Preference formation and working memory in Parkinson’s disease and normal ageing

Sylvia M.L. Cox a,*, Elka Stefanova b, Ingrid S. Johnsrude a, Trevor W. Robbins b, Adrian M. Owen a

a Medical Research Council Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK
b Department of Experimental Psychology, University of Cambridge, Cambridge, UK

Received 25 October 2000; received in revised form 14 May 2001; accepted 14 May 2001

Abstract

Recent studies in rats have suggested that the amygdala and the dorsal striatum may be differentially involved in the formation of stimulus-reward associations and stimulus-response associations, respectively. In a recent study in humans, conditioned preference learning deficits were observed in a group of patients with damage to the amygdala formation. In this study, patients with Parkinson’s disease, which is known to involve pathology of the dorsal striatum, were tested on the same conditioned preference task, together with a group of patients with circumscribed lesions of the frontal lobe. Unlike patients with frontal lobe damage, patients with Parkinson’s disease did not exhibit conditioned preferences. However, in this respect their behaviour was indistinguishable from that of age-matched (older) control subjects. In keeping with previous literature, working memory deficits were observed in both patients with Parkinson’s disease and patients with frontal-lobe lesions. Compared to young control subjects, a strong increase in preference for familiar, versus novel, items was observed in both patients with Parkinson’s disease and in older control subjects. Such a familiarity effect appears to overshadow the conditioning manipulation employed in this task and, therefore, preclude the expression of conditioned preferences in older subjects. These results suggest that there is a developmental progression in the degree to which different mechanisms of ‘learning to like’ are important over the life span.

Keywords: Conditioned preferences; Reward; Familiarity; Age effects; Dorsal striatum; Prefrontal cortex

1. Introduction

A large body of research has described the dissociation of different memory systems in terms of their underlying neural substrates [6,30,49,51,53]. McDonald and White [30] reported a triple dissociation among memory systems involved in the acquisition of different types of information, involving the amygdala, hippocampus and the dorsal striatum. In that study, rats performed three different memory tasks, carried out in a radial arm maze, and selective impairments in acquisition were found after damage to each of these systems separately. Specifically, the hippocampus appeared to be involved in the acquisition of information about relationships among stimuli and events, the dorsal striatum was shown to mediate the formation of reinforced stimulus–response associations, whereas the amygdala was found to be essential for the acquisition of associations between neutral stimuli and biologically relevant events. Although these results have been widely confirmed by other research in animals [7,10,15,16,19,21,39,41,44,46], only some aspects of this model have been tested in humans. For example, it is well documented that patients with damage to the hippocampal region and immediately surrounding cortex are impaired on tasks that require them to integrate information about different aspects of complex stimuli [47], and functional neuroimaging studies in healthy control subjects have reported activation in this area in tasks that require subjects to combine information about objects and locations [36].
Fewer studies have investigated the neural basis of the acquisition of stimulus-reward associations in humans, a process referred to as preference learning. This is a form of Pavlovian conditioning in which preferences towards previously neutral stimuli are induced after repeated pairings of a neutral stimulus (CS) and a reward (US). In animal research, as in the study described above, the most common procedure for assessing the acquisition of stimulus-reward associations is conditioned place preference (CPP). In this paradigm, a particular set of environmental cues is first paired with reward, and then an animal’s tendency to approach and spend time in that environment, compared to a neutral one, is assessed [5]. In a recent study, Johnsruude et al. [24] developed a paradigm to assess the acquisition of stimulus-reward associations in humans, based on the same place-preference procedure that has been used in non-human species. In this study, neutral stimuli are repeatedly paired with either rewarding or non-rewarding events in the context of a counting task requiring working memory. Healthy volunteers showed an increased preference for a reward-associated stimulus compared to a stimulus paired with non-reward. In order to investigate the neural substrate responsible for this effect, Johnsruude et al. [25] conducted a study in patients with unilateral anterior temporal lobe lesions or excisions restricted to the frontal-lobe. In all of the anterior temporal lobe patients the lesion included the amygdaloid nuclear complex (ANC) and periamygdalar cortices. The results demonstrated that patients with unilateral surgical lesions that included the ANC did not show conditioned preferences, but performed normally on the measure of working memory. In contrast, patients with unilateral damage confined to frontal regions exhibited normal conditioned preferences, but were impaired on the working memory task. This result provides clear evidence that in humans, as in other animals, the acquisition of stimulus-reward associations specifically depends on a circuit involving inferotemporal cortex and the ANC [25]. What remains less clear in terms of the presumed multiple memory systems model is the extent to which this result is anatomically specific. To our knowledge, preference learning has not been tested in patients with known damage to the dorsal striatum, a major component of the stimulus–response association system [30].

In this study, patients with Parkinson’s disease (PD) were tested on the conditioned cue preference (CCP) task designed by Johnsrude et al. [24]. PD is a condition resulting primarily from degeneration of dopamine producing cells in the substantia nigra and the consequent depletion of dopamine within the striatum. Although multiple regions of the striatum may be severely affected, much evidence suggests that dopamine depletion may be greater in the dorsal striatum than in ventral regions [26,31].

Recent investigations in PD patients have highlighted the similarity between the neuropsychological profile observed in these patients and that reported in patients with circumscribed lesions of the frontal-lobe [32–34]. For example frontal-like deficits on various tests of working memory have been reported in PD, reflecting, it has been argued, the effect of striatal dopamine depletion interrupting the normal flow of information through fronto-striatal circuitry in these patients [38]. The current study, therefore, compared the performance of patients with PD with that of the group of frontal-lobe patients in the study by Johnsrude et al. [25]. Since the primary role for the dorsal striatum is assumed to be in the formation of stimulus–response associations and not stimulus-reward associations [30], it was predicted that the performance of patients with PD would be indistinguishable from that of healthy age- and education-matched control subjects on the conditioned cue preference task. Furthermore, since working memory deficits, similar to those observed in patients with frontal-lobe lesions, have been reported in patients with PD, we predicted that PD patients would be impaired on the working-memory component of the task.

In addition to conditioning, preferences can be influenced by other stimulus characteristics such as familiarity or novelty. For example, Berlyne (1970) reported an increased ‘pleasingness’ and ‘interestingness’ with decreased familiarity of the exposed stimuli in humans, the so called ‘novelty effect’ [3]. In contrast, the ‘mere exposure’ effect describes the phenomenon whereby repeated, unreinforced presentation of a stimulus tends to result in an increased positive affect towards it. This effect does not depend on conscious awareness of exposure to the stimuli: explicit recognition of these stimuli is not required in order to induce a preference [4,23,29,42,54].

In the current study, the effects of exposure were also assessed within the context of the CCP task. Thus, comparisons were made in all groups between the preferences observed for stimuli that had been seen during the Formation phase of the task, regardless of their association with reward, and stimuli that had never been seen before.

2. Method

2.1. Participants

Table 1 shows a summary of characteristics of the experimental groups.
2.1. PD patients

The 22 PD patients included in this study were all patients at the Parkinson’s disease clinic at Addenbrooke’s Hospital, Cambridge. In all cases, idiopathic PD was diagnosed by a consultant neurologist. Patients with clinical dementia or with a significant medical history not related directly to their PD (e.g. stroke or head injury) were excluded from this study. The severity of clinical symptoms was assessed according to the Hoehn and Yahr [22] five-point rating scale. All 22 patients had mild to moderate clinical symptoms and were rated as either stage I or II on the Hoehn and Yahr [22] scale. A Mini Mental State Examination [13] was administered to identify clinical dementia. All patients were above the cut-off score (24), ranging from 27 to 30. To assess the incidence of affective disturbance in these patients, the Geriatric Depression Scale (GDS) was administered. This (self-administered) 30-item questionnaire is particularly suited for the assessment of depression in PD patients, since it contains relatively few somatic items that may relate directly to the patients’ physical disability. Patients with significant affective disturbance according to this scale were excluded from the study.

All individuals were receiving L-dopa preparations either alone or in combination with other medication. All were responding well, and none were suffering from a confusional state at the time of testing.

2.1.2. Control subjects (aged)

Twenty-two control subjects were chosen to match the PD group with respect to age and years of education, confirmed by t-statistics (age: t(42) = 0.780, P = 0.440; education: t(42) = 1.383, P = 0.174). The subjects were recruited from local advertisements in the London and Cambridge (UK) areas.

2.1.3. Frontal-lobe patients

The 13 frontal-lobe patients included in this study were recruited from the Montreal Neurological Institute, Quebec, Canada. The lesions in these patients were confined unilaterally to prefrontal cortex (seven left, six right). Pathological reports cited low grade gliomas in five cases (two left, three right) a cavernous hemangioma in one left-sided case, an aneurysm and hematoma in another left-sided patient, an arteriovenous malformation (AVM) in a right-sided patient and cortical dysplasia, gliosis and/or sclerosis in the other five patients [25].

2.1.4. Control subjects (young)

Twenty-one normal control subjects were closely matched to the frontal-lobe patients with respect to age (t(32) = 1.914, P = 0.065) and years of education (t(30) = −1.105, P = 0.278). The subjects were recruited from local advertisements in the Montreal area (Canada) [25].

Informed consent was obtained from all patients and control subjects before the testing session. The experimental protocol was approved by the ethical review committees of the McGill University Psychology Department, the Montreal Neurological Institute and Hospital, and by the Local Research Ethics Committee in Cambridge.

2.2. Apparatus

A computerised touch screen format was used. Custom software was written in Visual Basic 3.0 and run on either a Dell 486 PC DX2-50 computer or a Dell Pentium II PC with a SoundBlaster-16 sound card and a 40 × 30 cm² MicroTouch touch screen. The sound was played to the subject via Sennheiser headphones.

2.3. Procedure

The experimental task has been described in detail elsewhere [24]. Subjects were tested in three separate conditions, which were presented in a fixed order. The first condition, which we refer to as Formation, lasted about 35 min. The second and third conditions, which we refer to as Judgement and Questions, respectively, lasted about 5 min each. A schematic drawing of each condition is illustrated in Fig. 1. The participants were asked not to eat for at least 2 h before the study. Participants were required to choose either fruit-flavoured pellets (Willy Wonka’s Dweeb candies) or raisins as their food reward at the outset, and they were given only the chosen type of food reinforcement during the procedure.

Table 1

<table>
<thead>
<tr>
<th>Subject group</th>
<th>n</th>
<th>Men</th>
<th>Women</th>
<th>Age (in years)</th>
<th>Years of education</th>
<th>GDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>PD patients</td>
<td>22</td>
<td>11</td>
<td>11</td>
<td>58.6</td>
<td>6.7</td>
<td>11.9</td>
</tr>
<tr>
<td>Aged controls</td>
<td>22</td>
<td>9</td>
<td>13</td>
<td>59.9</td>
<td>4.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Frontal patients</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>30.0</td>
<td>7.7</td>
<td>14.2</td>
</tr>
<tr>
<td>Young controls</td>
<td>21</td>
<td>10</td>
<td>11</td>
<td>37.1</td>
<td>11.9</td>
<td>13.2</td>
</tr>
</tbody>
</table>
2.4. Formation

The subjects were presented with three black squares or 'boxes' on the screen. Subjects were told that one of the squares was hiding a red ball and the other two were hiding black balls. The subjects had to guess where the red ball was hidden and try to find as many as they could. A response was made by touching the selected box on the screen. Following each guess, the selected box would 'open up' revealing one of the three stimulus patterns, and either a red or a black circle (or 'ball') superimposed on the centre of that pattern (see Fig. 1A). If the circle was red, the participants would hear a melodic flourish and would receive the chosen type of food reward (one candy or one raisin). If the circle was black, they would hear a buzzer and no food would be given. After 3 s, the selected 'box' returned to black and the subject was required to make the next guess. In addition to searching for red balls, the subjects had to keep track of the number of red balls they had seen during each block. Unknown to the subjects, the stimulus pattern and circle colour seen were predetermined for each trial, regardless of the location chosen.

The three underlying patterns were associated with the red and black balls at different contingencies. Pattern A was accompanied by reward (red ball, melodic flourish and food) on 90% of trials in which it appeared and by negative feedback (black ball, buzzer sound and no food) on 10% of those trials. Pattern B was accompanied by reward on 50% of the trials in which it appeared and by negative feedback on the other 50%. Pattern C was accompanied by reward on 10% of the trials and by negative feedback on the remaining 90%.

Three versions of this task were prepared. In each version, a different set of pattern-reinforcement contingency pairings was used. Each subject was tested using one of the three different versions, chosen pseudorandomly, in such a way that the distribution of the versions across the patient groups, sexes and across the reward types (candy or raisins) was approximately equal.

A total of 180 trials were presented over six blocks comprising 20, 30, 40, 40, 30 and 20 trials, respectively. In total, each of the stimulus patterns was presented 60 times, together with either a red ball or a black ball according to the contingency relationship for that pattern. At the end of each block, the participants were asked how many times they had found the red ball in
each of the three boxes during the previous block of trials.

The trial order was also pseudorandom and fixed. The rarest combinations were always presented just before or just after the more frequent combinations. In addition, an identical pattern/reinforcement pair could not occur more than twice in a row. These provisions served to break up runs of similar trials which might otherwise have alerted the subjects to the different reinforcement contingencies. In addition, each block of trials contained an equal number of red and black balls, and at least one occurrence of each of the six possible combinations of balls and patterns.

2.5. Judgement

Six different patterns were used in this part of the experiment. Three of the patterns were those used in the Formation condition above, while three others were novel (see Fig. 1B). The subjects were asked to choose the one they preferred by touching it. There were a total of 30 trials, and each pattern was presented 10 times; five times on the left, and five times on the right, in combination with each of the other five patterns.

2.6. Questions

All six patterns that were seen in the Judgement condition were presented simultaneously on the screen (see Fig. 1C), and a number presented on top of each pattern indicated how many times the subject had chosen that particular pattern during the Judgement condition (out of a possible 10). The question, ‘Why did you prefer this pattern?’ was posed to the subject for the three most preferred patterns, in order that the subjects’ perceptions of their preferences and their awareness of the conditioning manipulation could be assessed. If they attributed their preference to their previous experience with the patterns (during the Formation condition), it was assumed that they were aware of the effect of the conditioning procedure, and they were to be excluded from the analysis. At the end of this condition, each participant was informed of the nature of the study.

3. Results

3.1. Preference learning

No subjects were excluded from the analysis, since none of the subjects related their preferences to the previous stage of the task during debriefing. In fact, preferences were invariably attributed to the physical characteristics of the patterns. In this study, the term ‘preference learning’ is used for the dependent variable created by comparing the judgement score for the pattern paired most often with reward (positively conditioned pattern) to that for the pattern paired least often with reward (negatively conditioned pattern), within subjects. Judgement scores for the 50% pattern were not included in the statistical analysis, since its conditioned reward value depends on the relative salience of reward and non-reward, and we do not know what these are. These judgement scores were compared among groups (PD patients, aged normal control subjects, frontal-lobe patients and young normal control subjects), using repeated measures analysis of variance, see Fig. 2.

A comparison among all experimental groups showed a significant interaction of group by pattern ($F(3, 74) = 5.62, P = 0.002$), indicating that a different pattern of preference learning was observed between the experimental groups. Planned comparisons between the frontal-lobe patients and their matched normal control subjects demonstrated no interaction of group by pattern ($F(1, 32) = 0.705, P = 0.407$), nor a main effect of group ($F(1, 32) = 1.297, P = 0.263$), but a significant main effect of pattern was observed ($F(1, 32) = 15.828, P < 0.001$): the positively conditioned pattern was significantly preferred to the negatively conditioned pattern. Therefore, as in young healthy control subjects, normal conditioned pattern preference learning was observed in the frontal-lobe group (see Fig. 2) [25].

Comparing PD patients with their matched normal control subjects, a tendency towards an interaction between group and preference learning was observed, although this did not reach significance ($F(1, 42) = 3.745, P = 0.060$). Fig. 2 shows that aged normal con-
control subjects did not exhibit any conditioned preferences ($F(1, 21) = 0.582, P = 0.454$), whereas the PD patients tended, non-significantly, to prefer the negatively conditioned pattern to the positively conditioned pattern ($F(1, 21) = 3.726, P = 0.067$). No significant main effect of pattern ($F(1, 42) = 0.199, P = 0.658$) nor main effect of group ($F(1, 42) = 0.807, P = 0.374$) was observed, indicating that the expected preferences were not observed in either PD patients or older control subjects and no significant differences existed between the two groups.

Finally, young normal control subjects were compared to the aged normal control subjects with respect to preference learning. The interaction of group by pattern approached significance ($F(1, 41) = 3.799, P = 0.058$), suggesting an effect of age on the formation of conditioned preferences. As already described above, the young control subjects exhibited a preference for the positively conditioned pattern versus the negatively conditioned pattern ($F(1, 20) = 15.990, P = 0.0005$), whereas the aged normal control subjects did not ($F(1, 21) = 0.582, P = 0.454$) (see Fig. 2). To investigate the effects of ageing on preference learning in more detail, a Pearson’s correlation was performed, but no significant correlation between age and preference learning in the young and aged normal control subjects was observed ($r = -0.247, P = 0.111, n = 43$).

3.2. Novelty and familiarity effects

The lack of any apparent conditioning effects in the older control subjects versus young control subjects may be owing to exposure effects, since a strong preference for familiar (or novel) items would obscure the effects of the conditioning manipulation. To determine whether there were any effects of exposure on the expression of preferences, the average judgement score for the three novel patterns was compared to the average preference score for the three (‘familiar’) patterns presented in the Formation condition (the positively conditioned, negatively conditioned and the 50% pattern). Since these scores are complementary (the average judgement score for the familiar pattern equals 10 minus the average judgement score for the novel patterns), a one-way ANOVA was applied to look at differences in exposure effects between our experimental groups. A significant difference in judgement score for familiar versus novel patterns was observed between the four experimental conditions ($F(3, 74) = 8.38, P < 0.001$).

Post-hoc comparisons between PD patients and their age-matched control subjects ($P = 0.886$), and between frontal-lobe patients and young control subjects ($P = 0.871$), revealed no significant difference in exposure effects. In contrast, the difference in judgement score for familiar versus novel patterns between young and older control subjects was highly significant ($P = 0.003$), see Fig. 3.

To investigate this difference in exposure effect between older and young control subjects further, the difference in judgement score for the familiar patterns versus that for the novel patterns was compared to 0 (the expected score if no exposure effects are present) within each group. In the aged control group the familiar patterns were significantly more preferred than the novel patterns ($t(21) = 3.527, P = 0.002$). In contrast, the young normal control subjects exhibited a preference for the novel patterns compared to the familiar patterns that almost reached significance ($t(20) = -2.068, P = 0.052$) (see Fig. 3). These findings suggest that there is a remarkable effect of age on the degree to which exposure can influence the formation of preferences. We performed a Pearson’s correlation between age and preference for familiar patterns in the two control groups together. A significant correlation was found ($r = -0.426, P = 0.004, n = 43$), indicating an age related increase in preference for familiar patterns. This is shown in Fig. 4. However, it is important to point out that the expression of exposure effects is confounded by conditioning effects, because all familiar patterns were associated with some kind of feedback in the Formation condition.

3.3. Counting task

Estimation scores for the counting task were used to assess working memory function in the four groups of subjects. Estimation error scores were calculated by
subtracting the number of red balls actually observed during the Formation condition from each subject’s estimate of the total number of red balls seen, summed over blocks of trials. The estimation error scores were classed as either underestimation (all negative values) or overestimation (all positive values). These scores are illustrated in Fig. 5 for each experimental group.

Comparing estimation error scores across the four groups using one-way ANOVA, a significant effect of group was observed in underestimation \( (F(3, 74) = 7.813, P < 0.001) \), but not in overestimation \( (F(3, 74) = 1.371, P = 0.258) \).

Planned comparisons between PD patients and their aged normal control subjects revealed a significant difference in underestimation \( (F(1, 42) = 7.760, P = 0.008) \), in that PD patients underestimated significantly more than their control subjects.

Frontal-lobe patients also underestimated significantly more than their matched control subjects \( (F(1, 32) = 13.275, P = 0.001) \) [25]. Given that these patients performed well on the preference conditioning task (as compared to their control group), this result demonstrates that the underestimation of reward frequency does not affect preference formation.

Finally, significant differences in underestimation were found between aged normal control subjects and young normal control subjects \( (F(1, 41) = 4.375, P = 0.043) \), in that the older subjects underestimated more than their younger control subjects (see Fig. 5). Further investigation of ageing effects on estimation scores with Pearson’s correlation revealed no significant correlation between age and underestimation \( (r = −1.89, P = 0.224) \) nor between age and overestimation \( (r = 0.230, P = 0.137) \).

4. Discussion

In this study, patients with known striatal pathology, age-matched control subjects, patients with frontal-lobe damage and young control subjects were assessed on a test of conditioned pattern preference learning. The comparison between older and young control subjects revealed some surprising results. Unlike young subjects, older volunteers failed to exhibit conditioned preferences. The examination of the effects of exposure to the stimuli suggests a likely explanation: both PD patients and older control subjects exhibited a strong preference for the familiar stimuli irrespective of conditioning, which was reflected in the strong positive correlation between familiarity and age. In contrast, no familiarity effects were observed in frontal-lobe patients and young control subjects. In fact, young control subjects tended to prefer the novel stimuli. The familiarity effect in older subjects (control subjects and PD patients) may effectively overshadow the effects of preference conditioning. Corresponding results have been reported elsewhere; studies have demonstrated that in general, stimulation-seeking is significantly higher in middle-aged people compared to older subjects [3,8,17]. Studies in non-human species have shown that older rats and
dogs spend less time exploring a novel stimulus and exhibit lower levels of exploratory behaviour [14,20,52]. Nevertheless, complexity of the stimuli and motivational effects play an important role in preference formation, which reduces the comparability of the previously reported results with those of the current study concerning novelty and familiarity effects [27,52]. This observed effect of ageing is particularly interesting, since our older subjects had a mean age of only 59 years (see Table 1 for details).

PD patients also did not exhibit conditioned preferences. Although their performance on the CCP task was not significantly different from that of the (aged) control subjects, their pattern of performance was quite different and this was revealed in the interaction that just missed significance. Whereas the control subjects exhibited a pattern of performance that was similar to that of the young control subjects (and frontal-lobe patients), the PD patients, if anything, tended to prefer the negatively conditioned pattern. This observed marginal effect may reflect some degree of ventral striatal dysfunction in these patients given that this region is known to be involved in the acquisition of stimulus-reward associations by virtue of its intimate relationship with the amygdala [11,12]. It is important to acknowledge that while dorsal sectors of the striatum may be most severely affected in the early stages of PD, the ventral striatum is also affected, albeit less severely, and has been shown to become more seriously involved in the later stages of the disease [31]. However, further investigation of preference conditioning in older subjects, independent of familiarity effects, is required. Further research is also required to investigate the effect of disease severity on preference conditioning.

Both groups of patients were impaired on the component of the task that assesses working memory ability, in that they both underestimated when reporting the number of red balls occurring during the Formation phase of the task [48]. With regard to the PD group, the results of this study confirm and extend previous findings [32,33] and suggest that, like frontal-lobe patients, medicated patients with mild to moderate PD are impaired on tests that require aspects of working memory. In several recent studies, medicated and non-medicated patients at different stages of PD have been compared on tests known to be sensitive to frontal-lobe damage and on other, non-frontal, tests of visuospatial memory and learning [32–35,37]. The results clearly demonstrate that ‘frontal’ tests are more sensitive to deficit in patients with PD than ‘non-frontal’ tests, although, importantly, both types of task may be sensitive to deficit in patients with more severe clinical symptoms.

A number of possible neural accounts have been put forward to explain the occurrence of ‘frontal-like’ cognitive deficits in PD. These deficits may reflect damage to one or more of the cortico-striatal circuits that parallel the ‘motor loop’ described by Alexander et al. [2], but which subserve cognitive, rather than motor, functions. According to this model, the widespread topographically organised cortical projections, which converge upon the striatum, project back, via pallidal, nigral and thalamic structures, to discrete frontal regions. PD is associated with profound dopamine depletion both in the striatum and, to a lesser degree, in the prefrontal cortex [1,26,45], and ‘frontal-like’ deficits could arise from either, or both, of these forms of pathology [28]. In one recent study, positron emission tomography (PET) was used to examine how blood flow in the frontal cortex and in the basal ganglia may be affected in PD, during a working memory task known to involve fronto-striatal circuitry [38]. Relative to control conditions, the working memory task was associated with an increase in cerebral blood flow centered on the internal segment of the right globus pallidus in the age-matched control subjects, and a decrease in the same region in the patients with PD. A similar inverse relationship between the task-specific blood flow change observed in the control group and that observed in the PD patients was not found in any other subcortical or cortical area examined, including regions of the dorsolateral frontal cortex known to be involved in this task. One possible interpretation of these results is that striatal dopamine depletion in PD disrupts the normal pattern of basal ganglia outflow through the globus pallidus, and consequently, affects the expression of frontal cortical functions by interrupting normal transmission of information through fronto-striatal circuitry. Thus, on the basis of those results one can postulate that the ‘frontal’ cognitive deficits in working memory seen in mild-moderate PD in the current study are the result, not of intrinsic prefrontal dysfunction per se, but rather of abnormal processing of the prefrontal input through malfunctioning basal ganglia circuitry. This possibility is entirely consistent with the fact that dopamine deficiency in early PD affects the striatum and not the frontal cortex, as demonstrated both pathologically [1] and in a recent PET study using 18F-Dopa [40].

Furthermore, deficits on the working memory task were shown in the ageing control population relative to the young subjects. Frontal-like deficits in many tasks, including working memory, have been reported previously in older subjects [43]. The prefrontal cortex has been consistently implicated as one of the areas most sensitive to the effects of ageing in both morphological and functional studies [50]. The neural substrate of this deficit may well be reduced dopamine levels in the frontal cortex in the older subjects; for example, Goldman [18] has reported reduced frontal dopamine levels in aged monkeys. Such an effect would concur fully with the observation that the PD patients in this study were even more severely impaired than their age-matched control subjects. Moreover, such deficits in PD
patients have previously been shown to be at least partly reversible by the administration of L-Dopa therapy [28].

Our observed familiarity effects in the PD patients and their control subjects, as well as the conditioning effect observed in the frontal-lobe patients, are also in line with previous studies that demonstrate that implicit memory systems are dissociable from explicit memory systems [9,23]. First, the working memory deficits observed in the PD patients did not prevent them from forming (implicit) preferences based on familiarity. Secondly, the working memory impairment in the frontal-lobe patients did not affect their ability to condition preferences. Furthermore, these results suggest that the dorsal striatum, which is severely affected in PD, is not essential in forming preferences for familiar items.

In conclusion, these results suggest a developmental progression in the degree to which different mechanisms of ‘learning to like’ are important over the life span. One must be cautious however, about drawing any stronger conclusions on the basis of the current results since the exposure effects were confounded by the effects of the conditioning procedure and vice versa. Further research in this area will seek to investigate the observed ageing effects on preference formation and establish how they relate to conditioning and exposure effects, measured using fully independent paradigms.

Acknowledgements

This study was made possible by a Royal Society Travelling Grant to E.S. This work was funded, in part, by a Welcome Trust award to T.W.R. We thank R.A. Barker for referring patients.

References

[26] Kish JS, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkin-


