and Yahr score</th>
<th>Disease duration (years)</th>
<th>Tremor score UPDRS</th>
<th>Akinesia</th>
<th>L-dopa daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>65</td>
<td>II</td>
<td>5</td>
<td>Sup limb 2</td>
<td>Sup limb 1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>II</td>
<td>13</td>
<td>Inf limb 1</td>
<td>Inf limb 2</td>
<td>Axial</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>II</td>
<td>6</td>
<td>Sup limb 2</td>
<td>Sup limb 2</td>
<td>Right sup limb</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>II</td>
<td>2</td>
<td>Inf limb 0</td>
<td>Inf limb 0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>II</td>
<td>14</td>
<td>Sup limb 3</td>
<td>Sup limb 2</td>
<td>Right hemibody</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>III</td>
<td>11</td>
<td>Sup limb 0</td>
<td>Sup limb 3</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>II</td>
<td>3</td>
<td>Sup limb 2</td>
<td>Sup limb 1</td>
<td>Right sup limb</td>
</tr>
</tbody>
</table>