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Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing

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The ability to learn stimulus-reward associations on the basis of reward prediction errors critically depends on the mesolimbic dopaminergic system including the dopaminergic midbrain and the ventral striatum. It is known that healthy elderly and patients with Parkinson's disease are less proficient than healthy young adults in learning stimulus-reward contingencies, but it is unclear whether this is due to dysfunctional mesolimbic reward prediction or due to deficiency in processing the rewards *per se*. We used a well-established event-related fMRI reward-prediction paradigm to address this question. Young adults showed the well-replicated pattern of midbrain and ventral striatal activation for stimuli that predicted monetary reward when compared with stimuli that predicted neutral feedback. Also, as expected, the predicted reward feedback itself did not elicit a mesolimbic response. Healthy elderly subjects and unmedicated early-stage idiopathic Parkinson's disease patients showed the opposite pattern with an absent mesolimbic reward prediction response, but mesolimbic activation to the reward feedback itself. This suggests that the healthy elderly and Parkinson's disease patients were less proficient in learning the predictive value of the reward cues despite preserved mesolimbic processing of reward prediction errors. Parkinson's disease patients additionally displayed a relatively increased response of the anterior cingulate during reward feedback processing and diminished functional connectivity of the midbrain and ventral striatum. Our results are compatible with existing behavioural evidence that both groups exhibit a particularly pronounced deficit in learning from positive feedback and support the view that a tendency to underestimate expected values of reward cues might underlie this deficit. Furthermore, alterations in reward processing in Parkinson's disease extend beyond accelerated ageing effects and include altered connectivity within the mesolimbic system.

Keywords: ageing; Parkinson's disease; reward; expected value; accumbens; fMRI; functional connectivity

Abbreviations: CS+ = conditioned (i.e. reward-predicting) stimulus; DA = dopamine; NAcc = nucleus accumbens; PD = Parkinson's disease; PFC = prefrontal cortex; SN = substantia nigra; VTA = ventral tegmental area

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Introduction

The ability to learn stimulus-reward associations on the basis of reward prediction errors is generally believed to depend critically upon the functional interplay of the ventral striatum, particularly the nucleus accumbens (NAcc), and the midbrain dopaminergic system. A key mechanism in mesolimbic reward processing is phasic activity of dopamine (DA)-containing neurons in the ventral tegmental area (VTA) and the medial substantia nigra (SN; for a review see Schultz, 2004). During unexpected primary (e.g. food) or secondary (e.g. money) rewards, the NAcc receives dopaminergic signals from these midbrain structures. Once a reward becomes predictable by a conditioned (i.e. reward-predicting) stimulus (CS+), the dopaminergic signal in the NAcc shifts forward from the time of reward outcome to the presentation of the CS+. Conversely, omission of a reward after presentation of a CS+ leads to decrease of DA signalling below baseline.

It has thus been hypothesized that the DA signal in the NAcc codes for both reward prediction and prediction error. In accordance with these findings in animals, human functional neuroimaging studies have reliably shown activation of the dopaminergic midbrain and the ventral striatum during reward anticipation (Knutson and Cooper, 2005). Studies using delayed monetary incentive tasks have essentially shown that the mesolimbic response codes both the unexpected reward (i.e. prediction error) and the prediction of an expected reward upon presentation of a cue (i.e. reward anticipation) (Knutson *et al.*, 2001; O'Doherty *et al.*, 2003; Wittmann *et al.*, 2005, Yacubian *et al.*, 2006). More specifically, the ventral striatal response shift from the time of the reward to the time of the presentation of the CS+ depends upon successful learning of a stimulus-reward relationship (O'Doherty *et al.*, 2003) and increases with the amount of the expected value (Knutson *et al.*, 2005). Several studies have also shown a co-activation of the medial dopaminergic midbrain, i.e. the medial SN and the VTA along with the ventral striatal response to reward prediction (Wittmann *et al.*, 2005; Adcock *et al.*, 2006; O'Doherty *et al.*, 2006). While the fMRI correlates of reward anticipation in the ventral striatum have been relatively well established, the contributions of the medial prefrontal cortex (PFC) and the anterior cingulate are less clear. Activations in these regions have been observed during positive reward outcome of expected rewards (Knutson *et al.*, 2001; Wittmann *et al.*, 2005), but also as a function of reward probability during the anticipation phase (Critchley *et al.*, 2001; Knutson *et al.*, 2005), and it has been suggested that the anterior cingulate/medial PFC might code for the probability component of expected values (Knutson *et al.*, 2005).

These earlier studies had been carried out in healthy, young adults. It is thus far unknown how reductions in dopaminergic neurotransmission, as they occur, for example, in normal ageing or in Parkinson's disease, affect the neural correlates of human reward anticipation and outcome processing. The human dopaminergic system is subject to physiological changes during ageing. PET has revealed loss of both pre- and post-synaptic marker molecules involved in dopaminergic neurotransmission during ageing (Volkow *et al.*, 1998b), which has been associated with psychomotor, cognitive and behavioural parameters (Volkow *et al.*, 1998a; Bäckman *et al.*, 2000; Kaasinen and Rinne, 2002; Erixon-Lindroth *et al.*, 2005; Bäckman *et al.*, 2006).

An extreme case of loss of pre-synaptic dopaminergic function is found in Parkinson's disease (PD), a condition characterized by relatively selective loss of dopaminergic neurons in the SN. While motor symptoms related to degeneration of the nigro-striatal DA pathway dominate the clinical picture in PD, cognitive alterations (Carbon and Marie, 2003) and depressive symptoms (Ishihara and Brayne, 2006) are not uncommon, and converging evidence from behavioural pharmacology and neuroimaging suggests that these findings could at least in part relate to impairment of the mesolimbic and mesocortical DA pathways (Ito *et al.*, 2002; Mattay *et al.*, 2002). While most neuroimaging studies on cognitive dysfunction in PD have focused on frontal-lobe-dependent processes such as working memory and executive function (Cools *et al.*, 2002; Mattay *et al.*, 2002; Rowe *et al.*, 2002), accumulating behavioural evidence suggests that another cognitive process frequently affected in PD is reward-related learning. In a recent study impaired reward-related learning was observed in unmedicated PD patients, that is, under conditions of DA depletion. However, in medicated PD patients, it improved significantly above the level of the healthy age-matched elderly (Frank *et al.*, 2004). Other recent behavioural findings show that normal ageing itself is also associated with a deficit in stimulus-reward learning, which is dissociable from performance in tests assessing executive function (Marschner *et al.*, 2005; Mell *et al.*, 2005).

While both normal ageing and PD have been associated with reduced performance in reward-related learning, little is known about how the neural mechanisms of DA-dependent reward processing in the ventral striatum are affected by ageing or PD. Particularly, it is unclear whether impaired reward-related learning in ageing and PD is related to an impairment in computing dopaminergic prediction errors or to a reduced ability to utilize these prediction errors in computing expected values—a critical mechanism for the generation of future reward predictions. It is also unclear whether alterations of reward-related mesolimbic processing in healthy ageing and PD qualitatively differ from each other.

Here we used event-related functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms underlying reward prediction and reward outcome processing in a cohort consisting of young and elderly healthy subjects and of unmedicated patients with early, unilateral Parkinson's disease. We used a delayed monetary incentive task that has previously been shown in young adults to allow a dissociation of brain activity related to reward prediction and outcome (Wittmann *et al.*, 2005). We reasoned that an impairment in learning stimulus-reward associations and the resulting problem to correctly predict rewards would be associated with reduced mesolimbic reward prediction response. A combination of a reduced prediction response with a preserved response to the reward feedback would show that reward processing and prediction error of reward is preserved which, in turn, would indicate an impairment to use reward prediction errors as learning signals for stimulus-reward associations. A reduced response to the reward feedback itself, on the other hand, would indicate a fundamental dysfunction in mesolimbic reward processing. We conceptualized mesolimbic dysfunction not only as reduction in activity levels but also

considered the possibility of altered functional coupling of the SN/VTA and the NAcc.

Material and methods

Participants

A total of 48 subjects participated in the study, including 18 young, healthy adults (mean age 23.3 years, range 19–28, three left-handed, nine females), 19 healthy elderly adults (mean age 69.0 years, range 62–78, one left-handed, nine females) and 11 elderly patients with early-stage idiopathic Parkinson's disease (mean age 66.4 years, range 62–72 years, all right-handed, three females). Diagnosis of idiopathic PD was confirmed by thorough clinical investigation, asymmetric dopamine transporter reduction in [^{123}I]-FP-CIT single photon emission computed tomography (SPECT) and a positive clinical response to the dopamine precursor L-dopa. Asymmetric hyperechogenicity of the SN as assessed by brain parenchyma sonography was used as a complementary tool to further support diagnosis (Becker *et al.*, 1995; Walter *et al.*, 2003). At the time of participation, all patients had mild, lateralized disease without relevant disability (Hoehn and Yahr stage I), and carried out button press responses with their unaffected side (see later). All patients had been unmedicated for at least 48 h before participation (three patients had previously used L-dopa or a dopamine agonist for no longer than 3 months; all others had never been medicated). All participants gave written informed consent to participate in accordance with the Declaration of Helsinki, and the study was approved by the ethics committee of the University of Magdeburg, Faculty of Medicine.

Experimental paradigm

The experimental paradigm has previously been shown to allow a dissociation of reward anticipation and outcome (Wittmann *et al.*, 2005). This dissociation was achieved by first presenting a cue picture that predicted a potential reward—or the absence of a reward—in a following simple arithmetic task. Reward outcome was then instrumental upon the response in this arithmetic task rather than the response to the cue itself (Kirsch *et al.*, 2003; Wittmann *et al.*, 2005). Before entering the scanner, participants were given a short demonstration of the task and completed a practice version lasting 3.5 min, which was already rewarded. This practice session was intended to reduce learning effects during functional data acquisition and thereby lead to a switching of reward responses from the moment of reward receipt to the time of reward anticipation (Knutson *et al.*, 2001; Wittmann *et al.*, 2005). Furthermore, the reaction times of the subjects obtained from the practice session were used to define individual response deadlines (see later). Once in the scanner, anatomical and functional scans were collected. Participants engaged in two 8-min sessions of the reward task.

Each of the two rewarded sessions consisted of 60 trials lasting 4.6–8.6 s (Fig. 1). During each reward trial, participants saw a grey-scale cue picture (Rossion and Pourtois, 2004) for 1500 ms, responded to it with a button press (index or middle finger) indicating whether they expected a reward or not, waited a variable interval (delay, 500–4500 ms) and then responded to a target number (target, 100 ms) with a button press. 1000 ms after the presentation of the target, a visual feedback (1500 ms) was given. The intertrial interval was jittered from 500 to 4500 ms independently of the jitter between the cue picture and the target

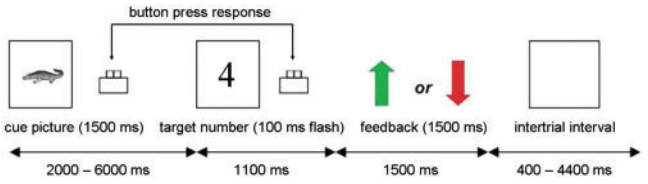

Fig. 1 Trial structure of the reward paradigm, exemplarily shown for a reward trial. On neutral trials, a question mark appeared instead of the green or red arrow.

number, thus leading to a temporal decorrelation of reward anticipation and reward outcome. The trial sequence and temporal jitter had been optimized for a maximally efficient estimation of the hemodynamic response function (HRF) to the different trial types (Hinrichs *et al.*, 2000).

On rewarded trials, 0.50 € reward feedback was represented by a green arrow pointing upward, and loss of 0.20 € was represented by a red arrow pointing downward. On non-rewarded trials, a question mark was shown regardless of outcome. Approximately half of the participants (9 young, 9 elderly, 8 patients) were told that they could gain money in the reaction time task following a picture depicting a living thing or part of a living thing (animal, plant, fruit, vegetable or human body part), the other half rewarded in trials following the presentation of a man-made object. Each category constituted half of the cues.

The number comparison task (Pappata *et al.*, 2002) required participants to decide whether the target number (1, 4, 6 or 9) was larger or smaller than 5. They responded as quickly as possible by a button press with their index or middle finger. Whenever participants responded incorrectly or too slowly for the response deadline in the rewarded trials, a negative feedback was given, otherwise they received a positive feedback. The response deadline was adjusted individually based on reaction times in the immediately preceding session (the training session outside the scanner for the first session) to attain a correct response rate of ~80%, thereby leading to an 80% contingency in rewarded trials. In unrewarded trials, contingency was 100%, as neutral cues were never followed by a rewarded outcome in the number comparison task.

The times of occurrence of target buttons as well as numbers were counterbalanced for each session. To reduce confounding effects of PD-related impairment of motor function on behaviour and fMRI activations, all patients responded with their unaffected hand (as assessed by clinical examination and SPECT), and response hands were counterbalanced for young and elderly healthy controls, so that half of the participants responded with their dominant or non-dominant hand, respectively.

MRI acquisition

Two sessions of 240 T2*-weighted echo-planar images (EPIs) were acquired on a GE Medical Systems Signa 1.5 T MRI scanner at a TR of 2 s and a TE of 35 ms. Images consisted of 23 axial slices [64 × 64, voxel size = 3.13 × 3.13 × 6 mm^3 (slice thickness = 5 mm with 1 mm gap)] and were acquired in an interleaved manner (1 to 23 in steps of 2, 2 to 22 in steps of 2, from bottom to top). Prior to data collection of each session, six EPI volumes were acquired to allow for magnetic field stabilization; these volumes were discarded from the analysis.

Data processing and analysis

Data analysis was performed using Statistical Parametric Mapping (SPM2, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). EPI images were corrected for acquisition delay, realigned to the first image of the session, normalized (voxel size: $3 \times 3 \times 3\,mm^3$) into a common reference frame (Montreal Neurological Institute, MNI) and smoothed using a Gaussian kernel of $8 \times 8 \times 8\,mm^3$. A high-pass filter with a cut-off of 128 s was applied to the data.

Statistical analysis was carried out using a two-stage mixed effects model. In the first stage, the hemodynamic response was modelled by convolving a delta function at stimulus onset with a canonical HRF (Friston *et al.*, 1998). The resulting time courses were downsampled for each scan to form covariates of a general linear model (GLM). The model included separate covariates for each of the conditions of interest (reward-predicting cues, neutral cues, feedback to correct and false responses to reward-predicting and neutral cues, respectively). The six rigid-body movement parameters determined from realignment were included in the GLM as covariates of no interest. In the second stage of the model, contrasts of the parameter estimates for each covariate were submitted to a random-effects analysis, with each participant being treated as a random effect. Specifically, one-sample *t*-tests were computed over images of each contrast of interest (anticipate reward vs. anticipate neutral outcome; positive reward feedback versus neutral feedback to a correct response in the non-rewarded condition) to test overall effects of reward anticipation and reward outcome in the three subject groups. To test for between-group differences, a one-way analysis of variance (ANOVA) was computed over the same contrast images for the three groups, followed by *post hoc* *t*-tests (young versus elderly adults and patients; healthy elderly adults versus patients), using the ANOVA results as an inclusive mask, thresholded at 0.05 (uncorrected). The *a priori* statistical threshold was set to $P = 0.001$ (uncorrected) for all comparisons, with an extent threshold of five adjacent voxels. For anatomical localization all coordinates were transformed into a common stereotactic reference frame (Talairach and Tournoux, 1988).

To investigate the relationship between the response in the NAcc during reward anticipation versus outcome and the behavioural benefit in the rewarded relative to the neutral condition, we computed the relative reaction time (RT) advantages $[(RT_{no\_reward} - RT_{reward})/RT_{no\_reward}]$ for all subjects, separately for responses to cues and to target numbers. Pearson's correlation coefficients were computed between the thus obtained reaction time advantages and the differences of the fitted and adjusted responses in the NAcc during reward anticipation and outcome, respectively (Fig. 3B). Since we hypothesized that reaction time advantages would correlate positively with ventral striatal activation during reward anticipation rather than reward outcome, the significance level for the correlations was set to $P = 0.05$, one-tailed.

Functional connectivity analysis

To investigate the effects of healthy ageing and Parkinson's disease on the neural circuitries between the ventral striatum, the midbrain and the anterior cingulate/medial PFC, functional connectivity analyses were performed. Guided by our results suggesting a right lateralization of the reward anticipation and outcome effects, we selected the right NAcc, a right medial midbrain region (containing the VTA and the right medial SN) and the right rostral anterior cingulate as seed regions. Spheres (radius = 6 mm; containing up to 33 super-threshold voxels) were centered on the individual local maxima of activation within the right NAcc and anterior cingulate, respectively, for each subject; another sphere (radius = 5 mm; containing up to 19 voxels) was centred on the suprathreshold voxel closest to $[x\ y\ z] = [6\ -18\ -15]$ with the lowest z value being –24. The seed voxels belonged to different clusters of activation in all subjects. Representative volumes of interest (VOIs) are depicted in Fig. 5A. The first eigenvariate time series from these VOIs were extracted and adjusted for the effects of interest (Menon and Levitin, 2005). Pearson's correlation coefficients of the resulting time courses in the three VOIs were computed for all subjects. To allow further statistical testing, Fisher's z-transform, an inverse hyperbolic tangent transform was applied to the correlation coefficients to make them approach normal distribution (Fisher, 1921). Whenever the correlation between the time courses of two regions was significantly different from 0 across the entire cohort, between-group comparisons were carried out by computing one-way ANOVAs, followed by *post hoc* *t*-tests when significant effects of subject group were found. The thusly obtained connectivity measures were also submitted to correlation analyses with the overall reaction time advantages for the cue and target responses, as described above for the response differences.

Results

Behavioural results

Table 1 displays demographic data and behavioural results for the three subject groups (young, elderly, PD patients). All participants correctly recognized the cues signalling rewarded or neutral trials, with the recognition rate being highest in young subjects [main effect of subject group: $F(2,45) = 5.34$, $P = 0.008$; ANOVA for repeated measures (per cent correct responses to reward cues versus neutral cues) with subject group as between-subjects factor].

Table 1 Demographic and behavioural data of young healthy subjects, elderly healthy subjects and Parkinson's patients

	Young	Elderly	Patients
N	18	19	11
Age (years)	23.3 (±2.5)	69.0 (±4.0)	66.4 (±3.5)
M/F	9/9	10/9	8/3
% reward cues correct	98 (±2.6)	94 (±10.8)	86 (±20.3)
RT (reward cues)	662 (±106.7)	854 (±100.4)	886 (±237.3)
% neutral cues correct	97 (±3.2)	91 (±9.4)	92 (±10.4)
RT (neutral cues)	736 (±97.0)	889 (±122.4)	907 (±208.2)
% rewarded trials correct	86 (±8.9)	82 (±11.2)	78 (±15.4)
RT (rewarded targets)	503 (±84.9)	581 (±77.4)	585 (±118.5)
% neutral trials correct	77 (±16.7)	80 (±10.5)	73 (±16.5)
RT (neutral targets)	546 (±80.5)	585 (±72.0)	603 (±115.3)

Note: RT: reaction time.

Post hoc *t*-tests revealed that recognition of reward-predicting cues was slightly lower in patients relative to young subjects [$t(27) = 2.57$, $P = 0.016$], and recognition of neutral cues was slightly lower in the healthy elderly relative to the young [$t(35) = 2.40$, $P = 0.022$]. No significant differences were observed in a direct comparison of recognition rates for healthy elderly subjects and patients. Young subjects had shorter reaction times (RTs) to both reward-predicting and neutral cues than elderly subjects or patients, but RTs to reward-predicting cues were shorter than for neutral cues in all subject groups [main effect of reward: $F(2,45) = 6.61$, $P = 0.014$; main effect of subject group: $F(2,45) = 11.23$, $P < 0.001$; no interaction ($P = 0.39$); one-way ANOVA for repeated measures (RT reward cue versus RT neutral cue) with subject group as between-subjects factor].

The average correct response rate to the target cue was higher in rewarded as compared with non-rewarded trials, but there was no difference in response accuracy between the groups, reflecting that individual response timeouts were correctly set by the experimenter [main effect of reward: $F(2,45) = 12.89$, $P = 0.001$; no main effect of subject group or interaction (all $P > 0.17$); ANOVA for repeated measures (per cent correct responses to rewarded vs. non-rewarded trials) with subject group as between-subjects factor]. Reaction times to the target numbers were significantly shorter in rewarded trials than in non-rewarded trials across the entire cohort, with young subjects showing the largest reaction time advantage [main effect of reward: $F(2,45) = 17.17$, $P < 0.001$; interaction reward × subject group: $F(2,45) = 5.46$, $P = 0.008$; the main effect of subject group approached significance [$F(2,45) = 2.94$, $P = 0.063$); one-way ANOVA for repeated measures (RT rewarded trial versus RT non-rewarded trial) with subject group as between-subjects factor]. *Post hoc* *t*-tests comparing reaction times for rewarded and neutral trials within the three groups revealed significant reaction time improvements for rewarded trials only in young healthy subjects [reward anticipation: $t(17) = 5.26$ $P < 0.0001$; reward outcome: $t(17) = 5.76$, $P < 0.0001$], but not in either healthy elderly subjects or patients (all $P > 0.210$).

Neural correlates of reward processing in young subjects

As expected, the reward anticipation contrast which compared reward predicting cues with neutral cues revealed significant activations ($P < 0.001$, $k = 5$ voxels) of several brain regions known to be activated during reward anticipation, including large portions of the dorsal and ventral striatum (bilateral putamen, right caudate, bilateral NAcc), a midbrain region encompassing the VTA and the right SN (Fig. 2, top), the bilateral insula, portions of the medial PFC and the anterior cingulate and the thalamus. Also as expected, reward outcome (reward versus neutral feedback) was not associated with activation of the striatum or midbrain in young subjects. On the other hand, portions of the medial PFC and anterior cingulate were also activated during positive reward outcome in young subjects (Fig. 2, bottom).

Effects of normal ageing and Parkinson's disease on reward-related fMRI activation

Unlike the young, the healthy elderly showed no activation of the ventral striatum and midbrain during reward anticipation. A one-sample *t*-test directed at the neural correlates of reward anticipation in elderly subjects revealed a cluster of activation in the thalamus and a smaller cluster in the right cerebellum at $P < 0.001$ (at $P < 0.005$ additional clusters were observed in the left prefrontal cortex, right precuneus, left amygdala and bilateral dorsal, but not ventral striatum). In contrast to their lack of activation at the time of reward anticipation, elderly subjects showed a robust activation of the ventral striatum during reward

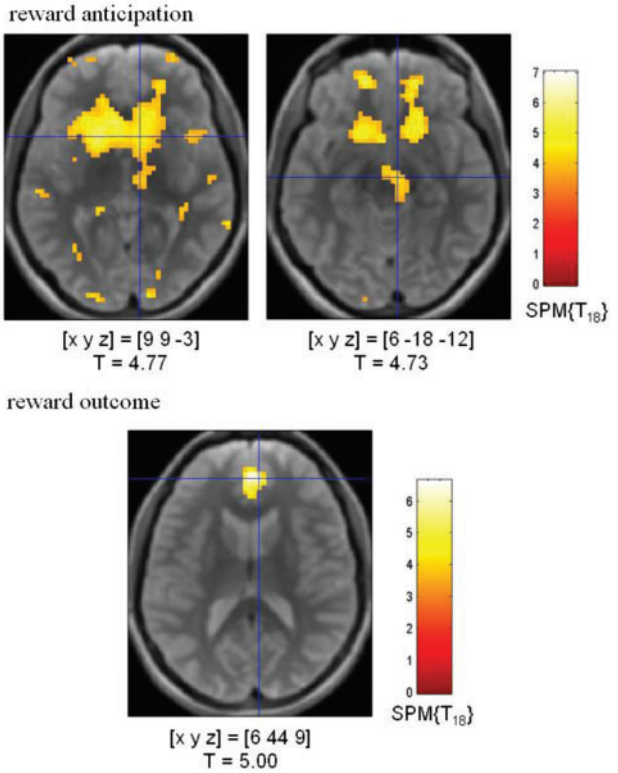

Fig. 2 Neural correlates of reward anticipation and reward outcome in young, healthy subjects. Top: reward anticipation was associated with increased activation of the ventral striatum (left panel) and a midbrain region encompassing the VTA and the medial SN (right panel). Bottom: reward outcome was associated with activation of a large cluster encompassing portions of the anterior cingulate and the medial prefrontal cortex. All coordinates are given in Talairach space. Clusters of activation are shown at $P < 0.001$, uncorrected, with an extent threshold of $k = 5$ adjacent voxels.

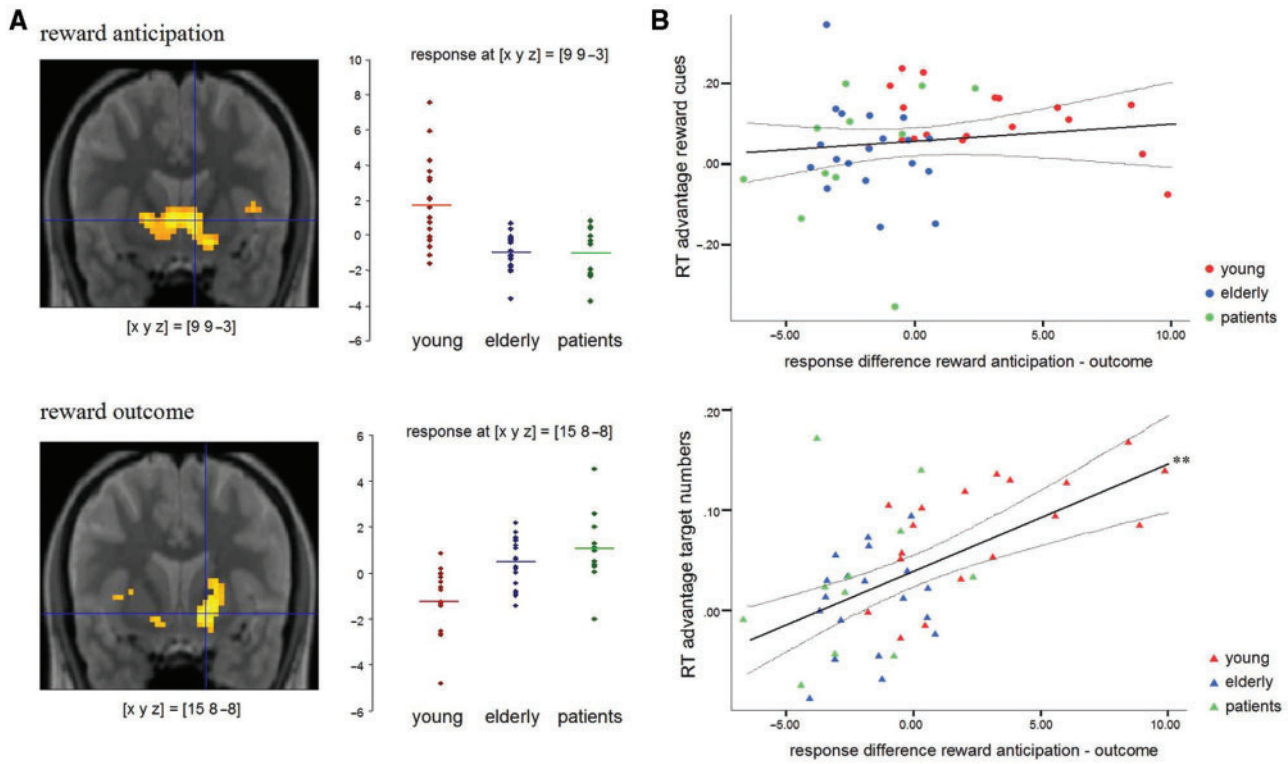

Fig. 3 Age-related alterations of brain responses to reward anticipation and reward outcome. (**A**) Activation of the ventral striatum during reward anticipation (reward cues vs. neutral cues) was significantly higher in the young relative to the healthy elderly and to Parkinson's patients (top). A reverse pattern was observed during reward outcome (positive feedback versus neutral feedback) (bottom). *Y* coordinates in top and middle panel depict the fitted and adjusted response at the denoted peak voxels. See Fig. 4 for more legends. (**B**) The response difference in the ventral striatum (reward anticipation—outcome) was significantly correlated with the reaction time advantage for responses to target numbers, but not to cues. *X* coordinate denotes differences of the fitted responses for reward anticipation versus outcome, *y* coordinate denotes composite ranks of reaction time advantages. Fitted regression lines and 95% confidence intervals of the mean are shown. **: $P < 0.001$.

outcome (reward feedback versus neutral feedback), as revealed by a one-sample *t*-test.

The pattern of ventral striatal activation during reward anticipation versus outcome was essentially similar in patients and in the healthy elderly. While no ventral striatal activation was observed during reward anticipation, the nucleus accumbens was activated bilaterally during reward outcome, i.e. during presentation of the reward feedback image.

To test for the between-group differences, we first computed a one-way ANOVA over the contrast images for reward anticipation and outcome, respectively, followed by *post hoc* two-sample *t*-tests, masked for the ANOVA contrasts. The ANOVA contrasts revealed robust between-group differences in the bilateral ventral striatum during both reward anticipation and outcome. A two-sample *t*-test comparing the brain responses to reward anticipation (reward cues versus neutral cues) in young subjects and healthy elderly subjects revealed significantly higher activations ($P < 0.001$, $k = 5$ voxels) of the ventral and dorsal striatum in young relative to elderly subjects (Fig. 3A, top; Table 2). In a *t*-test statistic of the reward anticipation contrasts of young subjects and patients we observed that patients, similar to the healthy elderly, exhibited a similarly reduced reward anticipation response in the ventral striatum (Fig. 3A, top). There were no significant activation differences between patients and healthy elderly subjects during reward anticipation.

When we directly compared the reward outcome contrasts in young versus healthy elderly subjects and patients, we noted significantly higher activation of several brain regions, including the ventral and dorsal striatum and the insula, in the healthy elderly relative to young subjects (Fig. 3A, bottom; Table 3). Like the healthy elderly, patients also showed significantly stronger activation of the ventral striatum during positive reward feedback when compared with young subjects (Fig. 3A, bottom).

Relatively to the healthy elderly subjects, patients showed clusters of relatively stronger activation in the medial prefrontal cortex/anterior cingulate and also in a midbrain region encompassing the right SN (two-sample *t*-test comparison; Fig. 4; Table 4). Because of the unequal gender distribution in the healthy elderly and patients, an additional *t*-test statistic was computed between the patients

Table 2 Brain regions that showed higher activations for young relative to elderly subjects during reward anticipation

	x	Y	z	SPM {T}
Left Caudate	−3	15	−1	5.31
Right Caudate/Nucl. accumbens	9	6	−3	4.77
Left midbrain/VTA	−6	−24	−11	3.72
Right midbrain/VTA	3	−27	−14	3.61
Left inferior frontal gyrus, BA 46	−42	35	7	3.39
Left middle frontal gyrus, BA 10	−36	55	−3	3.56
Left precentral gyrus, BA 6	−24	−17	64	3.82
Right midle frontal gyrus, BA 6	30	−3	61	3.75
Right inferior frontal gyrus, BA 47	18	11	−13	4.75
Right medial frontal gyrus, BA 6	3	−3	61	4.07
Right anterior cingulate, BA 24, 32	6	44	1	4.06
	6	16	24	3.58
	18	44	1	3.56
Left insula, BA 13	−53	−34	21	3.87
	−36	−9	3	3.98
Right insula, BA 13	36	−28	24	4.23
Left transverse temporal gyrus, BA 41	−53	−23	12	4.53
Left superior temporal gyrus, BA 22	−36	−49	16	3.62
Right superior temporal gyrus, BA 42	65	−20	12	4.15
	56	−18	−2	3.55
Right middle temporal gyrus, BA 22, 39	65	−46	5	4.21
	39	−72	15	3.75
Right transverse temporal gyrus, BA 41	50	−23	12	3.55
Left inferior parietal lobule, BA 40	−50	−36	43	3.93
Left superior parietal lobule, BA 7	−27	−55	58	3.82
Right angular gyrus, BA 39	30	−57	33	3.90
Right parietal cortex, BA 2, 3, 40	36	−45	35	3.53
	48	−19	29	3.44
	59	−25	18	3.83
	21	−29	65	3.55
Right cuneus, BA 17, 18	18	−89	18	4.28
	21	−81	21	4.03
	15	−93	2	3.82
	9	−77	29	3.41
Left thalamus	−3	−23	15	4.28
	−21	−26	12	3.72
Right thalamus	18	−23	12	4.17
	15	−11	12	3.90
Left cerebellum	−3	−54	−23	4.12
	−45	−60	−25	3.46
Right cerebellum	30	−48	25	4.89
	3	−63	−32	4.05
	30	−57	−32	3.53

Note: Local maxima of activation of all significant clusters ($P < 0.001$, uncorrected; $k = 5$ voxels; masked for effects of interest, thresholded at 0.05, uncorrected) are displayed. All coordinates are given in Talairach space.

and a subgroup of the healthy elderly cohort ($N = 15$, 5 females, mean age = 68.3 years, the largest possible subgroup allowing for similar mean age and gender distribution), showing essentially the same differences as a comparison of the entire cohorts.

Because the response accuracy to reward-predicting cues was slightly, but significantly lower in both patients and healthy elderly, analysis of covariance (ANCOVA) contrasts including the response accuracy to the reward-predicting and neutral cues as covariates of no interest were computed across the entire cohorts. Including these covariates in our model had no notable influence on any of the observed between-group differences during reward anticipation and outcome; most importantly, the observed lack of a response shift from reward outcome to anticipation in the elderly and patients was still observed when controlling for response accuracy.

To investigate the relationship of the responses in the NAcc during reward anticipation and outcome, Pearson's correlation coefficient was computed for the fitted responses to reward anticipation and outcome at the respective local maxima (Fig. 3). The responses showed a strong negative correlation across the entire cohort ($r = -0.649$, $P < 0.0001$), suggesting that subjects

Table 3 Brain regions that showed higher activations for elderly relative to young subjects during reward outcome (positive reward versus neutral outcome)

	x	y	z	SPM {T}
Left ventral putamen	−27	−17	4	4.01
	−15	3	3	3.99
Right ventral putamen/Nucl. accumbens	18	8	−5	3.94
	21	9	2	3.75
Left inusula	−33	9	0	3.95
Right insula	39	−14	6	4.72
	36	−3	6	3.55
	33	−3	−2	3.41
Left medial frontal gyrus, BA 6	−3	−26	59	4.11
Left middle frontal gyrus, BA 8	−24	25	40	4.00
Left precentral gyrus, BA 6	−48	−13	26	3.71
Left paracentral lobule, BA 3, 5	−18	−35	54	4.08
	−9	−41	57	3.43
Right precentral gyrus, BA 4	33	−29	59	3.65
Left superior temporal gyrus, BA 22, 41	−50	−14	9	3.93
	−48	−26	4	3.91
Left middle temporal gyrus, BA 21	−53	−29	−1	4.08
	−48	1	−30	3.76
Right superior temporal gyrus, BA 21, 22	53	−29	7	3.92
	65	−15	−2	3.77
Right middle temporal gyrus, BA 21, 39	56	−66	12	4.06
	56	−1	−20	3.65
Left parahippocampal gyrus	−30	−7	−15	4.59
	−33	−13	−22	4.51
Right fusiform gyrus, BA 20	27	−42	−23	3.62
Right cuneus, BA 18	18	−87	18	3.48

Note: Local maxima of activation of all significant clusters ($P < 0.001$, uncorrected; $k = 5$ voxels; masked for effects of interest, thresholded at 0.05, uncorrected) are displayed. All coordinates are given in Talairach space.

who showed a ventral striatal response during reward anticipation tended not to activate the striatum during reward outcome and vice versa. This negative correlation between anticipation and outcome is compatible with the view that the mesolimbic system computes a prediction error of reward, with the error at reward outcome being largest if the reward was not predicted. According to this view, the reduction of reward prediction responses should correlate with reduced reaction time advantage from reward anticipation. We assessed the behavioural reward benefit by computing the relative reaction time advantages for reward cues relative to neutral cues and for rewarded target numbers relative to non-rewarded target numbers, respectively. Pearson's correlation coefficients were computed for these reaction time measures and the hemodynamic response differences (fitted response to reward anticipation – fitted response to reward outcome, at their respective local maxima). There was a positive, but non-significant correlation ($r = 0.123$, $P = 0.202$) between the ventral striatal response difference and the RT advantage to the reward cues. The reward-related reaction time advantage in the response to the target numbers showed a strong significant positive correlation with the striatal response difference, which was highly significant ($r = 0.572$, $P < 0.001$, one-tailed), suggesting that

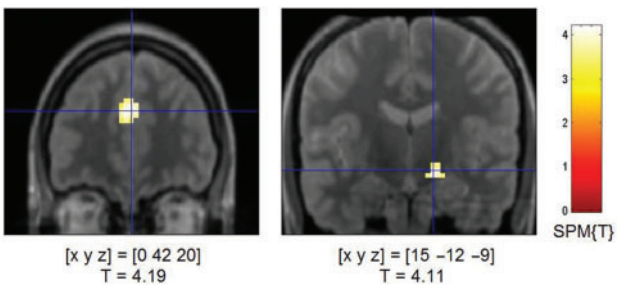

Fig. 4 Increased response to reward outcome in the anterior cingulate/medial PFC (left panel) and in the right midbrain (right panel) in Parkinson's patients relative to healthy elderly subjects. See Fig. 2 for more legends.

the mesolimbic shift of activation from reward outcome to anticipation is associated with a higher reward-related reaction time advantage in tasks upon which reward is instrumental (Fig. 3B, bottom).

Changes in functional connectivity related to ageing and Parkinson's disease

Figure 5B depicts the degrees of functional connectivity between the right nucleus accumbens and the medial midbrain (top) and between the right NAcc and the anterior cingulate/medial PFC (bottom) (Fisher-*z*-transformed

Table 4 Brain regions that showed higher activations for patients relative to healthy elderly subjects during reward outcome (positive reward versus neutral outcome)

	x	y	z	SPM {T}
Medial prefrontal cortex/anterior cingulate, BA 9	0	42	20	4.19
Right midbrain	15	−12	−9	4.11
Left superior frontal gyrus, BA 10	−15	64	8	3.86
Right middle frontal gyrus, BA 10	42	52	−5	3.97
Right inferior frontal gyrus, BA 44	59	15	16	3.76
Left middle temporal gyrus, BA 21	−59	−21	−14	4.06
Right inferior parietal lobule, BA 40	50	−56	39	3.73

Note: Local maxima of activation of all significant clusters ($P < 0.001$, uncorrected; $k = 5$ voxels; masked for effects of interest, thresholded at 0.05, uncorrected) are displayed. All coordinates are given in Talairach space.

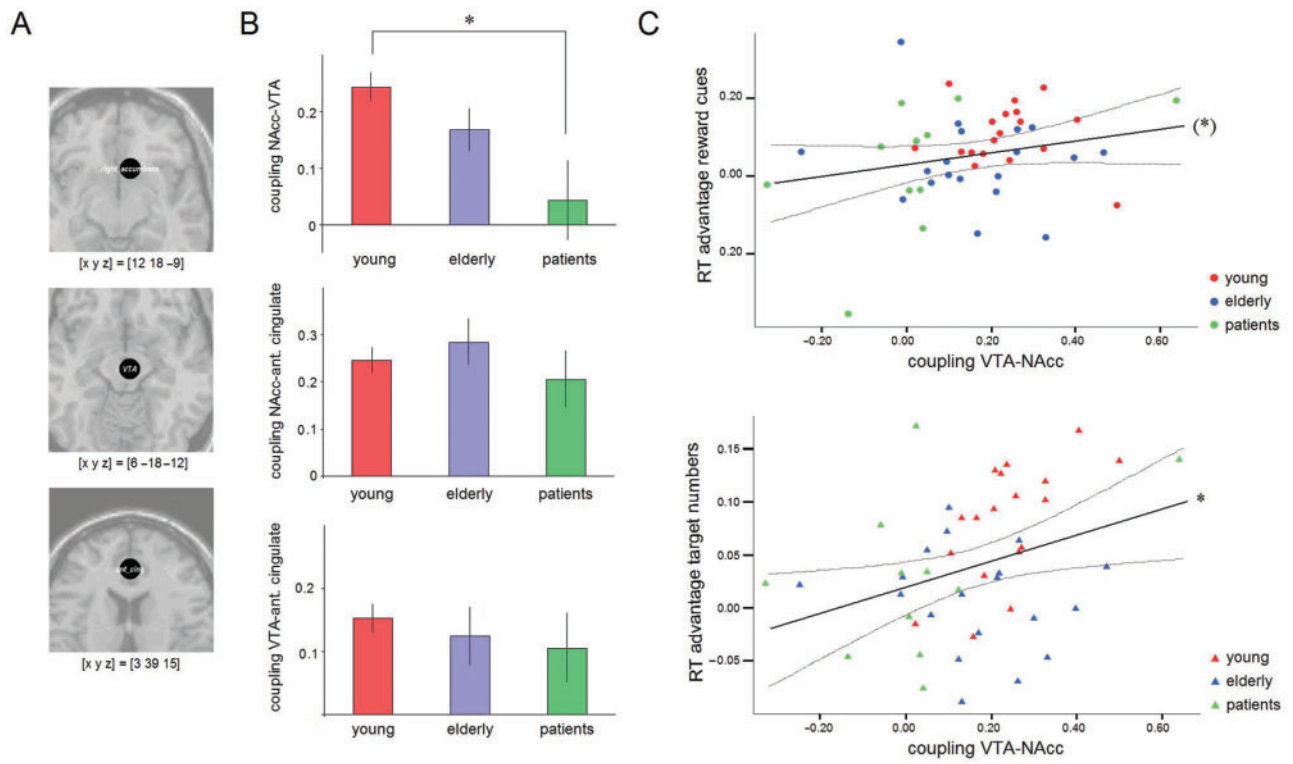

Fig. 5 Effects of healthy ageing and Parkinson's disease on midbrain-striatal functional connectivity. (**A**) Representative VOIs in the right nucleus accumbens (top), the right medial midbrain/VTA (middle) and the anterior cingulate (bottom). (**B**) Functional connectivity of the ventral striatum with the midbrain (top), of the ventral striatum and the anterior cingulate (middle) and of the midbrain and the anterior cingulate (bottom) in young subjects, healthy elderly subjects and patients (Fisher-z-transformed correlation coefficients). Mean values ± standard error are shown. Asterisk denotes a significant between-group difference in NAcc-VTA functional connectivity for patients relative to young subjects ($P < 0.01$). (**C**) Functional connectivity of the midbrain and ventral striatum was positively correlated with the reaction time advantages for responses to cues and target numbers, respectively. *X* coordinate denotes Fisher-z-transformed correlation coefficients of the time courses in the VOIs, *y* coordinate denotes composite ranks of reaction time advantages. Fitted regression lines and 95% confidence intervals of the mean are shown. *: $P < 0.01$; (*): $P < 0.1$.

correlation coefficients of the time courses in the VOIs, see Fig. 5A) in young and elderly healthy subjects and in the patients. Across the entire cohort, the functional connectivity of the ventral striatum and the midbrain was significantly positive [$t(47) = 6.48$, $P < 0.001$]. A one-way ANOVA over the connectivity values of the three groups revealed a significant effect of subject group [$F(2,45) = 4.91$, $P = 0.012$], and *post hoc* *t*-test statistics showed a reduction of functional connectivity in patients relative to young subjects [$t(27) = 3.12$, $P = 0.004$], but no other significant between-group differences (all $P > 0.098$] (Fig. 5B, top).

To test whether the apparent reduction of midbrain-striatal functional connectivity in the patients was related to reward-related reaction time advantages, Pearson's correlation coefficients were computed for the Fisher-*z*-transformed correlation coefficients of the time courses in

the midbrain and ventral striatum and the relative reaction time advantages to the reward cues and to the target numbers (see earlier). There was a positive correlation between the functional coupling of the VTA and the NAcc and the reaction time advantage to reward-predicting cues that approached significance ($r = 0.228$, $P = 0.059$) (Fig. 5C, top). The reaction time advantage to the target numbers was also positively correlated with the functional connectivity of the VTA and the NAcc ($r = 0.337$, $P = 0.010$) (Fig. 5C, bottom). In a partial correlation analysis controlling for the mesolimbic response difference during reward anticipation versus outcome, the correlation of the functional connectivity between the midbrain and ventral striatum with the reaction time advantage to target numbers remained positive, but failed to reach significance at $P < 0.05$ ($r = 0.167$, $P = 0.267$).

The functional connectivity between the NAcc and the anterior cingulate was significantly positive in our study cohort [$t(47) = 9.61$, $P < 0.001$], but there were no between-group differences in functional coupling between these brain structures [$F(2,45) = 0.608$, $P = 0.512$] (Fig. 5B, middle). There was also no correlation of the functional connectivity between the NAcc and the anterior cingulate and the reward-related reaction time advantages (all $P > 0.274$). We further observed a weak (mean $r = 0.13$), but significant [$t(47) = 5.49$, $P < 0.001$] level of functional connectivity between the midbrain/VTA and the anterior cingulate (Fig. 5B, bottom) which did also not show any between-group differences [$F(2,45) = 0.301$, $P = 0.742$]. Despite the lack of between-group differences, the functional connectivity of the midbrain with the anterior cingulate was positively correlated with the reaction time advantages for cues ($r = 0.293$, $P = 0.022$) and for target numbers ($r = 0.352$, $P = 0.007$).

Discussion

In young adults, pictures of object drawings that predicted monetary reward in 75% of trials, but a (smaller) monetary loss in 25% of trials, were associated with stronger fMRI activity in the ventral striatum and in the midbrain than drawings that predicted the absence of reward-related feedback. As expected from previous studies, this reward prediction response was not followed by a mesolimbic response when the predicted reward was signalled via a positive feedback. Healthy elderly subjects and patients showed the opposite pattern: While no ventral striatal reward prediction responses were observed, the NAcc responded reliably to the positive reward feedback itself, suggesting that elderly subjects made positive prediction errors of reward. This finding makes the possibility that prediction error processing was impaired in the healthy elderly and patients very unlikely, but instead suggests alterations in the mesolimbic prediction of future rewards.

Mesolimbic reward prediction error processing in ageing and Parkinson's disease

The impaired shift of the mesolimbic response from reward outcome to anticipation in the healthy elderly and patients suggests an age-related impairment of reward prediction. It seems unlikely that this impairment was due to a poor performance in the number comparison task. All groups performed similarly on this task and hence the gain probability was comparable across groups. Deficits in cue processing are also unlikely to have caused the impairment as the observed pattern was robust even after covarying out the recognition rates for cues. Finally, an age-related delay of the BOLD response is also unlikely to explain this finding, as the onsets of reward anticipation and outcome were temporally decorrelated, and, moreover, age-related changes in neurovascular coupling have been associated with an earlier rather than later peak of the BOLD response (Huettel *et al.*, 2001). A more plausible explanation for the lack of a mesolimbic reward prediction response might be that older adults and PD patients have underestimated the expected value of predicted rewards—which would be compatible with their known tendency to overestimate aversive outcomes (Frank *et al.*, 2004). Expected values are the summed products of the values of possible outcome times their probabilities (Knutson *et al.*, 2005). As reward trials had a 25% risk of losing a small amount of money, accurate learning of expected values was required for correct reward prediction. Overestimating the probability of aversive outcomes (losing money) could have led to an underestimation of expected values in reward trials.

Values and probabilities of reward outcomes are coded in a medial prefrontal-mesolimbic network (Knutson *et al.*, 2005) and a deficit in learning expected values might either be a result of age-related deficiency in dopamine signalling, or medial prefrontal dysfunction or possibly a combination of both factors. One explanation for the reduced ability of elderly people to accurately estimate expected values might be a dopamine-dependent decrease of signal-to-noise ratio in the mesolimbic system, as predicted by a computational model of paired-associate learning under age-related DA deficiency (Bäckman *et al.*, 2006; Li *et al.*, 2006). This explanation is supported by the previously reported age-related pre- and post-synaptic attenuation of dopamine signaling (Volkow *et al.*, 1998*a*, *b*; Bäckman *et al.*, 2000; Kaasinen and Rinne, 2002). Our findings are compatible with the possibility of a medial prefrontal dysfunction. The older adults exhibited reliable activation of the medial PFC during reward outcome only, while young subjects showed medial PFC activation during both reward anticipation and outcome. As the medial PFC plays a role in computing the probability component of the expected value (Knutson *et al.*, 2005), age-related structural or functional alterations in this region might also contribute to the inability of elderly people to accurately predict rewards. Compatible with this view, normal ageing

has been associated with grey matter reductions in the prefrontal and temporal cortices, including the medial PFC (Tisserand *et al.*, 2004; Gong *et al.*, 2005). Interestingly, the medial PFC/anterior cingulate cortex (ACC) showed an even stronger activation during reward outcome in the patients as compared to the healthy elderly. Increased activity in the ACC during an attention task has been related to reduced processing efficiency under conditions of relative dopamine deficiency (Blasi *et al.*, 2005) and a similar mechanism might contribute to the increased ACC activation in the patients. However, reaction times in the number comparison task, one potential measure of processing efficiency in our experiment, were not correlated with the ACC activation during reward outcome (data not shown), leaving the functional significance of increased ACC activation in PD patients uncertain.

The right medial midbrain also showed a stronger activation during reward outcome in the patients compared to the healthy elderly. We tentatively suggest that this might indicate a stronger prediction error in PD patients than in the healthy elderly. However, the observation of higher midbrain activation in patients must be interpreted with caution. Overactivation of brain regions affected by neurodegenerative disease has been observed previously, for example in pre-clinical Alzheimer's disease (Bookheimer *et al.*, 2000), and the possibility thus remains that the increased activation of the midbrain in PD patients is also contaminated by disease-related dysregulation of neural circuits and therefore not a pure reflection of a cognitive problem.

Decreased midbrain-striatal connectivity in Parkinson's disease

In addition to the overall brain activity patterns related to reward anticipation and outcome we also investigated the functional connectivity between the medial midbrain and the ventral striatum. Young subjects showed a moderate degree of functional connectivity between these brain areas similar to that observed previously (Menon and Levitin, 2005). While functional coupling of the VTA and the NAcc was not significantly reduced in the healthy elderly, it showed a pronounced, significant, reduction in PD patients. This finding is compatible with the almost exclusively pre-synaptic degeneration of the dopamine system in Parkinson's disease as opposed to age-related changes, which—apart from being far less drastic in nature—affect both the pre- and post-synaptic elements of DA neurotransmission to a similar degree (Volkow *et al.*, 1998*b*) and indicates qualitative pathophysiological differences between healthy elderly and PD patients. Notably, there was a trend for a positive correlation of the mesolimbic functional connectivity [NAcc-VTA] and the reaction times to reward cues, not only to target numbers. The relationship between dopaminergic neurotransmission and functional connectivity within dopaminergic circuitry is complex (Ruskin *et al.*, 1999; Brown *et al.*, 2001; Rowe *et al.*, 2002; Williams *et al.*, 2002; Honey *et al.*, 2003; Hutchison *et al.*, 2004) and depends on the balance between D1 and D2/D3 stimulation (Rahman *et al.*, 2001). It is therefore not clear whether reduced functional connectivity in our study is directly related to reduced dopaminergic neurotransmission or possibly related to compensatory mechanisms observed in early stages of the disease (Cropley *et al.*, 2006).

The observation that patients showed additional functional alterations in reward cue processing qualitatively different from those observed in the elderly is generally in line with a recent electrophysiological study on reward-motivated probabilistic classification learning (Mattox *et al.*, 2006), in which PD patients performed more poorly than healthy elderly subjects. In that study, performance reduction was related to a reduced stimulus-preceding anticipatory negative slow wave in PD patients. Whether reduced anticipatory slow waves and reduced subcortical connectivity in PD patients are functionally related phenomena will need to be addressed using multimodal approaches.

Conclusions

Taken together, our results show that both normal ageing and Parkinson's disease are associated with deficits in reward prediction despite preserved prediction error processing. They also demonstrate that alterations in reward processing in Parkinson's disease extend at least partly beyond accelerated ageing effects and suggest mesolimbic dysfunction as a promising neural candidate mechanism for further research on depression and cognitive deficits in Parkinsonian type disorders.

The lack of a consistent ventral striatal response to reward anticipation in the healthy elderly and patients might also have clinical implications. Dopaminergic circuitry has been shown to play a role in a variety of cognitive processes that are affected by age-related decline, including attention (Fan *et al.*, 2003; Blasi *et al.*, 2005), working memory (Mattay *et al.*, 2002; Aalto *et al.*, 2005) and episodic memory (Knecht *et al.*, 2004; Lisman and Grace, 2005; Adcock *et al.*, 2006; Schott *et al.*, 2006). Although it is clear that dopamine makes regionally specific contributions to these cognitive processes, our results also raise the possibility that impaired predictions of positive outcomes and related motivational deficits might indirectly contribute to age-related cognitive decline.

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