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Impaired recognition of anger following damage to the ventral striatum

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Summary

Comparative neuropsychology has identified a role for the ventral striatum (VS) in certain forms of aggression. To address whether the homologous region in humans also contributes to the emotion anger, we studied a case series of four human subjects with focal lesions affecting the VS. All four demonstrated a disproportionate impairment in recognizing human signals of aggression. By contrast, a control group of individuals with damage to more dorsal basal ganglia (BG) regions showed no evidence of an anger impairment. Our findings demonstrate that the VS makes a significant contribution to coding signals of aggression in humans, and emphasize the importance of an approach to human affective neuroscience based on cross-species homologies. The results are discussed in relation to the ventral striatal dopamine system's role in the pursuit of biological resources in general. We propose that the role of the VS in the recognition of human signals of anger may reflect a more general role in the coordination of behaviour relevant to the acquisition and protection of valued resources, including detection of signals of conspecific challenge (anger).

Keywords: ventral striatum; anger; aggression; facial expressions; vocal expressions

Abbreviations: BG = basal ganglia; IQ = intelligence quotient; VS = ventral striatum

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Introduction

There is accumulating evidence that particular brain regions contribute disproportionately (although not exclusively) to the recognition of certain emotions in humans. For example, the amygdala has a special role in coding signals of fear (Adolphs *et al*., 1994; Calder *et al*., 1996; Morris *et al*., 1996; Sprengelmeyer *et al*., 1999), while the insula is important for disgust (Phillips *et al*., 1997; Calder *et al*., 2001; Krolak-Salmon *et al*., 2003). These findings parallel observations from comparative neuroscience demonstrating the amygdala's contribution to fear conditioning and detection of threat (Davis, 2000), and the insula's involvement in the distaste response (Kiefer and Orr, 1992). A central current question, however, is whether emotions other than fear and disgust might show a similar degree of neural segregation in humans. On the basis of comparative research, one obvious candidate is anger (Blanchard and Blanchard, 1988, 1989).

The idea of a neural system that contributes disproportionately to anger processing in humans already has an empirical basis. In recent research we showed that acute administration of sulpiride (a dopamine D_2-class receptor antagonist and anti-aggressive agent) produced a transient selective reduction in healthy human volunteers' recognition of anger from facial expressions (Lawrence *et al*., 2002). But although this study highlighted the involvement of dopamine in anger recognition, it gave little indication of the neural structures involved. In this respect it is relevant that comparative research has demonstrated altered dopamine activity during aggressive encounters between conspecifics (Simon *et al*., 1989; Redolat *et al*., 1991; Miczek *et al*., 2002; Ferrari *et al*., 2003), with a number of studies highlighting the involvement of dopamine in the ventral striatum (VS) (Louilot *et al*., 1986; Ferrari *et al*., 2003). Moreover, these experiments demonstrate that changes in dopamine levels are not simply a direct consequence of the altered autonomic or somatomotor activity associated with an aggressive exchange (Louilot *et al*., 1986; Redolat *et al*., 1991; Ferrari *et al*., 2003). Similarly, human research has demonstrated that violent alcoholic offenders show increased striatal dopamine transporter density relative to controls, whereas non-violent alcoholics show reduced dopamine transporter (Tiihonen *et al*., 1995). On the basis of these observations, we investigated whether damage to the VS would impair anger processing in humans.

Previous research has shown that the recognition of human signals of emotion provides an effective index of processing individual emotions. Moreover, brain regions implicated in recognizing signals of fear and disgust in humans (Adolphs *et al*., 1994; Calder *et al*., 1996, 2000; Morris *et al*., 1996; Phillips *et al*., 1997; Sprengelmeyer *et al*., 1999; Krolak-Salmon *et al*., 2003; Wicker *et al*., 2003) have also been implicated in the experience of these emotions and associated behaviours in both comparative and human research (Kiefer and Orr, 1992; Sprengelmeyer *et al*., 1999; Calder *et al*., 2000; Davis, 2000; Krolak-Salmon *et al*., 2003); but see Anderson and Phelps (2002). Thus, our current study investigated whether both the recognition of anger and self-reported experience of anger would be affected by damage to the VS.

In addition to neurologically intact controls, we compared the performance of subjects with VS damage with that of a second comparison group with damage extending into more dorsal basal ganglia (BG) regions.

Material and methods

Subjects

Our study included seven individuals with focal lesions affecting the BG. Details of aetiology and lesions are provided in the following sections. The study was approved by the Cambridge Local Research Ethics Committee, and all subjects gave written informed consent. In line with our hypothesis, the patients are presented as two groups. The first group contained individuals with lesions affecting the VS, while the second comparison group comprised individuals with damage to more dorsal BG regions. Neurologically intact controls were also included.

VS group

The VS group contained four individuals. Each patient's aetiology and the brain regions affected by their lesions (shown in brackets) were as follows: UI, spontaneous haemorrhage (right putamen, caudate and dorsal anterior insula); BS, arteriovenous malformation (left ventral basal ganglia); MT, intraventricular haemorrhage (left putamen, nucleus accumbens and caudate); KC, infarct (left putamen and left ventral anterior insula).

Three VS patients had left hemisphere lesions (KC, MT, BS), while UI's lesion was restricted to the right hemisphere. MRI scans were available for three of the VS group (KC, UI and MT). The MRI for the fourth patient (BS) was corrupted, and she sadly suffered an additional haemorrhage after testing and before a second MRI was performed. Consequently, BS's lesion cannot be confirmed with MRI. However, her CT scan (Fig. 1C) shows a lesion of the left ventral basal ganglia proximal to the region of maximal lesion overlap in the other three VS patients. Hence, there is good reason to believe that BS's lesion may also affect the region of maximal lesion overlap identified in the other VS group members, and she is included for that reason.

To calculate the area of maximum lesion overlap in KC, UI and MT, UI's MRI was flipped in the *x*-axis so that all lesions were in the left hemisphere and the scans were normalized to the Montreal Neurological Institute/International Consortium for Brain Mapping template. Figure 1A illustrates that a region of the VS (ventral putamen) was damaged in all three individuals according to the definition of the VS provided by Mawlawi *et al*. (2001); this definition includes the ventral caudate, ventral putamen and nucleus accumbens. Figure 1B shows that the regions damaged in the BG control group did not overlap with the region of maximal lesion overlap in the VS group.

BG controls

The BG control group contained three individuals. Each patient's aetiology and the brain regions affected by their lesions (shown in brackets) were as follows: BX, infarct following clipping for middle cerebral artery aneurysm (left putamen and internal capsule); LD, infarct (left globus pallidus and internal capsule); NK, embolic cerebral vascular accident (left insula, putamen, caudate, globus pallidus and internal capsule).

The BG control group was selected according to the criterion that the lesions did not overlap with the region of maximal lesion density in the VS group (Fig. 1). Figure 1B illustrates that the BG control group's lesions are concentrated more in the mid/dorsal BG regions. Included in the BG controls is case NK, a male with an insula and BG lesion who shows a selective impairment in recognition and experience of disgust. NK has been described in a previous report (Calder *et al*., 2000). Note that although NK has damage to the BG, he does not show impairment of anger. Hence, the fact that his lesion falls outwith the region of maximal lesion overlap in the VS group is relevant and he is included for that reason. Full background information on the BG controls is shown in Table 1. Because NK shows a slight speech production impairment, his verbal intelligence quotient (IQ) was assessed using 'Spot the Word' from the Speech and Capacity of Language Processing Test (Baddeley *et al*., 1992), rather than the National Adult Reading Test.

Control data for the tests were collected from subjects who were similar to the patients in age and IQ. Details of the controls' age and gender for the different tests are provided in each of the relevant sections that follow.

Background tests

Verbal IQ was estimated with National Adult Reading Test (Nelson, 1991) and performance IQ with Raven's progressive matrices (Raven *et al*., 1983). Basic visual processing was assessed with the VISTECH 6000. For audiometric testing we used a DSP pure tone audiometer. Left and right ears were tested separately across the range of frequencies critical for speech perception (500, 1000, 2000 Hz); Table 1 reports average hearing thresholds for each subject's better ear.

Face perception

Ability to match pictures of unfamiliar faces was assessed with the Benton Test of Facial Recognition (Benton *et al*., 1983). On each trial of this test the subject is shown a target face and an array of six faces. The task is to find further examples of the target face among the array of six. Changes in head orientation and lighting can occur between the target and array faces.

Recognition of familiar faces was assessed with pictures of 30 famous faces intermixed with 10 unfamiliar face foils. The faces were presented individually in pseudorandom order. For each face, subjects were asked whether the person was familiar, and, if so, to give his or her occupation and name. Control data for face perception tests (Benton and familiar face recognition) were collected from 11 females and 11 males; mean age (SD) = 47.2 (6.8), mean IQ (SD) = 108.9 (11.2).

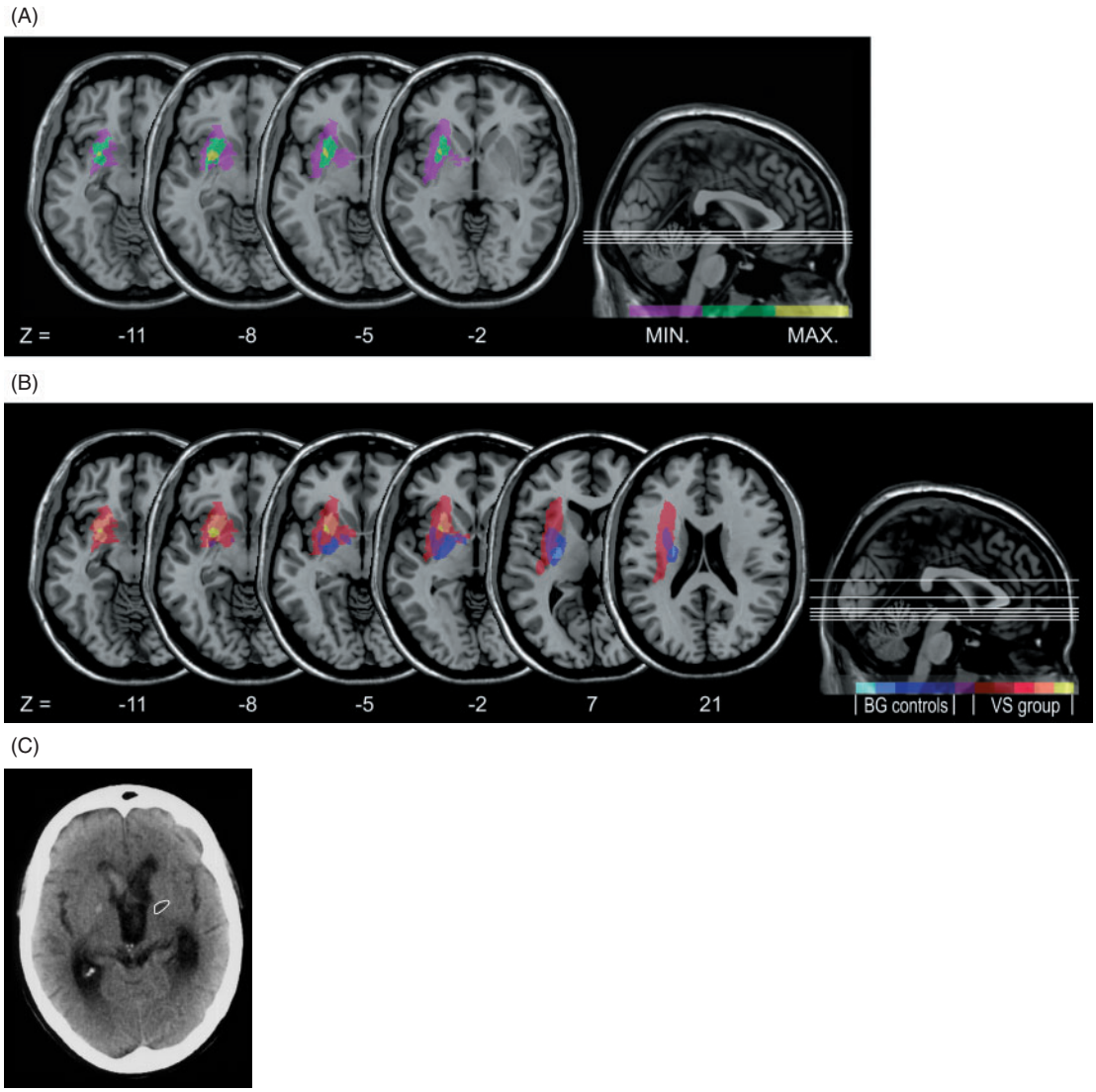

Fig. 1 Lesion maps. (**A**) MRI scans were available for three of the VS group subjects (KC, UI and MT). Two (KC and MT) have lesions affecting the left BG, whereas the third (UI) has a right BG lesion. In order to identify the region of overlap among these three patients, UI's MRI was flipped in the *x*-axis. This panel illustrates that a region of the ventral striatum (yellow region) was damaged in all three patients. (**B**) The degree of overlap between the regions damaged in the VS group (hues ranging from red to yellow) and regions damaged in the BG controls (blue hues). The colours indicate the relative percentage overlap between the VS and BG control groups' lesions. The darkest red hue indicates damage in just one VS patient, while yellow indicates damage in all VS patients with MRIs. The lightest shade of blue indicates a region damaged in all three BG controls, while the darkest shade of blue indicates a region damaged in just one of the BG controls. The central purple hue indicates an area damaged in equal numbers of VS and BG control patients. The important point to note is that there is no overlap among the regions damaged in all VS patients with MRIs (shown as yellow in **A** and **B**) and the areas damaged in the BG controls. Lesion mappings were performed with MRIcro (Rorden and Brett, 2001) and are shown superimposed on the Colin27 template (Montreal Neurological Institute). Min = minimum overlap; Max = maximum overlap. (**C**) CT for case BS showing a region of damage in the left ventral basal ganglia within the area highlighted by the white oval.

Facial expression recognition

Subjects completed two tests of facial expression recognition – the Ekman 60 and the Emotion Hexagon (Calder *et al*., 1996; Young *et al*., 2002). Both of these tests have been used in previous research demonstrating disproportionate, and in some cases highly selective, impairments in recognizing fear or disgust (Calder *et al*., 1996, 2000; Sprengelmeyer *et al*., 1996, 1997, 1999). Hence, any impairments in anger recognition that we might observe cannot simply be attributed to level-of-difficulty explanations, such as anger being more susceptible to non-specific brain injury.

Ekman 60

Photographs of six facial expressions (happiness, sadness, anger, fear, disgust and surprise), posed by each of 10 models (six female, four male), were taken from Ekman and Friesen's (1975) pictures of facial affect series; a total of 60 pictures. The 10 models were selected so that each emotion was well recognized in Ekman and Friesen's (1975) norms. Each face was presented on a computer monitor for a maximum of 5 s and subjects were asked to select one of the six expression labels (listed above) that best described the emotional expression. The labels were visible throughout testing and subjects were given as much

Table 1 *Background information on the subjects from the VS group and BG control group*

	VS Group				BG control group			Controls	
	UI	BS	MT	KC	BX	LD	NK	Mean	SD
Age (years)	49	44	36	52	48	59	24	44.6	9.3
Sex	M	F	F	F	M	M	M		
Verbal IQ	97	89	110	107	118	121	105	109.0	6.8
Raven's SPM	33	43	47	40	53	45	46		
VISTECH 6000	Normal	Normal	Normal	Normal	Normal	Normal	Normal		
Hearing thresholds									
Mean dB for 500–2000 Hz	11.7	21.7	35.0	16.8	26.7	21.7	0.0		
Face processing									
Benton (/54)	41	41	49	50	41	48	50	46.8	4.1
Face recognition									
Faces									
Familiar (/30)	28	21**	30	30	29	29	30	28.3	2.7
Occupation (/30)	27	20**	29	29	29	27	30	27.7	3.1
Name (/30)	25	18	27	28	25	25	30	25.0	4.5
Unfamiliar (/10)	7**	10	5***	9	5***	7**	10	9.2	0.9
Names									
Familiar (/30)	30	29	30	30	30	30	30	29.9	0.3
Occupation (/30)	30	28	30	30	30	30	30	29.8	0.4
Unfamiliar (/10)	10	10	8***	10	10	10	10	9.9	0.3

$Z < -2.33$, $P < 0.01$; *$Z < -3.10$, $P < 0.001$.

time as they required to respond. No feedback was given regarding the appropriateness of any response. Control data for Ekman 60 were collected from 25 females and 25 males; mean age (SD) = 51.8 (5.7), mean IQ (SD) = 107.4 (6.8).

Emotion hexagon

This experiment contained morphed (blended) facial expressions posed by model JJ from the Ekman and Friesen (1975) pictures of facial affect series. A detailed description of the test can be found in Calder *et al*. (1996). Briefly, the test comprises morphed (or blended) continua ranging between the following six expression pairs: happiness–surprise, surprise–fear, fear–sadness, sadness–disgust, disgust–anger, anger–happiness. Each continuum consisted of five morphed images blended in the same proportions. For example, the images in the happy–surprise continuum contained the following percentages of the happy and surprise expressions: 90% happy – 10% surprise, and then 70% – 30%, 50% – 50%, 30% – 70%, and 10% – 90% of the same two expressions. Data from neurologically intact controls show that stimuli that contain 90 or 70% of an expression are consistently identified as the intended emotion (Calder *et al*., 1996; Sprengelmeyer *et al*., 1996; Young *et al*., 1997). The stimulus set consisted of 30 images in total (6 continua × 5 morphed faces).

The 30 morphed images were presented individually on a computer monitor in random order (i.e. they were not grouped by the underlying continua or emotions). Each face was presented on a computer monitor for a maximum of 5 s and subjects were asked to select one of the six expression labels (listed above) that best described the emotional expression. The labels were visible throughout testing and subjects were given as much time as they needed to make their selection. No feedback was given regarding the appropriateness of any response. Subjects undertook a total of six blocks of trials. Each block contained one presentation of each of the 30 morphed faces in random order. The first block of trials was discounted as practice, leaving five blocks of 30 trials for analysis.

Performance on the Emotion Hexagon was assessed as follows. The 30 morphed faces were divided into six sections containing morphs that the controls consistently identified with one of the six expression labels. Each expression region comprised four morphs; two of these contained 90% of the target expression and the other two 70%. For example, the surprise section contained the morphs 70% surprised – 30% happy, 90% surprised – 10% happy, 90% surprised – 10% afraid, and 70% surprised – 30% afraid. Performance was based on five presentations of each image, giving a total score out of 20 for each emotion. Control data for the Emotion Hexagon were collected from 26 females and 26 males; mean age (SD) = 48.1 (6.9), mean IQ (SD) = 107.9 (7.4).

Vocal expression recognition

Vocal expression recognition was assessed with two tests tapping recognition of emotion from non-verbal emotional sounds (i.e. laughter for happiness, growls/grunts for anger, etc.) and from emotional prosody (i.e. emotional tone in speech). As with the facial expression tasks, the vocal tasks have also been used in previous studies showing selective impairments of disgust and fear (Calder *et al*., 2000, 2001; Scott *et al*., 1997; Sprengelmeyer *et al*., 1999).

Non-verbal emotional sounds

Subjects were presented with 10 examples of non-verbal vocalizations associated with each of six basic emotions: happiness, sadness, anger, fear, disgust, and surprise (e.g. laughter for happiness, crying for sadness, grunts and growls for anger etc.). Stimuli were presented individually and in random order. The subjects' task was to select one of the six emotion labels (listed above) that best described the emotion conveyed. Labels were visible throughout testing and subjects were given as much time as they required to respond. No feedback was given regarding the appropriateness of any response. The stimuli were selected from a larger database recorded by one

male and one female actor according to the criterion that they were consistently identified as the intended emotion in a pilot study including 10 subjects. Control data for Nonverbal Emotional Sounds were collected from 10 females and 10 males; mean age (SD) = 47.8 (6.8), mean IQ (SD) = 112.3 (9.8).

Emotional prosody

The Emotion Prosody task tapped recognition of emotion from speech prosody using sequences of random digits (e.g. 1, 7, 4, 6, 8) spoken by actors in a manner to convey that they were happy, sad, angry, afraid or disgusted. There were 10 examples of each emotion category, presented individually and in random order. The subjects' task was to select one of the six emotion labels (listed above) that best described the emotion conveyed. Labels were visible throughout testing and subjects were given as much time as they required to respond. No feedback was given regarding the appropriateness of any response. Digit sequences were selected from a larger database recorded by 12 actors. Digits sequences spoken in a surprised tone of voice were not used in this test because previous work has suggested that surprise is not associated with distinctive prosodic features (Murray and Arnott, 1993). Control data for the Emotion Prosody task were collected from 11 females and 11 males; mean age (SD) = 45.4 (7.2), mean IQ (SD) = 114.8 (9.3).

Experience of emotion

Previous research has shown a possible link between experience of emotion and recognition of emotion in others (Sprengelmeyer *et al*., 1999; Calder *et al*., 2000). Consequently, we addressed subjects' experience of anger with three self-assessment questionnaires: the Spielberger (1983) Trait Anger Questionnaire, Buss and Perry's (1992) Aggression Questionnaire, and the Aggression Provocation Scale of O'Connor and colleagues (O'Connor *et al*., 2001). The Disgust Sensitivity Scale of Haidt and colleagues (Haidt *et al*., 1994) was also included to compare the patients' experience of anger to their experience of another related emotion. Each of these questionnaires has been validated as a measure of the relevant emotions in previous research. Control data for anger questionnaires were obtained from 28 females, mean age (SD) = 41.1 (12.6), and 21 males, mean age (SD) = 41.1 (12.6). Controls for the disgust questionnaire were obtained from 44 females, mean age (SD) = 52.7(14.9), and 30 males, mean age (SD) = 53.9 (13.2). Data for male and female controls are reported separately because males often report increased experience of anger relative to females. Note that control data for the recognition of human signal tasks were not broken down by gender because an analysis of the control data reported for all four emotion recognition tests showed no significant effects relating to the sex of control participants; see also (Young, *et al.*, 2002). Similarly, previous neuropsychological investigations using these tests have not divided the control data by sex.

Results

Background tests

Table 1 summarizes the VS and BG control group's performance on a series of background tests examining verbal and performance IQ, basic visual (VISTECH 6000) and auditory processing (hearing thresholds), and face processing skills (unfamiliar face matching, familiar face recognition). All patients showed preserved ability to match unfamiliar faces. With the exception of BS (VS group), the identification of familiar celebrities' faces (i.e. recognition of a face as familiar and recall of relevant semantic information and name) was preserved. UI and MT (VS group) and BX and LD (BG control group) showed a tendency to categorize unfamiliar faces as familiar, a pattern that has been observed following frontal lobe damage (Rapcsak *et al*., 1999), and is consistent with the view that lesions of the frontal cortex and basal ganglia can cause similar impairments (Lawrence, 2002). Mann–Whitney comparisons between the two groups for each of the background measures showed no significant effects (all P values were between 0.16 and 0.85).

Facial expression recognition

Data for the tests of facial expression recognition (Ekman 60 and Emotion Hexagon) are summarized in Table 2.

VS group

Anger was the most frequently impaired emotion in the VS group—87.5% of anger scores across the two facial expression tests were impaired (i.e. $Z < -1.65$, $P < 0.05$). By contrast, impairments for other emotions were comparably sparse and inconsistent across patients, with the exception of MT, who showed impairments for fear and sadness on both facial expression tests. MT differed from the other patients in that she had the most extensive VS damage (left) that almost entirely included the nucleus accumbens; recall that the region of maximal lesion overlap in the VS group was in the ventral putamen.

Table 2 *Recognition of facial expression (Ekman 60 and Emotion Hexagon)*

	VS Group				BG control group			Controls	
	UI	BS	MT	KC	BX	LD	NK	Mean	SD
Ekman 60									
ang (/10)	4**	4**	4**	9	10	10	9	8.1	1.7
dis (/10)	8	7	9	9	7	10	5**	8.8	1.5
fea (/10)	9	5	3*	7	5	5	7	7.3	1.8
hap (/10)	10	9	10	10	10	10	10	9.9	0.4
sad (/10)	9	9	5*	8	9	6	8	8.4	1.6
sur (/10)	9	9	9	8	8	10	8	8.6	1.4
Emotion Hexagon									
ang (/20)	12*	6***	7***	10***	15	18	17	17.6	3.1
dis (/20)	19	18	19	12*	19	20	14[b]	18.5	2.9
fea (/20)	16	13	7**	18	15	17	20	16.5	4.1
hap (/20)	19	19	20	20	20	15***	19	19.7	0.7
sad (/20)	19	18	11*	18	17	20	20	18.5	3.2
sur (/20)	16	19	19	19	18	20	16	17.9	2.0

Individual data are shown for the VS and BG control groups together with mean and SD for age- and IQ-matched controls. [b]$Z < -1.29$, $P < 0.1$; *$Z < -1.65$, $P < 0.05$; **$Z < -2.33$, $P < 0.01$; ***$Z < -3.10$, $P < 0.001$. ang = anger; dis = disgust; fea = fear; hap = happiness; sad = sadness; sur = surprise.

In this respect it may be relevant that the nucleus accumbens has also been implicated in defensive responding to threat-related cues (Reynolds and Berridge, 2001; Levita *et al*., 2002) and receives projections from a number of amygdaloid nuclei.

BG control group

The BG controls showed no evidence of anger deficits on the facial expression tasks, even if the significance level is dropped to borderline criterion (i.e. $Z < -1.29$, $P < 0.1$). To compare the performance of the VS and BG control groups on the facial expression tests, individual subject's average Z scores for each emotion category on the two face tasks (Ekman 60 and Emotion Hexagon) were compared with Mann–Whitney tests; Z scores for each test were calculated in relation to control performance. The analyses revealed a significant effect for anger only (anger, $U = 0.00$, $Z = -2.12$, $P < 0.05$; all other emotions, $P > 0.5$). Individual Mann–Whitney tests comparing VS and BG control groups' scores for each emotion category for the individual tests showed the same pattern, with significant effects for Ekman 60 anger ($U = 0.50$, $Z = -2.06$, $P < 0.05$) and Emotion Hexagon anger ($U = 0.00$, $Z = -2.12$, $P < 0.05$), but not any other emotion on either test ($P > 0.15$). Thus, the results of the BG control group provide additional evidence that the region of maximal lesion overlap in the VS group is indeed important for processing anger from facial expressions.

Vocal expression recognition

Data for the tests of vocal expression recognition (Nonverbal Emotional Sounds and Emotion Prosody) are summarized in Table 3.

Table 3 *Vocal expression recognition (Nonverbal Emotional Sounds and Emotion Prosody)*

	VS Group				BG control group			Controls	
	UI	BS	MT	KC	BX	LD	NK	Mean	SD
Nonverbal Emotional Sounds									
ang (/10)	7	5**	10	6*	7	10	8	8.1	1.1
dis (/10)	10	10	9	10	10	10	1***	9.8	0.4
fea (/10)	10	7	3***	8	5*	9	6	8.3	1.5
hap (/10)	8	7	8	7	9	7	7	8.0	1.0
sad (/10)	10	7	10	7	6*	9	9	7.9	1.0
sur (/10)	9	8	9	8	8	9	7	8.7	1.3
Emotion Prosody									
ang (/10)	4**	5*	2***	6	7	6	7	7.8	1.5
dis (/10)	1***	6	6	3*	8	8	4*	7.0	1.8
fea (/10)	6	3***	7	10	7	6	8	7.9	1.3
hap (/10)	3***	10	9	6	8	8	9	8.0	1.4
sad (/10)	9	8	9	7	8	9	7	8.2	1.6

Individual data are shown for the VS and BG control groups together with mean and SD for age- and IQ-matched controls.
*$Z < -1.65$, $P < 0.05$; **$Z < -2.33$, $P < 0.01$; ***$Z < -3.10$, $P < 0.001$.
ang = anger; dis = disgust; fea = fear; hap = happiness; sad = sadness; sur = surprise.

VS group

Although the VS group showed less striking evidence of anger impairment on the vocal expression tasks, anger was again the most consistently impaired emotion [62.5% of anger scores were impaired ($Z < -1.65$, $P < 0.05$) compared with 25% fear, 25% disgust and 12.5% happiness]. Moreover, each patient in the VS group showed anger impairment on at least one of the two vocal tests. Consistent with previous research showing general impairments in affective prosody recognition following BG damage (Blonder *et al*., 1989), performance on the prosody task was more variable than that on the other emotion recognition tests.

Reduced specificity of impairments on the vocal relative to facial tests is reminiscent of earlier neuropsychological investigations of human amygdala damage. These studies demonstrated that while patients with amygdala lesions showed consistent evidence of impaired fear recognition from facial signals, the corresponding deficit for vocal expressions was less prevalent, some patients showing impaired recognition of vocal fear cues (Scott *et al*., 1997; Sprengelmeyer *et al*., 1999) and others not (Adolphs and Tranel, 1999; Anderson and Phelps, 2000). It is also worth emphasizing that the patients in our study had unilateral lesions, hence complete disruption of anger processing is perhaps unlikely.

BG control group

Once again, the BG controls showed no evidence of anger deficits, even if the significance level is dropped to the borderline criterion (i.e. $Z < -1.29$, $P < 0.1$). To compare the performance of the VS and BG control groups on the vocal recognition tests, individual subjects' average Z scores for each emotion category on the two vocal tasks (Nonverbal Emotional Sounds and Emotion prosody) were compared with Mann–Whitney tests; Z scores for each test were calculated in relation to control performance. The analyses revealed a significant effect for anger only ($U = 0.00$, $Z = -2.12$, $P < 0.05$; all other emotions, $P > 0.4$).

Individual Mann–Whitney tests comparing VS and BG control groups' scores for each emotion category of the two individual vocal tests revealed a significant effect of anger for the Emotion prosody task ($U = 0.50$, $Z = -1.98$, $P < 0.05$) but not for the Nonverbal Emotional Sounds ($U = 3.00$, $Z = -1.08$, $P = 0.28$); none of the other emotions on the two vocal tests showed a significant difference (all P values > 0.15). Overall, the results of the vocal expression tests largely support the effects found for the facial expression tasks, in the sense that significant impairments were found for anger in VS group alone. However, the striking differentiation between performance on anger and other emotions in the facial expression tasks was not found for the vocal experiments.

We could find no evidence that the subjects' anger deficits were related to more basic factors, such as lesion volume or IQ, because the VS and BG control groups' anger scores for both face tasks or both voice tasks (i.e. average Z scores calculated relative to control performance) showed no significant

correlation with lesion volume, verbal IQ or Raven's test scores (all P values between 0.18 and 0.59). All subjects were also able to provide plausible examples of emotional situations corresponding to the six emotion labels (anger, happiness, etc.). Hence, the deficits observed do not reflect impaired understanding of these labels.

One additional point worth noting is that, consistent with a recent depth-electrode study specifically implicating the anteroventral (but not dorsal) insular region in the perception of disgust from facial expressions (Krolak-Salmon *et al*., 2003), the patients with the anteroventral insular lesions (KC and NK) showed evidence of impaired recognition of disgust on facial and vocal expression tasks. However, the patient with the anterodorsal insular lesion (UI) showed an impairment for disgust on the emotion prosody task alone.

Figure 2 summarizes the VS and BG control groups' recognition of facial and vocal signals of the five emotions that were represented in all four emotion recognition tests (happy, sad, anger, fear and disgust) in terms of the number of impaired scores (i.e. $Z < -1.65$, $P < 0.05$). The most consistently impaired emotion in the VS group was anger (75% of anger

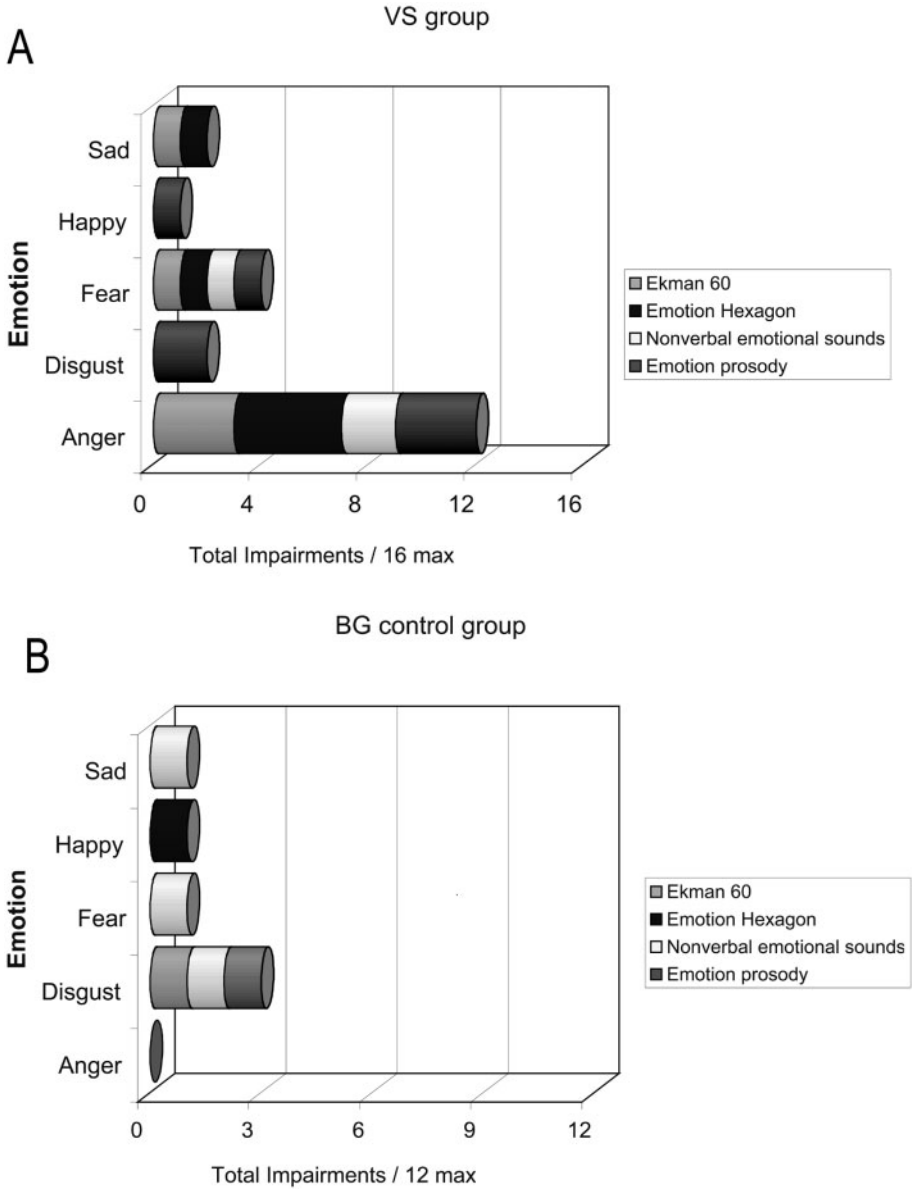

Fig. 2 Summary of emotion recognition. (**A**) VS group. Summary of the total number of impairments ($Z < -1.65$ relative to control performance) for the five emotion categories (happy, sad, anger, fear and disgust) that were represented in each of the four tests of emotion recognition (Ekman 60, Emotion Hexagon, Nonverbal Emotional Sounds and Emotion prosody). Out of a maximum of 16 for each emotion category (4 striatal lesion patients $\times$ 4 tests), anger clearly showed the most impairments (12/16), followed by fear (4/16), then disgust (2/16), sad (2/16) and happy (1/16). (**B**) BG control group. Data are summarized as described above. Note however, that there were three patients in this group; hence, the maximum number of impairments for each test is scored out of 12.

scores across the four tests were impaired), which showed three times as many impairments as the next most affected emotion: fear. Note also that the fear impairments in the VS group can be attributed almost entirely to MT, the patient with nucleus accumbens damage.

Despite the VS and BG control groups showing similar proportions of impairments for emotions other than anger (BG control group, 12.5% for non-anger scores; VS group, 16%), the BG controls showed no evidence of anger deficits, even if the significance level is dropped to the borderline criterion (i.e. $Z < -1.29$, $P < 0.1$). This difference was confirmed by a χ^2 analysis comparing the number of impaired anger scores and the total number of impaired scores for emotions other than anger across the two patient groups (VS and BG controls; $\chi^2 = 6.17$, $P < 0.02$). By contrast, a comparison of the two groups' scores for emotions other than anger showed no significant difference ($\chi^2 = 1.81$, $P > 0.6$).

In interpreting these results, it is important to be aware that fear is the most susceptible to non-specific brain injury (Rapcsak *et al*., 2000) or normal ageing (Calder *et al*., 2003) on these same tests. In addition, it is relevant that disproportionate or selective impairments of fear and disgust have been observed using the same facial and vocal tests in other patient groups (Calder *et al*., 1996, 2000; Scott *et al*., 1997; Sprengelmeyer *et al*., 1996, 1997, 1999). Consequently, the observed anger impairments in the VS group cannot simply be attributed to anger being more susceptible to brain injury than other emotions. The absence of anger impairments in BG control group provides further support for this conclusion.

Experience of anger

We addressed the patients' experience of emotion using three self-report questionnaires tapping anger (Spielberger *et al*., 1983; Buss and Perry, 1992; O'Connor *et al*., 2001) and a fourth addressing disgust (Haidt *et al*., 1994) for comparison.

From the VS group, KC and MT showed relatively consistent evidence of disrupted experience of anger, although this was expressed as a heightened anger reaction in KC and a reduction in MT. BS and UI showed only minimal disruption, and overall 25% of VS scores for anger questionnaires were above or below the control mean ($P < 0.05$) compared with just 9% for the BG controls (Table 4). Hence, our findings suggest that VS lesions can disrupt the experience of anger, rather than consistently reduce or enhance it, although this was not evident in all cases. In line with this pattern it is worth noting that Broks and colleagues have reported evidence of heightened and reduced experience of fear on different occasions in a single patient with bilateral amygdala damage (Broks *et al*., 1998). Similarly, heightened, unaltered or reduced emotional reactions to threat-related cues, such as a staring human, have been observed in different monkeys with amygdala lesions (Meunier *et al*., 1999; Machado and Bachevalier, 2000; Kalin *et al*., 2001).

In relation to this point, one of the reviewers drew attention to fact that there is some evidence of fluctuating scores across different aggression questionnaires in two of the patients in our own sample. For example, UI scores significantly below the control mean on the State Trait Anger Scale, around the control mean on the Trait Anger Questionnaire, and above the control mean (although not significantly so) on the Aggression

Table 4 *Experience of anger and disgust assessed with self-report questionnaires*

	VS Group				BG control group			Controls			
	UI	BS	MT	KC	BX	LD	NK	Females		Males	
								Mean	SD	Mean	SD
Sex	M	F	F	F	M	M	M				
Spielberger Trait Anger Survey	19*	33	29	49h***	25	24	26	27.5	6.4	28.5	5.1
Trait Anger Questionnaire											
Physical (/45)	16	13	20	14	13	9	25	14.1	5.6	18.3	7.6
Verbal (/25)	13	6*	6*	13	12	10	10	12.2	3.5	14.8	4.3
Anger (/35)	11	14	17	27h**	9	7*	15	14.2	5.8	15.6	4.8
Hostility (/40)	15	15	21	19	18	17	20	14.5	4.3	16.0	4.7
Total (/145)	55	48	64	73	52	43	70	55.0	16.8	64.7	15.5
Aggression Provocation Scale											
Angry (/48)	40	31	16*	41	26	41	29	29.2	7.7	31.1	8.9
Frustrated (/48)	37	28	5***	42h**	30	36	26	26.9	6.7	29.1	9.9
Irritated (/48)	41	35	14**	46h*	34	43	25*	32.1	6.8	36.7	6.2
Aggressive (/12)	2	0	0	0	3h*	2	0	0.4	0.6	0.6	1.1
Assertive (/12)	5	2*	8	6	6	7	6	6.2	2.3	6.9	2.3
Disgust Sensitivity Scale	34.4	42.2	75.0	39.0	25.0	48.4	21.9*	53.5	13.3	41.4	11.1

Individual data are shown for the VS and BG control groups together with mean and SD for age- and IQ-matched controls. Asterisks indicate a reduction relative to controls; asterisks accompanied by an 'h' (for hypersensitivity) indicate an increase. *$Z < -1.65$, $P < 0.05$; **$Z < -2.33$, $P < 0.01$; ***$Z < -3.10$, $P < 0.001$; h*$Z > 1.65$, $P < 0.05$; h**$Z > 2.33$, $P < 0.01$; h***$Z > 3.10$, $P < 0.001$.

Provocation Scale. Similarly, MT is at, or slightly above control performance on a number of scores on the State Trait Anger Scale and the Trait Anger Questionnaire (excluding Trait Anger Questionnaire verbal), but well below the controls on the Aggression Provocation Scale. Given that the questionnaires were administered on different occasions, it is possible that this fluctuating performance reflects an erratic aggression system. This could be investigated further by having the patients complete the same questionnaires on future occasions. Fluctuating performance across time on the same questionnaires would support the erratic hypothesis rather than an explanation relating to individual differences interacting with differences among the constructs measured by the different questionnaires.

In contrast to evidence of disrupted anger processing in the VS group, their experience of disgust did not fall outwith the significant cut-off point. Thus, the disrupted experience of anger shown by the VS subjects does not simply reflect a more general disruption of emotional experience. As reported in a previous study, however, NK from the BG control group showed a selective impairment in experience of disgust (Calder *et al*., 2000), in line with his selective impairment in recognizing disgust from facial and vocal signals.

Discussion

Previous research has highlighted the amygdala's role in fear processing and the insula's role in disgust. Here we have provided new evidence that the ventral striatum is important for coding human signals of aggression and experience of anger. By contrast, lesions to more dorsal BG regions had no significant impact on anger processing. As we have discussed, these findings are grounded in research showing that homologous brain regions in non-human species play related functional roles (Lawrence and Calder, 2004). In the case of anger, our current hypothesis was based on observations from comparative research implicating the dopamine system and ventral striatum in the production of displays of aggression (Redolat *et al*., 1991; Stern and Passingham, 1996; van Erp and Miczek, 2000; Ferrari *et al*., 2003), and more recent evidence highlighting the contribution of dopamine to humans' recognition of facial signals of anger (Lawrence *et al*., 2002) and aggressive behaviour (Tiihonen *et al*., 1995; Lawrence *et al*., 2003).

The anger impairment in the VS group was particularly evident on tests of facial expression recognition (7/8 impaired anger scores across two tests in the VS group versus 0/6 for the BG control group). The consistency of the impairment is all the more striking when we consider that the subjects' lesions were unilateral. Anger impairments for the vocal tests were also present (VS group, 5/8 impaired anger scores; BG controls, 0/6), although the vocal data did not show the degree of selectivity observed for facial expressions.

Of course there are different reasons why the vocal stimuli should produce less clear results. One explanation already discussed relates work showing impaired recognition of emotional prosody in general following BG damage (Blonder *et al*., 1989). A second relates to the fact that considerably less research has gone into delineating the essential acoustic features of different vocal signals of emotion than has been invested in identifying the physiognomy of facial expressions (Ekman, 1992). Hence, the vocal stimuli are likely to be more approximate simulations of the intended emotions than their facial counterparts from Ekman and Friesen's (1975) well-validated database. A third explanation is that the same neural systems may not underlie both facial and vocal expression recognition of signals of aggression. However, this final explanation would seem less likely on the basis of our current results, given that significant impairments were found in recognizing vocal signals of aggression, but not other emotions, for the comparison of VS and BG control groups.

The fact that the VS group showed lesser impairments for emotions other than anger is also worthy of discussion. However, with the exception of MT, these impairments were sparse and not tied to any emotion in particular. MT was the only patient who showed a consistent impairment for emotions in addition to anger, showing impaired recognition of fear on three out of four tests; thus, MT accounts for 75% of the VS group's impaired fear scores illustrated in Fig. 2. As discussed, MT differs from other patients in that her lesion includes the entire left nucleus accumbens. This may relate to research showing that the caudal shell of the accumbens is involved in defensive fear-related behaviour (Reynolds and Berridge, 2001).

Differences in lesions across patients are an inevitable complexity of neuropsychological research, leading to variable patterns of performance. Consequently, it is important to emphasize that the group analyses indicated that the VS patients showed impaired anger recognition on three out of the four expression recognition tasks relative to the BG controls. By contrast, the two groups' recognition of other emotions showed no significant difference. It is also worth emphasizing that one of the VS patients (BS) showed a highly specific disruption of anger recognition, showing selective impairments for anger alone on three out of four tests. In addition, UI showed a similar degree of selectivity for the face tasks. Hence, our study provides support for our hypothesis at the level of individual cases, as well as across the four VS patients as a group.

Performance on the questionnaires tapping experience of anger (or aggression) showed no consistent pattern across VS participants, with KC showing evidence of heightened aggression and MT reduced aggression. The observation that similar brain lesions should produce opposite effects in different individuals is not without basis, and heightened and reduced emotional reactions towards threat-related stimuli have been observed in monkeys with bilateral ibotenic acid lesions of the amygdalae (Meunier *et al*., 1999; Machado and Bachevalier, 2000; Kalin *et al*., 2001). Similarly, Broks and colleagues reported that a patient with bilateral amygdala damage showed heightened and reduced emotional responses towards threat cues on different occasions (Broks *et al*., 1998).

Hence, it is possible that lesions to the ventral striatum might produce unpredictable and erratic responses to anger-provoking situations. Indeed, this possibility is not without basis, because increased irritability/aggression is one of the most common behavioural manifestations of Huntington's disease (Craufurd and Snowden, 2002), a degenerative disorder that causes marked striatal pathology. Moreover, aggressive outbursts in these patients are often unpredictable (Craufurd and Snowden, 2002), consistent with the erratic hypothesis.

The fact that none of the VS patients showed impairments on the disgust questionnaire, however, argues for some degree of specificity in relation to their emotional experience impairments.

As already discussed, our study deliberately employed tests that have been used previously to demonstrate disproportionate or selective impairments of fear and disgust following damage to the amygdala (Calder *et al*., 1996; Scott *et al*., 1997; Broks *et al*., 1998; Sprengelmeyer *et al*., 1999) and insula (Calder *et al*., 2000) respectively. Thus, we can be sure that the disproportionate anger impairments reported here are not simply due to our choice of materials or experimental design. In one of these earlier studies we demonstrated that patients with Huntington's disease showed disproportionate impairments in recognizing human signals of disgust (Sprengelmeyer *et al*., 1996). On the basis of our current findings and the generally accepted view that Huntington's disease affects primarily the striatal regions, it is reasonable to ask why anger is not disproportionately impaired by Huntington's disease. In which case it is important to point out that disgust was not the only emotion affected in the Huntington's study, and, consistent with our current findings, anger recognition was indeed severely impaired. In other words, Sprengelmeyer and colleagues found that disgust was most affected by Huntington's disease, not that anger was intact (Sprengelmeyer *et al*., 1996). Secondly, recent work has shown that presymptomatic Huntington's gene carriers show reduced grey matter volume that extends beyond the striatum into cortical regions including the insula (Thieben *et al*., 2002). Consequently, a plausible hypothesis is that anger impairments in Huntington's disease may reflect striatal damage, while the disgust impairments reflect insula damage.

Functional imaging studies of anger processing

Although few studies have investigated the neural correlates of anger processing with functional imaging, the most consistent finding is the involvement of ventrolateral prefrontal regions in processing signals of aggression (Sprengelmeyer *et al*., 1998; Blair *et al*., 1999; Phillips *et al*., 1999). However, research has also implicated the ventral BG in mental imagery of anger-provoking scenarios (Schaefer *et al*., 2003) and in the perception of facial expressions of aggression (Phillips *et al*., 1999). Similarly, activity in midbrain and striatal regions has been observed for self-induced anger relative to self-induced anxiety (Kimbrell *et al*., 1999).

In the light of the connectivity between the ventrolateral prefrontal cortex and ventral striatum (Middleton and Strick, 2001), a plausible hypothesis is that human signals of aggression are processed by a frontostriatal system. This 'circuit' model is also consistent with the observation that lesions to the medial globus pallidus (a component of the lateral orbitofrontal frontostriatal circuit) affect aggressive displays in monkeys (MacLean, 1977).

It is worth noting that some functional MRI research has also implicated the amygdala in coding facial displays of anger (Whalen *et al*., 2001). In this respect it is relevant that ethologists have distinguished different forms of aggression, including offensive (or competitive) aggression relating to the acquisition and maintenance of valued resources (e.g. mates, food, social dominance), and defensive aggression relating to a threat-invoked fight response (Blanchard and Blanchard, 1988). While the neural basis of the defensive form is thought to include the amygdala (a region implicated in the detection of threat in humans) the neural basis of offensive aggression is not (Blanchard and Blanchard, 1988). A clear understanding of the biological basis of offensive aggression is yet to be established. However, consistent with our own findings, comparative research has implicated midbrain structures, including regions with dopaminergic projections to the ventral striatum (Adams, 1986; Blanchard and Blanchard, 1988) and the ventral striatum itself (Ferrari *et al*., 2003). A large body of research has also implicated reductions in serotonin in an 'impulsive' form of offensive aggression. However, it is important to note that recent manipulations of serotonin in humans have produced altered recognition of facial expressions of fear, not anger (Harmer *et al*., 2003); as we have discussed, anger recognition is affected by sulpiride, a dopamine antagonist (Lawrence *et al*., 2002).

The ventral striatum, reward and anger

Finally, it is worth considering that the ventral striatal dopamine system has not only been implicated in aggression but also in the pursuit of biological resources generally, including food, territory, mating opportunities and stimuli that reliably predict them (Ikemoto and Panksepp, 1999). Included in this research is a substantial amount of work implicating the dopaminergic system and ventral striatum in reward processing and incentive motivation, in both comparative (Hernandez and Hoebel, 1988; Pfaus *et al*., 1995) and human fields of research (Knutson *et al*., 2001; Koepp *et al*., 1998). In this respect it worth considering Blanchard and Blanchard's (1989) proposal that certain forms of aggressive encounter occur in the context of conspecific challenge and contests over valued resources. For example, in the case of a property dispute, the goal (or reward) is to gain possession of the disputed property (e.g. food, territory, mates), while the desire to achieve this goal provides the incentive for the attack. Thus, we propose that the role of the ventral striatal dopamine system in the recognition of human signals of anger may reflect a more general role in the coordination of behaviours relevant to the acquisition and

protection of valued resources, including the detection of signals of conspecific challenge (Lawrence *et al*., 2002).

In summary, our results provide the first evidence of a disproportionate deficit in coding human signals of aggression, particularly facial expressions, following focal damage to the ventral striatum. By contrast, damage to more dorsal BG regions had no significant impact on anger processing. These findings concur with comparative research highlighting the role of the ventral striatum and dopaminergic system in aggression (Ferrari *et al*., 2003; Redolat *et al*., 1991; Stern and Passingham, 1996), and more recent work demonstrating that acute administration of sulpiride (a dopamine antagonist) impairs humans' recognition of facial expressions of anger (Lawrence *et al*., 2002). These findings emphasize the utility of an approach based on cross-species homologies in understanding the neural basis of human emotion (Griffiths, 1997; Lawrence and Calder, 2003).

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