Disconnecting force from money: effects of basal ganglia damage on incentive motivation

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Bilateral basal ganglia lesions have been reported to induce a particular form of apathy, termed auto-activation deficit (AAD), principally defined as a loss of self-driven behaviour that is reversible with external stimulation. We hypothesized that AAD reflects a dysfunction of incentive motivation, a process that translates an expected reward (or goal) into behavioural activation. To investigate this hypothesis, we designed a behavioural paradigm contrasting an instructed (externally driven) task, in which subjects have to produce different levels of force by squeezing a hand grip, to an incentive (self-driven) task, in which subjects can win, depending on their hand grip force, different amounts of money. Skin conductance was simultaneously measured to index affective evaluation of monetary incentives. Thirteen AAD patients with bilateral striato-pallidal lesions were compared to thirteen unmedicated patients with Parkinson's disease (PD), which is characterized by striatal dopamine depletion and regularly associated with apathy. AAD patients did not differ from PD patients in terms of grip force response to external instructions or skin conductance response to monetary incentives. However, unlike PD patients, they failed to distinguish between monetary incentives in their grip force. We conclude that bilateral striato-pallidal damage specifically disconnects motor output from affective evaluation of potential rewards.

Keywords: apathy; anoxic/ischaemic damage; Parkinson's disease; reward; effort

Abbreviations: AAD = auto-activation deficit; GFR = grip force response; MADRS = Montgomery and Asberg depression rating scale; MMSE = mini mental state examination; MRI = magnetic resonance imaging; MVC = maximal voluntary contraction; PD = Parkinson's disease; SCR = skin conductance response; UPDRS III = unified Parkinson's disease rating scale III

Introduction

In 1981, a 25-year-old businessman became dramatically inactive following encephalopathy caused by a wasp bite. The patient would spend hours lying awake on his bed, asking no questions and expressing no interest in anybody. When stimulated, however, he was able to perform complex activities, such as playing high-level bridge. This was the first description of a syndrome characterized by a lack of self-initiated behaviour with preserved expression of motor and cognitive abilities when externally driven (Laplane et al., 1981). Here, following Laplane and Dubois (2001), we term this syndrome ‘auto-activation deficit’, although further cases received various names, such as ‘athymhoria’, ‘psychic akinésia’ and ‘reversible inertia’ (Luaute and Saladini, 2001; Habib, 2004). Typically, these patients do not complain about their situation and do not feel bored, frustrated or depressed, even if they correctly acknowledge that their behaviour has radically changed. When asked about what they think, they may say that their mind is empty or blank. When receiving good or bad news,
they may show appropriate emotional reactions, but without external stimulation they rapidly return to their habitual neutral state. Brain scans have revealed that such a syndrome is due to bilateral lesions of the striato-pallidal complex (Laplane et al., 1989).

Auto-activation deficit (AAD) may shed light on basal ganglia function. In modern terminology, AAD could reflect dysfunction of incentive motivation, which refers to a process that energizes behaviour according to the expected goal or reward (Berridge, 2004). Indeed, we recently showed that, in healthy volunteers, basal forebrain regions surrounding the ventral pallidum activate bilaterally in proportion to expected rewards, driving physical effort (Pessiglione et al., 2007). Conversely, we hypothesized that damage to these regions should prevent patients from adapting their effort in relation to expected rewards. However, consistent with AAD reports, patients should remain able to modulate their effort according to external instructions. To assess these predictions, we adapted our original behavioural paradigm, dissociating externally from self-driven conditions. In the externally driven condition, subjects are explicitly instructed about how hard they must squeeze a hand grip. In the self-driven condition, subjects are free to squeeze the hand grip as they wish, but are aware that the higher the force exerted the larger the monetary payoff. The manipulation consists in varying the instructed force (in the externally driven condition) or the monetary incentive (in the self-driven condition), to test whether subjects vary their force accordingly. Furthermore, to better specify dysfunction of incentive motivation in the self-driven condition, we also measured skin conductance, which has been shown to reflect autonomic sympathetic arousal (Bauer, 1998; Critchley, 2002), and which is considered in our case to reflect affective evaluation of the monetary incentives. A specific deficit in incentive motivation would mean that affective evaluation of the expected reward is preserved (normal skin conductance response) but does not consistently activate behaviour (impaired grip force production).

We reasoned that AAD would be interesting to contrast with Parkinson’s disease (PD), which also affects basal ganglia functioning (due to striatal dopamine depletion) and reduces self-initiated behaviour. Indeed, self-initiated movements were reported to be more impaired than externally guided movements in PD patients (Jahanshahi et al., 1995; Burleigh-Jacobs et al., 1997; Kelly et al., 2002). Poverty of movements (akinesia), a cardinal symptom of PD, is commonly considered to be a motor symptom, but, interestingly, some authors have suggested it could result from a motivational deficit in energizing muscle contractions (Hallett and Khoshbin, 1980; Agid et al., 2003; Mazzoni et al., 2007). Furthermore, PD patients score high on apathy scales, revealing loss of interest and flattening of affect (Starkstein et al., 1992; Isella et al., 2002; Pluck and Brown, 2002; Aarsland et al., 2005; Kirsch-Darrow et al., 2006). Apathy in PD has been proposed to result from dopamine depletion, as it improves with the use of levodopa medication (Czernecki et al., 2002). This might relate to the well-established role of dopamine in reward processing in both monkeys (Schultz et al., 1997; Schultz, 2000, 2007) and humans (Frank et al., 2004; Knutson et al., 2004; Pessiglione et al., 2006). To further explore the impact of dopamine depletion on incentive motivation, we included in our study, in addition to AAD patients and healthy matched controls, a group of PD patients in their ‘off state’, following overnight withdrawal from medication. Using the present behavioural paradigm, we searched in both groups of patients for dissociations between performance in instructed (externally driven) and incentive (self-driven) tasks, and between skin conductance (affective) and grip force (motor) responses in the incentive condition. We then searched for correlations between these measures of behavioural performance and ratings of both apathy, on Starkstein’s scale (Starkstein et al., 1992), and akinesia, on the Unified Parkinson’s Disease Rating Scale III (UPDRS-III).

Methods
Subjects
All study procedures were approved by the local ethics committee and written consent was obtained from all subjects. Subjects were informed that they would not be paid for their participation and that the monetary incentives used for behavioural assessment were fictive. Data were obtained from 26 healthy subjects, 13 patients with AAD and 13 patients with PD (Table 1).

Healthy subjects were screened for any history of neurological or psychiatric conditions. Initially, we divided the control group into two sub-groups of 13 healthy subjects, each matched to one patient group. However, because their behavioural results were not significantly different, we pooled all healthy subjects together, forming an extended control group (n = 26) with age ranging from 22 to 80 years. We checked that in this extended control group, the experimental dependent variables were not significantly influenced by age, gender or education level.

PD patients were consecutive candidates for deep brain stimulation, hospitalized for a clinical pre-operative examination. Inclusion criteria were a diagnosis of idiopathic PD, with a good response to levodopa (>40% improvement on the UPDRS-III scale), in the absence of dementia (MMS score >25) and depression (MADRS score <20). The mean disease duration was 9.7 ± 1.3 years (range 7–19 years). PD patients were assessed in their ‘off’ state, in the morning after overnight (>12 h) withdrawal of any medication.

AAD patients were tested during their hospitalization for a multi-approach investigation of the AAD. Inclusion criteria were history of AAD and bilateral lesions of the basal ganglia, either from a vascular or anoxic incident. AAD diagnosis was based on the symptoms described by Laplane and Dubois (2001), and quantified using a French rating scale (Habib, 1995), for which we provide an English version in the Supplementary material. Two patients had additional lesions outside the basal ganglia (Supplementary Table 1). AAD patients were undergoing various treatments (Supplementary Table 2), but were tested as PD patients in the morning, after overnight withdrawal of any medication. We checked that the main effects of incentives and instructions (Table 1) hold when removing from analysis the AAD patients.
Table 1 Demographic, clinical and behavioural data

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=26)</th>
<th>AAD patients (n=13)</th>
<th>PD patients (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laterality (R/L)</td>
<td>24/2</td>
<td>13/0</td>
<td>13/0</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>(13/13)</td>
<td>(8/5)</td>
<td>(2/11)</td>
</tr>
<tr>
<td>Age (years) ± SEM</td>
<td>45.8 ± 3.8</td>
<td>48.0 ± 5.0</td>
<td>51.1 ± 3.6</td>
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<tr>
<td>Education (years) ± SEM</td>
<td>6.2 ± 0.2</td>
<td>5.2 ± 0.4</td>
<td>5.1 ± 0.5</td>
</tr>
<tr>
<td>MMS score ± SEM</td>
<td></td>
<td>24.7 ± 0.9</td>
<td>28.8 ± 0.3</td>
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<tr>
<td>UPDRS III score</td>
<td>10.7 ± 3.2</td>
<td>17.7 ± 19.1</td>
<td>7.8 ± 1.2</td>
</tr>
<tr>
<td>Starkstein score ± SEM</td>
<td></td>
<td>41 ± 1.9</td>
<td>40.0 ± 8.0</td>
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<tr>
<td>MADRS subscore ± SEM</td>
<td>2592 ± 22.9</td>
<td>258.2 ± 42.0</td>
<td>252.2 ± 25.4</td>
</tr>
<tr>
<td>Maximal voluntary contraction ± SEM</td>
<td>295 ± 1.1%</td>
<td>24.9 ± 3.0%</td>
<td>23.3 ± 3.2%</td>
</tr>
<tr>
<td>Instructed grip force (80–40%) ± SEM</td>
<td>18 ± 1.9%</td>
<td>-0.6 ± 1.6% (NS)</td>
<td>6.9 ± 2.0%</td>
</tr>
<tr>
<td>Incentive grip force (50–1€) ± SEM</td>
<td>19.5 ± 3.4%</td>
<td>77 ± 2.2%</td>
<td>6.0 ± 2.2%</td>
</tr>
<tr>
<td>Incentive skin conductance (50–1€) ± SEM</td>
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*Behavioural measure showing a significant difference between instructions or incentives (paired t-test, P < 0.05); NS = non significant. SEM = standard error mean; MMS = mini mental state; UPDRS III = unified PD rating scale III; MADRS = Montgomery and Asberg depression rating scale. Note MADRS subscore (max is 36) only includes items related to dysphoria and vegetative symptoms, excluding those related to apathy.

Lesion localization

T1-weighted structural scans were acquired using an MRI scanner (GE Medical Systems, Milwaukee, Wisconsin, USA) of 1.5T for 10 AAD patients and of 3T for the remaining three AAD patients. The lesions of the 13 patients were manually segmented using MRIcro (Rorden, 1999-2005, Columbia, USA, http://www.sph.sc.edu/comd/rorden/mricro.html). Regions of interest corresponding to the segmented lesions were normalized to the MNI space using Statistical Parametric Mapping (SPM5) software (Wellcome Trust Centre for NeuroImaging, London, UK), then summed and registered to a canonical T1 template for illustration (Fig. 1).

Behavioural tasks

All subjects used their dominant hand to perform the tasks. Prior to performing the tasks, subjects were asked to squeeze the hand grip as hard as they could. The maximum reached over three trials was taken as the maximal voluntary contraction (MVC), which served as individual reference for both the instructed and incentive force tasks. The two tasks (Fig. 2) were programmed on a PC using Paradigm [Paradigm, e(ye)BRAIN, Paris, France, www.eye-brain.com]. Levels for instructions and incentives were selected from a preliminary study, where they were found to linearly increase grip force response in healthy subjects (Supplementary Fig. 1).

The instructed task was designed to assess whether subjects were able to modulate their force according to instructions. Subjects were told to squeeze the hand grip so as to reach the red line displayed on a computer screen. The red line could correspond to 40, 80 or 120% of MVC. The red line was drawn on a grid graduated from 0 to 100, which was scaled such that the 50 line corresponded to MVC. Thus, the 40, 80 and 120% were indicated by red lines drawn at 20, 40 and 60 on the grid. This number was shown on the screen at the start of every trial, so the subjects could prepare in advance. At the end of every trial, subjects were shown a written feedback (correct or incorrect), indicating whether they succeeded or failed.

The incentive task was designed to assess whether subjects would modulate their force according to incentives. They were not told what to do, but only that the more they squeezed the grip, the more they would win of the monetary incentive, which could be 1, 10 or 50 €. The monetary incentive was assigned to the top of the grid, which was scaled as in the instructed task. Thus, when subjects attained their MVC, they reached the midline and won half of the monetary incentive. The sequence of screenshots was kept as close as possible to the instructed task: first was shown the monetary incentive (instead of instructed force), then the graduated scale with the incentive at the top (instead of the red line), and finally the feedback (cumulative total instead of correct/incorrect). The cumulative total (of the money won so far) was indicated by an arrow pointing on an analogue scale (Fig. 1).

The instructed task included 12 trials, meaning four trials per instructed force. The incentive task included 45 trials, meaning 15 trials per monetary incentive. The order of trial types (instructed forces or monetary incentives) was randomized in both tasks. The instructed task was performed both before and after the incentive task, to control for fatigue effects on the ability to control one’s hand grip force. Because no significant difference was found between the two assessments, we pooled them together for the analyses presented hereafter.

Data recording

Force was recorded using a ‘pinch grip’ (MIE medical research ltd., Leeds, UK), with a sample rate of 25 Hz. The recorded signal was digitalized and fed into the PC running the task program [Paradigm, e(ye)BRAIN, Paris, France, http://www.eye-brain.com]. The stimuli presentation PC provided subjects with real time...
visual feedback of the force being exerted on the grip, as a cursor moving up and down a grid.

Skin conductance was recorded using Ag/AgCl electrodes (1 cm diameter) taped on the palmar surface of the midfinger and forearm of the non-dominant hand. The signal was fed into a skin conductance processing unit (Psylab SC5 Stand Alone Monitor System, Contact Precision Instruments, London, UK). The filtered analogue of the skin conductance was displayed online and recorded digitally, with a sample rate of 200 Hz, on a supplementary PC that received event markers from the PC running stimuli presentation and recording grip force. Skin conductance recordings were then down sampled to the frequency of motor acquisition (25 Hz).

**Data analysis**

To analyse grip force response (GFR), we extracted in every trial both the maximum reached and the area under the curve over the 0–5 s period following onset of the graduated scale. For illustration purposes, we chose the maximum in the instructed task, to allow direct comparison with instructions, and the area in the incentive task, to take into account how long in addition to how hard subjects tried. We conducted all analyses on both measures; results did not significantly differ. Skin conductance response (SCR) was taken as the difference between the maximum reached within the 2–9 s period and the minimum within the 0–2 s period following onset of the graduated scale. Both parameters, grip force and skin conductance, were expressed in proportion to the highest measure, to eliminate individual differences in maximal grip force and skin conductance. Moreover, because grip force and skin conductance might be compromised in AAD or PD independently of motivational deficits, we used differential instead of absolute measures. To assess modulation of grip force in the instructed task, we compared the 80% to the 40% condition. We chose 80 and 40% because it grossly fits the range of forces produced during the incentive task, and because subjects tended to stop...
trying their best in the 120% condition when they realized they could not reach the red line. To assess modulation of both grip force and skin conductance in the incentive task, we compared between the 50€ and the 1€ conditions. Affective and motor responses refer to these differences (50–1€) calculated for skin conductance and grip force, respectively. The null hypothesis was tested using one-tailed paired t-tests for within-group comparisons, two-tailed t-tests for two-group comparisons and analysis of variance (ANOVA) for three-group comparisons and interactions. Correlations between behavioural performance and demographic or clinical factors were searched using Pearson’s correlation coefficient.

Results
Patients
Examination of MRI scans (Fig. 1A) confirmed that all AAD patients had bilateral basal ganglia damage. More precisely, lesions were located in the caudate nucleus ($n = 6$), the putamen ($n = 8$) and the pallidum ($n = 3$). We also observed bilateral atrophy of the striatum accompanied by an enlargement of the lateral ventricles ($n = 7$). Superimposition of individual lesions (Fig. 1B) showed that damage was heterogeneous across patients, with a low lesion rate in all voxels: maxima were four in the caudate nucleus, five in the putamen and three in the pallidum. There were several significant differences (two-tailed $t$-test, $P < 0.05$) between AAD and PD patients (Table 1). As one could expect in a comparison between anoxic–ischaemic damages and degenerative disorders, AAD patients were younger than PD patients. Unfortunately, chance in the recruitment lead to more males being included in the PD group. AAD patients had some Parkinsonian signs as apparent in UPDRS-III ratings, but much fewer than PD patients. In contrast, they had higher apathy scores on Starkstein’s scale, as well as lower scores in the mini mental state examination (MMSE).

Instructed versus incentive tasks
Prior to examining differential effects of instructions and incentives, we checked that no significant difference in maximal forces existed between groups (one-factor ANOVA, $F_{2,49} = 0.015; P > 0.95$).

We first performed a 3-way ANOVA on GFR, including group (AAD versus PD) as a between factor, task (instructed versus incentive) and level (80 versus 40% for instructions or 50 versus 1€ for incentives) as within factors. We found no main effect of group ($F_{1,24} = 0.32$, $P > 0.5$), no interaction between group and task ($F_{1,24} = 0.01$, $P > 0.5$) and no interaction between group and level ($F_{1,24} = 0.96$, $P > 0.25$). However, the interaction between group, task and level was significant ($F_{1,24} = 5.39$, $P < 0.05$). We then performed post hoc $t$-tests to show that deficits specifically concerned AAD patients during the incentive task, where motor activation must be self-driven.

In the instructed task (Fig. 2A), control subjects, PD patients and AAD patients were equally able to modulate their force according to the instructions (Fig. 3). The difference in GFR between 80% and 40% instructions was significant for all three groups (one-tailed paired $t$-tests; $t_{37} = 26.4$, $t_{12} = 7.3$ and $t_{12} = 8.4$; all $P < 0.001$). There was no difference between the groups compared two by two (two-tailed $t$-tests; $t_{37} = 2.2$; $t_{37} = 1.8$ and $t_{24} = 0.4$; all $P > 0.05$).

In the incentive task (Fig. 2B), control subjects and PD patients modulated their grip force according to the magnitude of the incentive (Fig. 3). The difference in GFR between 50 and 1€ trials was significant in both groups (one-tailed paired $t$-test; $t_{37} = 9.3$ and $t_{12} = 3.4$; both $P < 0.01$), but smaller in PD patients compared to control subjects (two-tailed $t$-test; $t_{37} = 3.6$; $P < 0.001$). In contrast to PD patients and control subjects, AAD patients made no difference between 50 and 1€ trials (one-tailed paired $t$-test; $t_{12} = -0.4$; $P > 0.5$). Differential GFR between 1 and 50€ was significantly lower in AAD than in PD patients (two-tailed $t$-test; $t_{24} = 2.9$; $P < 0.01$). Although AAD patients produced more force for 1€, and less force for 50€, no post hoc comparison with PD patients, made separately for the different incentives, was significant (two-tailed $t$-test; $t_{24} = -1.3$, $t_{24} = -0.39$ and $t_{24} = 0.4$; all $P > 0.1$).
We therefore cannot know whether AAD patients failed to exert more force on higher incentives or to retain their force on lower incentives. More cautiously, we conclude that AAD patients failed to modulate their force according to monetary incentives.

**Skin conductance versus grip force**

We started with a 3-way ANOVA restricted to the incentive task, including group (AAD versus PD) as a between factor and response (SCR versus GFR) and level (50 versus 1€) as within factors. We found no main effect of group ($F_{1,24} = 0.09, P > 0.5$), no interaction between group and response ($F_{1,24} = 0.08, P > 0.5$) and no interaction between group and level ($F_{1,24} = 1.52, P > 0.25$). However, the interaction between group, response and level was significant ($F_{1,24} = 7.91, P < 0.01$). We then performed post hoc t-tests to show that deficits specifically concerned the motor response of AAD patients, without affecting the affective response to monetary incentives.

In control subjects, as well as in PD and AAD patients, the amplitude of SCR was greater for higher monetary incentives (Fig. 3). The difference in SCR between 50 and 1€ trials was significant in all three groups (one-tailed paired t-test; $t_{25} = 5.8$, $t_{12} = 2.8$ and $t_{12} = 3.6$; all $P < 0.01$). With respect to between-group comparisons, the SCR of both AAD and PD patients was significantly reduced in comparison to the SCR of control subjects (two tailed t-tests; $t_{37} = 2.6$ and $t_{37} = 2.3$; both $P < 0.01$). There was no significant difference in SCR between AAD and PD patients (two-tailed t-tests; $t_{34} = 0.5; P > 0.5$).

Thus, relative to controls, affective and motor responses in PD patients were reduced but still in proportion to monetary incentives. Relative to PD patients, AAD patients showed similar affective evaluation of monetary incentives, but failed to translate this affective evaluation into motor activation. Note this dissociation is also illustrated at the individual level in Supplementary Fig. 2.

**Correlations with demographic and clinical data**

Correlations were searched between GFR or SCR measured during the incentive task and demographic (age, gender and educational level) or clinical (Starkstein, UPDRS-III and MMSE scores) data, across the two groups of patients. The only significant correlation was found between GFR and Starkstein’s apathy score (Pearson's coefficient = −0.61, $P < 0.01$); all other correlation coefficients were below 0.5. Thus, the more severe the apathy, the lower the differential impact of monetary incentives on the force produced. When considering PD/AAD groups, respectively, correlations of GFR with apathy scores were not significant; Pearson’s coefficients were −0.52/−0.45 for GFR, and −0.57/−0.42 for SCR.

**Discussion**

Here, we assessed the behavioural performance of PD patients (suffering from dopamine depletion) and AAD patients (suffering from bilateral basal ganglia damage) on both instructed and incentive force tasks. The instructed task ensured that all patients were able to normally modulate their hand grip force according to external guidance. The incentive task revealed apathy in PD as an equal flattening of motor and affective responses, but apathy in AAD as a dissociation of motor activation from affective evaluation.

The only significant difference in our behavioural assessment between PD and AAD patients was found in the ability to modulate hand grip force according to monetary incentives. This difference could in principle be related to other differences noted in the demographic and clinical data: namely age, sex, UPDRS-III, MMSE and apathy scores. It seems difficult to conceive why age or sex would dissociate motor from affective responses. Parkinsonian signs might have interfered with the incentive task, but we controlled for this in the instructed task, where motor ability was efficient enough to accurately produce the required levels of force. Cognitive ability might also play a role in the incentive task, possibly by working out a strategy to save energy for when the monetary stakes are higher. However, we previously demonstrated that modulation of grip force occurs even without conscious awareness of the monetary incentives (Pessiglione et al., 2007), which suggests that the task involves basic motivational process rather than sophisticated executive control. In addition to these arguments, no correlation was observed between age, sex, UPDRS-III or MMSE scores and differential effect of monetary incentives on grip force. The only significant correlation was with apathy scores as measured by Starkstein’s scale (Starkstein et al., 1992). We therefore suggest that the incentive force task provides an independent, direct and objective assessment of apathy.

Apathy in PD was characterized by a reduction of both motor and affective responses to monetary incentives. This finding accords well with clinical descriptions of apathetic PD patients, which point out loss of interest, flattening of affect and poor behavioural activity (Pluck and Brown, 2002; Aarsland et al., 2005; Kirsch-Darrow et al., 2006). A likely cause of such apathetic signs is dopamine depletion, as patients were assessed while off their medication, although the contribution of other lesions observed in PD cannot be excluded (Braak et al., 1995). We must remain cautious, however, of our conclusions regarding the role of dopamine in incentive motivation, since we do not know the degree and regional extent of dopamine depletion in our PD patients. Further investigation of treatment effects (notably dopaminergic medication and deep brain stimulation) would be necessary to specify the role of dopamine in the incentive force task. Our data show nonetheless that, beyond the flattening of affective and motor responses, the
process that translates higher expected rewards into harder physical efforts is relatively preserved in PD. This is consistent with reports that reward preference still impacts behavioural performance in a primate model of PD (Pessiglione et al., 2004). Such functional preservation might be due to spared dopaminergic innervation of the limbic circuits passing through the basal ganglia, which was observed in both Parkinsonian monkeys (Jan et al., 2003) and PD patients (Kish et al., 1988). These limbic circuits, originating from the orbital and medial prefrontal cortices, and including the ventral striatum and ventral pallidum, have been suggested to play a key role in anticipating reward and motivating behaviour (Alexander et al., 1986; Robbins and Everitt, 1996; Brown and Pluck, 2000; Heimer and Van Hoesen, 2006; Salamone et al., 2007).

Apathy in AAD was characterized by a dissociation of motor response to incentives from both motor response to instructions and affective response to incentives. This finding accords well with clinical descriptions of AAD patients, as being able to activate behaviour under external instructions but not out of their own interests (Laplane et al., 1982; Ali-Cherif et al., 1984; Habib and Poncet, 1988; Trillet et al., 1990). In the incentive task, patients are under external stimulation, as they are asked by the experimenter to squeeze the hand grip. This they could do, but, crucially, they failed to differentiate between monetary incentives, missing the component of motor activation that should be driven by their financial interests. Because affective evaluation of monetary incentives and motor control of required forces were both correct, we suggest that the deficit lies between the two, in the process that translates expected rewards into motor activation. Such dysfunction of incentive motivation appeared to result from damage to the striato-pallidum complex. In some cases, current medication and/or pre-morbid traits may have influenced the behavioural performance. However, medication and history were various, whereas basal ganglia damage was constant, across patients. Furthermore, the link between striato-pallidal stroke and behavioural changes is supported by previous clinical reports (Laplane et al., 1989; Habib, 2004). One important feature of AAD is bilaterality of striato-pallidal damage, as unilateral lesions rarely lead to behavioural inertia or abulia (Bhatia and Marsden, 1994). Unfortunately, although we tried a voxel-based morphometry approach, we were unable to find convincing statistical relationship between a specific cluster and the behavioural deficit. Neither could we disentangle the contributions of focial lesions from those of global atrophy of the striato-pallidial complex. This difficulty relates to the small number of patients combined with the heterogeneity of damage, which resulted in a low lesion rate in every voxel of the striato-pallidial complex. Further studies will be necessary to specify the anatomical basis of incentive motivation dysfunction, notably in terms of fronto-striatal circuitry. Our data show nonetheless that bilateral damage to the striato-pallidal complex interrupts the translation of expected reward into physical effort. This is consistent with the general view that the basal ganglia integrate different domains of information, including those dealing with reward prediction and motor execution (Mogenson et al., 1980; Joel and Weiner, 1994; Yelnik, 2002; Haber, 2003).

In conclusion, our paradigm has proven useful not only in assessing severity of apathy following basal ganglia damage, but also in specifying dysfunction of incentive motivation, in terms of affective versus motor processing. Notably, we show that AAD patients assign adapted affective values to potential rewards, but fail to integrate these values into their motor behaviour. The reverse dissociation, meaning impaired affective response with preserved motor response, could in principle be observed as well, possibly due to amygdala damage. More generally, we suggest the present paradigm might also help understand other types of apathy in humans, such as those observed in depression or schizophrenia.

Supplementary material
Supplementary material is available at Brain online.

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