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Emotional blunting following left basal ganglia stroke: The role of depression and fronto-limbic functional alterations

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Abstract

Disorders of the basal ganglia (BG) alter perception and experience of emotions. Left hemisphere BG (LHG) stroke is also associated with depression. The interplay between depression and alterations in emotional processing following LHG stroke was examined. Evoked affective responses to emotion-laden pictorial stimuli were compared among LHG stroke and healthy participants and participants with stroke damage in brain regions not including the LHG selected to equate depression severity (measured using the Hamilton Depression Scale) with LHG damage participants. Brain activity {[O¹⁵]water PET} was measured in LHG stroke relative to healthy participants to identify changes in regions associated with emotion processing and depression. LHG stroke subjects reported less intense emotions compared with healthy, but not stroke comparison participants. Depression negatively correlated with emotional experience for positive and negative emotions. In response to positive stimuli, LHG subjects exhibited higher activity in amygdala, anterior cingulate, dorsal prefrontal cortex, and insula compared to healthy volunteers. In response to negative stimuli, LHG subjects demonstrated lower activity in right frontal-polar region and fusiform gyrus. Higher baseline activity in amygdala and ventral and mesial prefrontal cortex and lower activity in left dorsal lateral prefrontal cortex were associated with higher depression scores. LHG stroke led to blunted emotions, and brain activity alterations accounting for reduced affective experience, awareness and depression. Depression and fronto-limbic activity changes may contribute to emotional blunting following LHG stroke.

Keywords

Basal ganglia; amygdala; anterior cingulate cortex; frontal lobe; mesial prefrontal cortex; insula; affective experience; emotion awareness; emotion perception

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1. Introduction

Individuals with damage to the basal ganglia (BG) often show changes in a variety of behavioral and psychological domains (Rosenblatt and Leroi, 2000; Ring and Serra-Mestres, 2002; van Duijn et al., 2007; Aarsland et al., 2009). Consistent with views positing that functions of BG extend beyond motor control (Bhatia and Marsden, 1994; Sprengelmeyer et al., 1996; Berridge and Robinson, 2003; Paulsen et al., 2006), damage to the BG including the left BG (LBG) has been associated with alterations in emotion processing (e.g., perception and experience) (Sprengelmeyer et al., 1996; Calder et al., 2000). Lesions of the BG, especially the LBG, also increase risk for depression (Starkstein et al., 1991; Fang and Cheng, 2009; Nishiyama et al., 2010).

Given that mood and emotion processing changes occur often simultaneously in the same individual with LBG damage, the interplay between depression and emotion processing changes following LBG damage needs further examination. To begin, because depression has been consistently associated with changes in emotion perception (Gotlib and McCabe, 1992; Gur et al., 1992; Mikhailova et al., 1996; Hale, 1998; Bouhuys et al., 1999; Langenecker et al., 2005), emotion processing deficits generally attributed to BG damage (Sprengelmeyer et al., 1996; Calder et al., 2000) may actually be related to depression brought on by the damage to the LBG. Therefore, changes in emotion perception and experience observed after LBG damage (Calder et al., 2000) may be in part due to LBG stroke-associated depression.

The present study sought to better characterize the association between depression, emotion processing and LBG damage using a number of approaches. The analyses were designed to 1) confirm that LBG damage is associated with emotional processing deficits; 2) ascertain whether LBG critically subserves emotion processing abilities independent from depression; and 3) examine the extent to which brain activity following LBG stroke is associated with depression. Confirmation of the first point entailed the investigation of 6 subjects with damage restricted to the LBG and 12 age-equated and sex-matched volunteers without cerebrovascular damage who were compared on responses (perception and emotion experience) to emotion-laden visual stimuli. Additionally, following up on a case report of emotion processing deficits after LBG (and nearby brain regions) damage (Calder et al., 2000), the present study compared individuals with damage restricted to the LBG with 10 participants with stroke damage in brain regions not including the LBG or the left hemisphere (stroke damage comparison or SDC) selected with the goal of reaching comparable average severity of depression between the two samples with stroke. This approach allowed controlling both for the effect of non-specific brain damage and for the effect of depression. To expand and recapitulate, the first analysis was designed to confirm that LBG damage is associated with emotional processing deficits when healthy volunteers are used as comparison subjects. It was expected that subjects with LBG damage would show weaker emotional responses (perception and experience), consistent with an earlier report (Calder et al., 2000). Because participants with LBG damage are expected to have high rates of depression, simply comparing LBG damage to healthy non-depressed volunteers raises the possibility that any observed difference may be secondary to

depression (Gotlib and McCabe, 1992; Gur et al., 1992; Mikhailova et al., 1996; Hale, 1998; Bouhuys et al., 1999; Langenecker et al., 2005). Therefore, discernment of the role of LBG versus depression in emotion processing (#2) entailed the investigation of a group of comparison participants selected based on similar mechanisms (i.e., brain damage) and severity of depression as in LBG subjects (SDC subjects). If depression indeed plays a role in the reduction of emotion processing abilities observed after LBG damage, SDC subjects should show similar emotion processing impairment as LBG participants (Gotlib and McCabe, 1992; Gur et al., 1992; Mikhailova et al., 1996; Hale, 1998; Bouhuys et al., 1999; Langenecker et al., 2005). On the contrary if subjects with LBG damage are found to show weaker emotional responses relative to SDC subjects with depression, it may be concluded that LBG critically subserves emotion processing abilities independent from depression. Note that the latter comparison serves also to control for non-specific brain damage (Beadle and Tranel, in press).

The third goal of this study was to examine the extent to which brain activity following LBG stroke is associated with depression (Drevets, 2001; Mayberg, 2002). Brain activity elicited by viewing emotional and neutral stimuli and measured using [^{15}O]water positron emission tomography (PET) (Turner et al., 2007; Paradiso et al., 2008a; Paradiso et al., 2011) is reported in individuals with LBG damage relative to healthy volunteers. Because idiopathic (i.e., depression without gross brain damage) and post-stroke depression (Paradiso et al., 1997a) show essentially overlapping phenomenology, it was expected that depression following LBG lesion would be associated with the characteristic patterns of brain activity observed in idiopathic depression including higher activity in amygdala and mesial prefrontal cortex and lower activity in dorsal lateral prefrontal cortex (Drevets, 2001; Mayberg, 2002; Zhong et al., 2011). In addition, brain activity measurements allowed an examination of regions of altered activity distant from the site of (LBG) damage (Turner et al., 2007; Paradiso et al., 2011). Based on expectations that LBG damage is associated with reduction in emotion processing, regions supporting emotion experience and awareness including the mesial prefrontal cortex and cingulate gyrus, and the insular cortex (Craig, 2009; Etkin et al., 2011) were expected to show significant brain activity alterations.

2. Methods

2.1 Participants

Subjects were selected from a larger cohort recruited to study brain networks effects of focal brain damage during emotion experience using PET and the [^{15}O]water method (Paradiso et al., 2003; Turner et al., 2007; Paradiso et al., 2011). Subjects with stable strokes to the LBG (i.e., time from acute stroke greater than 3 months), confirmed by neurological exam and MRI scan (Figure 1), constituted the experimental group. Non-stroke, non-depressed healthy (NSNDH) volunteers were selected based on a negative neurological and psychiatric history and an MRI scan showing no brain abnormalities. An additional group of stroke subjects with stable lesions located in regions other than the left basal ganglia (e.g., the territories of the right middle cerebral artery or cerebellum) (Figure 2) and selected so that mean severity of depression (measured using the Hamilton Depression Scale) was equated to that of LBG subjects served as a SDC group. All stroke subjects screened negative for history of

psychiatric or neurological disorder prior to the stroke, additional life-threatening or cognitively impairing physical illness. Participants failing to complete Part One of the Token Test (De Renzi and Vignolo, 1962) were excluded. Participants scored 23 or higher on the Mini-Mental State Exam. Groups were equated based on age, education and IQ. LBG and NSNDH subjects were also matched (1:2) on sex. Approval for this project was obtained from the University of Iowa Institutional Review Board. Informed consent was obtained and subjects were compensated for participating in the study.

2.2 Psychiatric and neuropsychological assessment

Psychopathology was assessed by a single trained research assistant using the Present State Examination (PSE), a semi-structured mental status interview (Wing et al., 1974). The Hamilton Depression Scale (HamD) (Hamilton, 1960) and Hamilton Anxiety Scale (HamA) (Hamilton, 1959) measured depressive and anxiety symptoms. The 20-item Toronto Alexithymia Scale (Bagby et al., 1994) was administered to measure degree of alexithymia, a psychological construct introduced by Sifneos (Sifneos, 1973) and describing difficulty identifying emotions and distinguishing between body sensations and feelings, and little interest in one's own mind's workings (widely-known as externally-oriented cognitive style) (Taylor et al., 1997). The following functioning variables were also assessed: global functioning (Global Assessment of Functioning, GAF) (Jones et al., 1995), functioning on activities of daily living (John Hopkins Functioning Inventory, JHFI) (Robinson and Benson, 1981), functional independence (Adult Functional Independence Measure, Adult FIM) (Hamilton et al., 1987) strength of social ties (Social Ties Checklist, STC) (Starr et al., 1983) and strength of social functioning (Social Functioning Exam, SFE) (Starr et al., 1982). The Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) and National Adult Reading Test (NART) (Nelson, 1982) were used to evaluate current and premorbid general intelligence. The Rey-Osterreith Complex Figure Test - Copy Condition (Meyers and Meyers, 1995) and Facial Recognition Test (Benton et al., 1994) were administered to assess visuospatial processing ability. The Rey Osterreith Complex Figure Test (Meyers and Meyers, 1995) immediate and delayed recall conditions and the Benton Visual Retention Test (Sivan, 1992) were used to evaluate visual memory abilities. The WAIS-R Digit Span (Wechsler, 1981) subtest was used to measure attention. The Boston Naming Test (Kaplan et al., 1983) and Controlled Oral Word Association (Benton et al., 1994) were used to assess language. Assessment of executive functions was attained by examining the frequency of perseverative errors made while performing the Wisconsin Card Sorting Test (Heaton et al., 1981). Motor function was assessed with the Reitan Finger Tapping Task (Reitan and Wolfson, 1985). Presence and severity of visual neglect was evaluated through use of the Line Bisection task (Lezak, 1995).

2.3. MRI imaging acquisition and processing

T1-, T2-, and proton density (PD)-weighted images were acquired using contiguous coronal slices from a 1.5 tesla GE Signa Scanner. The field of view for all images was 26 x 26 cm and the matrix was 256 x 192. Technical parameters were as follows: T1-weighted images had a 1.5 mm slice thickness, SPGR sequence, flip angle = 40 degrees, echo time (TE) = 5 ms, repetition time (TR) = 24 ms, and number of excitations (NEX) = 2; PD-weighted images had a 3.0 mm slice thickness, TE = 36 ms, TR = 3000 ms, and NEX = 1; T2-

weighted images had a 4.0 mm slice thickness, TE = 96, TR = 3000 ms, and NEX = 1. MRI images were analyzed with locally developed software (BRAINS2) (Magnotta et al., 2002). All brains were placed into standard Talairach space (Talairach and Tournoux, 1988) and realigned parallel to the anterior-posterior commissure (AC-PC) line and interhemispheric fissure to ensure comparability of head position across subjects. Images from all subjects were co-registered and resliced in three orthogonal planes to produce a three-dimensional “average” image that was used for visualization and localization of neural activity. MR images were then processed using methodology previously utilized in our laboratory and automated neural networks to quantify grey, white matter and cerebral spinal fluid volumes (Andreasen et al., 1996). Visual inspection determined anatomic accuracy of identification of the above structures by the automated neural network before volumes were measured. In addition T2 -weighted MR images were examined to assess presence of hyperintensities in frontal, parieto-occipital and temporal lobes and basal ganglia using a widely used semi-quantitative rating method (Wahlund et al., 2001).

2.4 Emotion induction stimuli

Testing conditions were the same for LBG, NSNDH and SDC participants. While in the scanner all participants were presented with single valence (fear/disgust-evoking, happiness-evoking or neutral) blocks of stimuli. Each block was comprised of either 18 images including emotionally expressive human faces or 18 emotionally evocative scenes and objects. Number of blocks was 8, and within the block each image was shown for 6 seconds (total block time = 108 seconds). Stimuli were chosen from the International Affective Picture Systems (Lang et al., 1995), as described in previous studies (Paradiso et al., 2003; Turner et al., 2007). Subjects had not seen these stimuli before the scanning session. Block presentation was counterbalanced.

Responses to sadness evoking stimuli were also available (Paradiso et al., 2003) but were not examined because whereas depression may affect perception of most positive and negative emotions, patients with depression may show better than normal recognition accuracy for sad emotions (Gur et al., 1992; Bouhuys et al., 1999; Gollan et al., 2010). Appropriate (or even enhanced) response to sad stimuli would have not allowed discriminating the extent to which this was influenced by the subjects' sad mood or the result of intact appreciation of the sad stimuli.

Subjects were instructed to allow the stimuli to affect their emotional state. Seconds after viewing each block of images, participants were asked to report the intensity of their experienced emotion (happiness, amusement, fear, anger and disgust) with the assistance of a visual Likert scale (0 - absence of any emotion and 10 - very intense emotional experience). After completion of the emotion induction experiment, participants were shown the same stimuli and asked to rate the hedonic value (how pleasant?) of each block using a Likert scale anchored at -7 (very unpleasant) to 7 (very pleasant) providing an assessment of emotion perception as opposed to subjective emotional experience.

2.5 PET imaging acquisition and processing

Regional brain activity was imaged during each block of stimuli using [^{15}O] water positron emission tomography (PET) (50 mCi/injection) using a GE-4096 PLUS scanner and methods reported previously for work at this institution (Hichwa et al., 1995). Fifteen slices (6.5 mm center to center) with an intrinsic in-plane resolution of 6.5 mm full width at half maximum and a 10 cm axial field-of-view were acquired. Images were reconstructed using a Butterworth filter (cutoff frequency = 0.35 Nyquist). A preliminary “scout” injection (15 mCi) was used to estimate bolus arrival time for each participant; stimulus onset was adjusted accordingly to begin 15 seconds prior to estimated bolus arrival (Hurtig et al., 1994). Functional imaging began at the time of injection and lasted for 100 seconds. Count-based activity information was collected in five second bins; a 40-second summed image containing the activity information immediately post bolus transit were utilized in the analyses. Co-registration of each subject’s PET and MRI images utilized a two-stage process with an initial coarse fit based on surface matching of MRI and PET images and then a variance minimization program using surface fit data as input (Woods et al., 1993). The hand-traced outlines of lesion extent from the MRI were used to exclude damaged regions from the PET analyses. The filtered PET image was clipped to a hand-edited outline of the brain drawn on each individual’s MR scan to minimize motion artifacts. Based on the normalized MR scan for each individual, a histogram threshold of 160 units was used to retain gray and white matter within the brain while eliminating motion artifacts surrounding the ventricles. PET activity images, excluding the damaged areas, were normalized to an average value of 1 by dividing by the global activity level. Finally, an 18 mm Hanning filter was applied to the PET images to account for structural and functional variability.

2.6 Data analysis

2.6.1 Clinical and emotion response data—Demographic, psychiatric, neuropsychological, psychosocial and physical functioning data and emotional responses were analyzed using nonparametric Mann-Whitney U tests (or equivalent) to evaluate between-group differences and Wilcoxon Signed Rank Testing to evaluate within-group differences. Happiness and amusement were the dependent variables in response to the positive stimuli (happiness-evoking faces and scenes/objects) whereas fear, anger and disgust were the dependent variables in response to the negative stimuli (fear-evoking faces and scenes/objects). Affective responses of LBG subjects were compared both to NSNDH and to SDC subjects. Spearman’s correlation coefficients were computed between Hamilton depression scale scores, emotion response, and baseline functional activity (reported are only significant volumes exceeding 50 voxels) using pooled LBG and NSNDH subjects (Zeki et al., 1991; Horwitz, 1994; Silbersweig et al., 1994). Correlations between emotion experience and alexithymia were also computed.

2.6.2 PET imaging data—First, in order to examine the participation of the LBG in the experience of positive and negative emotion, a within-group, voxel-wise brain-wide analysis was computed on NSNDH volunteers comparing brain activity elicited by responses to emotion and neutral conditions using in-house developed software based on a modification of the Montreal method (Worsley et al., 1992; Andreasen et al., 1995). Second, differences in regional brain activity between LBG and NSNDH groups were examined using

nonparametric randomization (permutation) analysis (Holmes et al., 1996; Arndt et al., 1996a) consisting in the contrast of the “difference images” computed from the initial comparison of PET images obtained in response to emotional face stimuli with those obtained in response to neutral face stimuli in LBG and NSNDH subjects separately. In this way the brain activity difference in response to emotional stimuli between experimental and comparison subjects is examined taking into account the respective activity in response to neutral stimuli. This randomization analysis sampled groups of 6 and 12 participants without regard for the original group assignment. Voxel-wise t-maps were generated after each sampling. After 3,000 randomizations, the distributions of the voxel-wise t-values provided an estimation of the probability that an associated t-value could occur by chance. Regions exceeding chance t-values were identified on the t-map images and corrected for the large number of t-tests performed, the lack of independence between voxels, and the resolution of the processed images (Holmes et al., 1996; Arndt et al., 1996a). Consistent with our previous studies (Arndt et al., 1996b; Crespo-Facorro et al., 2001; Paradiso et al., 2011), an uncorrected p-value of 0.005 was used in association with the volume criterion (i.e., only volumes of activation exceeding 50 contiguous voxels with $\alpha = 0.005$ are reported) thus generating a composite threshold for defining significant activations robust against false positives. Region identification was based on direct visual inspection of coregistered individual subjects MRI scans and PET images. Interpretation of the direction of the change in activity in each group was determined by examining the T-max for each significant peak and the T-max for the within-group comparisons. Imaging data relative to responses to scenes and objects is not reported for brevity as behavioral data attained using these stimuli did not show significant group effects (see below Results: Emotion experience and perception).

3. Results

3.1 Background assessment

Participants were 6 subjects with LBG damage (2 female, 33.3%; mean age = 67.5 ± 9.40 years; 16.7% left-handed), 12 NSNDH volunteers (4 female, 33.3%; mean age = 65.5 ± 6.27 years; 33.3% left-handed or ambidextrous), and 10 SDC subjects (1 female, 10%; mean age = 67 ± 7.01 years; 0% left-handed). Demographic, psychiatric, social and physical functioning variables are shown in Table 1. Cognitive data are shown in Table 2. Between LBG and NSNDH participants there were no significant differences in age, education, social functioning, current or premorbid intelligence. The LBG group showed significantly poorer global functioning, activities of daily living and functional independence and greater severity of depression and alexithymia compared to NSNDH volunteers. No significant group differences were found on attention, visual memory, facial recognition and visual construction. LBG subjects showed significantly lower performance on Line Bisection Task and Reitan finger tapping task (dominant hand), language and some executive function measures (WCST perseverative errors) (Table 2).

LBG and SDC subjects (Table 2) showed limited differences in neuropsychological performance (i.e., a group effect on the 20-mm Line Bisection Task). Five of 6 LBG and 6 (of 10) SDC participants met criteria for major depression at time of study. Two LBG and 2

SDC participants were treated with selective serotonin reuptake inhibitors (SSRIs). In order to characterize the depressive phenomenology of participants with stroke, percentage of subjects with DSM-IV-TR (American Psychiatric Association, 2000) depressive symptoms are reported. There were 33% participants in the LBG and 40% in the SDC group endorsing sadness, whereas 33% in the LBG and 60% SDC reported anhedonia. There were no subjects in the LBG and 20% in the SDC group who reported guilt, whereas none in the LBG and 10% in the SDC group reported suicidal ideation. All subjects in both groups reported sleep problems (insomnia or hypersomnia) and all LBG and 90% SDC subjects reported psychomotor disturbances. Weight or appetite changes were found in 33% of SDC and 50% of LBG subjects.

3.2 Structural imaging

All LBG stroke subjects had damage localized to left basal ganglia structures (Figure 1, Table 3). As expected, LBG subjects exhibited significantly smaller brain volumes than NSNDH subjects (Table 4). Analyses of the grey, white matter and cerebral spinal fluid compartments showed that volume differences were largely accounted for by white matter while grey matter and CSF showed nonsignificant differences. Analyses of white matter lesions for LBG and NSNDH groups showed no significant differences (Table 4).

3.3 Emotion experience and perception

The stimuli evoked the intended emotions (happiness and amusement for positive stimuli; anger, fear and disgust for negative stimuli) among NSNDH volunteers (Table 5). Consistent with previous studies (Paradiso et al., 2003; Mezulis et al., 2004), neutral stimuli generated moderate levels of happiness and amusement. Compared to NSNDH, LBG subjects experienced consistently lower emotional intensity in response to all facial expressions (Table 6). Differences in emotional experience in LBG subjects reached statistical significance for amusement in response to positive stimuli ($U=13.5$, $p=0.033$) and for disgust in response to negative stimuli ($U=14.5$, $p=0.039$). Because emotion differences may be conceivably ascribed to group differences in brain atrophy, emotion responses were reanalyzed correcting for brain volume. After controlling for whole brain volume, LBG subjects continued to show greater depression [F (on ranks, $df = 1$) = 8.36, $p = 0.011$] and reported experiencing significantly lower disgust to negative stimuli [F (on ranks, $df = 1$) = 5.05, $p = 0.04$]. Amusement was lower in response to positive stimuli but failed to reach significance [F (on ranks, $df = 1$) = 3.56, $p = 0.079$].

There were no statistically significant differences between LBG and SDC subjects (Table 6). The mean amusement score in response to positive face stimuli among LBG subjects not taking SSRIs was 5 ($SD=1.5$) while the scores of LBG subjects taking SSRIs were 8 and 5. The mean disgust score in response to negative face stimuli among LBG subjects not taking SSRIs was 5.5 ($SD=16.3$) while the scores of LBG subjects taking SSRIs were 8 and 7. Group differences elicited by emotion evoking scenes and objects were not significant (data available from the authors).

Subjects' perception of facial expression stimuli was consistent with the intended hedonic ("how pleasant?") value of the stimuli (positive stimuli: LBG mean = 5.6 ± 0.9 , SDC

mean = -5.4 ± 2.3 , NSNDH mean = 6.2 ± 1.5 ; negative stimuli: LBG mean = -5.3 ± 1.8 , SDC mean = -4.0 ± 3.0 , NSNDH mean = -6.3 ± 2.0). As for emotional experience, LBG subjects rated negative stimuli as significantly less unpleasant than NSNDH volunteers ($U = 13.5$, $p < 0.02$). The difference on positive stimuli did not reach significance ($U = 17.5$, $p > 0.1$). There were no significant differences between LBG and SDC subjects ($U_s > 17.0$, $p_s > 0.1$).

3.4 Association between experienced emotion, depression, and alexithymia

Depression severity was found to be negatively associated with happiness ($n = 28$, Spearman $\rho = -0.44$, $p = 0.01$) and amusement responses (Spearman $\rho = -0.48$, $p = 0.005$) to positive facial expressions. The association between depression and fear ($\rho = -0.33$, $p = 0.041$) and anger responses (Spearman $\rho = -0.35$, $p = 0.033$) to negative expressions was also statistically significant. The association with disgust just failed to reach statistical significance (Spearman $\rho = -0.30$, $p = 0.059$). The alexithymia factor representing externally-oriented thinking negatively correlated with disgust (Spearman $\rho = -0.34$, $p = 0.047$) and anger (Spearman $\rho = -0.37$, $p = 0.03$) responses to negative stimuli. Alexithymia total score and difficulty identifying emotions and distinguishing between body sensations and feelings were not significantly correlated with emotion experience.

3.5 Brain activity

Based on the above findings on emotion experience and perception, functional imaging data evoked by face expression stimuli are presented. Brain-wide within-group function of interest analyses on the NSNDH subjects were carried out to confirm participation of LBG in emotional experience evoked by facial expressions. LBG structures showed a tendency towards greater activity in the emotion-laden relative to the neutral conditions, with some reaching the a priori statistical significance level [i.e., left putamen in the negative relative to the neutral condition, Talairach's coordinates $x = -29\text{mm}$, $y = -8\text{mm}$, $z = 5\text{mm}$, $t = 3.0$ ($df = 2662$), $p < 0.005$], and others [i.e., left caudate in the negative relative to the neutral condition, Talairach's coordinates $x = -18\text{mm}$, $y = 22\text{mm}$, $z = 5\text{mm}$, $t = 2.02$ ($df = 2662$), $p < 0.05$; left putamen in the positive condition, $x = -27$, $y = -6$, $z = 5$, $t = 2.3$ ($df = 2662$), $p < 0.05$] trending in the same direction. No significant effects were found in the right BG.

LBG subjects exhibited multiple regions of increased and decreased activity relative to NSNDH volunteers (Table 7). All reported data is controlled for activity during exposure to neutral stimuli. Participants with LBG damage showed relatively lower activity in response to positive stimuli in the posterior (retrosplenial) cingulate cortex bilaterally, in primary visual cortex and cerebellum. Greater activity was found in response to positive stimuli in the right amygdala, in the mesial (including the anterior cingulate) and dorsal prefrontal cortex (bilaterally), in the right insula, pons and cerebellum. Lower activity in response to negative stimuli was found in the right frontal-polar region and in the fusiform gyrus, in primary visual cortex and cerebellum, whereas higher activity was observed in the right posterior cingulate and right entorhinal cortex. Notably, participants with LBG damage showed lower activity independent of stimulus valence in the cerebellum, the right entorhinal, and primary and association visual cortices.

Correlations between severity of depression and normalized baseline brain activity were computed (Figure 3). Positive correlations between depression severity and brain activity in the right amygdala (Spearman $\rho = 0.73$, $p = 0.005$), the right ventral and mesial prefrontal cortex (Spearman $\rho = 0.55$, $p = 0.019$) were found. Additionally, there was a negative correlation between depression severity and left dorsal lateral prefrontal activity (Spearman $\rho = -0.60$, $p = 0.008$). No other region larger than 50 voxels reached statistically significant association with depression scores.

In summary, subjects with LBG stroke showed altered activity in brain regions subserving emotion processing and awareness including amygdala, insula and mesial prefrontal and cingulate cortex. Some of these brain regions (right amygdala and right ventral and mesial prefrontal cortex) correlated positively with severity of depression, whereas others (the left dorsal lateral prefrontal cortex) showed a negative correlation with depression severity.

4. Discussion

In the present study clinical, structural and functional neuroimaging data were integrated in order to better characterize the role of the LBG in emotion processing and its relationship with depression. As expected, subjects with LBG damage showed greater depression and blunted emotional experience in response to emotion-evoking stimuli containing facial expressions compared to non-stroke non-depressed volunteers. Because differences in emotion experience between LBG and comparison subjects with damage in the right hemisphere or cerebellum with similar depression severity were not significant, the findings of the present research suggest that LBG-related blunted emotionality is either non-specific (i.e., the LBG effect is non-significant in the comparison with participants with damage elsewhere in the brain) (Calder et al., 2000) or is due to depression. The significant correlation between severity of depression and blunted emotional experience suggests a role for depression in LBG-related emotional blunting. Baseline brain activity correlated with severity of depression in regions consistent with idiopathic depression (positively with amygdala and ventral mesial prefrontal cortex, negatively with left dorsal lateral prefrontal cortex). Relative to non-depressed non-stroke volunteers, LBG patients also showed expected functional alterations in brain regions (mesial prefrontal cortex, cingulate gyrus, insula) subserving emotional awareness. These findings support a tight link between depression and blunting of emotion processing that follow LBG damage, and suggest that remote brain activity changes to **fronto-limbic structures participate** to the emotional blunting following LBG damage.

4.1 Limitations

Before discussing the study results some caveats should be acknowledged. First, the percentage of left-handed subjects differed across groups and this may have influenced laterality findings. While future studies should attempt to match for handedness, it should be noted that over 90% of left-handed individuals are left hemisphere dominant for language (similar to right-handed persons) and it is, at best, unclear whether handedness affects brain asymmetry for emotions (Heller and Levy, 1981; Springer and Deutsch, 1998). Some LBG participants showed damage in white matter connecting tracts that may have contributed to an interruption in the communication with distant brain regions and, therefore, affected

distant brain activity. Patients with stroke are prone to brain-wide changes of vascular origin (e.g., atrophy, white matter lesions), but emotional blunting associated with LBG damage was found to be independent from brain-wide vascular changes. Other methods for quantification of white matter alterations (e.g., diffusion tensor imaging) may have given differing results. Depression and emotional blunting were measured concurrently. Further research is needed to determine if LBG-associated emotion processing changes are a precursor (and therefore causal) or a consequence of depression. Finally, the lack of emotion response differences between LBG and SDC participants might have been due to the presence of (right) basal ganglia lesions in the SDC group (and not exclusively depression). This view is tempered by observations using the same methods as in the present study that individuals with stroke damage including the right basal ganglia tend to show impairment in experience of positive (not negative) emotions (Paradiso et al., 2011). In addition, this study (Paradiso et al., 2011) showed that blunting of emotional responses for positive stimuli following stroke including the basal ganglia was largely independent from depression. Therefore it is plausible that LBG damage is a particular underpinning for depression/emotional blunting association.

4.2 Left basal ganglia damage, depression, and blunted emotionality

BG functions extend beyond motor control (Adolphs, 2002; Peters and Buchel, 2010). Studies of patients with Parkinson's (Gray and Tickle-Degnen, 2010) and Huntington's disease (Sprengelmeyer et al., 1996; Gray et al., 1997; Halligan, 1998a; Paradiso et al., 2008a) posited that the BG are critical for emotion perception. The high frequency of psychiatric co-morbidity (and particularly depression) in these neurodegenerative diseases (Rosenblatt and Leroi, 2000) limits conclusions from these studies (Sprengelmeyer et al., 1996; Gray et al., 1997; Halligan, 1998a; Gray and Tickle-Degnen, 2010) because depression per se may induce emotion processing deficits (Gotlib and McCabe, 1992; Gur et al., 1992; Mikhailova et al., 1996; Hale, 1998; Bouhuys et al., 1999; Langenecker et al., 2005). In addition, depression among patients with BG disorders (e.g., Parkinson's disease) appears to have a clear anhedonic phenomenology with preeminent loss of reactivity to emotional stimuli (Lemke, 2008).

The most frequent psychiatric disorder associated with damage to the BG (including stroke) is depression (Ring and Serra-Mestres, 2002; van Duijn et al., 2007; Aarsland et al., 2009). Results of the present study are in part consistent with prior research documenting a link between BG damage and emotion processing (Sprengelmeyer et al., 1996; Gray et al., 1997; Halligan, 1998a; Calder et al., 2000) but also highlight the tight association between emotion processing deficits and depression. Consistent with the literature (Fang and Cheng, 2009), five of six patients with LBG stroke met criteria for Major Depression (American Psychiatric Association, 1994). Notably, the single LBG subject with low depression scores (HamD = 4) (anxiety score, HamA = 4) and who did not meet Major Depression criteria was a 68 year old woman with lesions in the left caudate, putamen and globus pallidus externa who responded with strong emotional experience to negative (fear = 8/10, disgust = 9/10, anger = 9/10) and positive stimuli (amusement = 7/10 and happiness = 8/10).

Wide consensus on whether SSRIs can cause clinically relevant emotional blunting has not been achieved (Balon, 2002; Opbroek et al., 2002). Nonetheless, the possibility that treatment with SSRI may have contributed to the emotional blunting of participants with LBG damage is worth discussing (McCabe et al., 2010; Sansone and Sansone, 2010). In the present study the emotional responses of subjects with LBG damage who were taking SSRI medications were non-significantly different from the responses of subjects with LBG who were taking SSRIs. Hence, for the focused scope of the present study SSRI treatment exerted at best a small effect on the emotional responses of participants with LBG damage.

To recapitulate, while on the one hand the association between depression and emotional blunting was subsequent to damage to the LBG, on the other hand, the present report cannot definitively demonstrate that this association *exclusively* follows damage to the left and not right BG. However, whereas a large enough sample of participants with *focal* right BG damage was not available for direct comparison, results from subjects with right middle cerebral artery stroke (including basal ganglia damage) tested with the same methods, showed no obvious association between emotional blunting and depression (Paradiso et al., 2011). Further studies will need to include more participants with BG lesions without depression.

4.3 Basal ganglia and depression: caudate nucleus and putamen

Classic descriptions of the brain damage associated with depression following stroke have included the caudate nucleus (Starkstein et al., 1988), but the significance of the putamen in depression has more recently emerged (Baumann et al., 1999). Two meta-analyses examining magnetic resonance imaging studies in unipolar depression have shown that volume reduction in the basal ganglia include both the caudate nucleus and the putamen with effects sizes often larger for the putamen (Kempton et al., 2011). An intriguing putative role for the putamen in the mechanisms of depression has been recently posited based on volume increases in the putamen following 6 weeks of antidepressant therapy in patients with first-onset major depression (Lai, 2011).

4.4 Blunted emotion in response to facial expressions: LBG damage or depression?

Although LBG patients demonstrated a mild degree of emotional blunting to scenes and objects (no group effect approached statistical significance), emotional blunting was more pronounced for human facial expression stimuli (Sprengelmeyer et al., 1996; Gray et al., 1997; Halligan, 1998a; Adolphs, 2002). Healthy non-depressed volunteers showed higher LBG activity in response to stimuli including facial expressions (disgust included). Hence, an aspect of the present study supports the notion that LBG participates in processing emotion conveyed by human facial expressions (Phillips et al., 1998; Phan et al., 2002).

The present study also sought to investigate if the LBG was *critical* to emotion processing when controlling for non-specific brain damage and depression. Results were consistent with a large body of literature showing that depression per se is sufficient to cause changes in emotion processing conveyed by human face stimuli, (Gotlib and McCabe, 1992; Gur et al., 1992; Mikhailova et al., 1996; Hale, 1998; Bouhuys et al., 1999; Langenecker et al., 2005). This raises an important question regarding the extent to which emotion processing

deficits for human face stimuli caused by LBG damage (Calder et al., 2000) are critically intertwined with mood alterations and influenced by concurrent depression.

Processing of emotional face expressions in LBG-related depression and depression without gross brain damage requires additional comment. A recent review of the literature on face processing in major depression (Bourke et al., 2010) showed a tendency of patients with depression to evaluate positive or ambiguous facial expressions as less positive or more sad, together with increased attention towards negative (e.g., sad) and away from positive (e.g., happy) expressions. This pattern of responses is consistent with a response bias phenomenon. On the other hand, reduced recognition accuracy for both positive and negative stimuli as observed among patients with depression following brain damage is more consistent with a deficit phenomenon. However, the distinction between depression in patients with and without gross brain damage on emotion processing may not be as clearly demarcated. One example comes from a recent influential study that showed that patients with severe depression displayed a specific deficit in the recognition of facial expressions of disgust (Douglas and Porter, 2010). This finding was interpreted as deficit and therefore as an indication of basal ganglia dysfunction (Douglas and Porter, 2010).

4.5 Neurofunctional alterations

Although knowledge on the functional neuroanatomy of idiopathic depression has significantly evolved (Drevets, 2001; Mayberg, 2002), functional mechanisms of post-stroke depression have remained elusive or incomplete [with some exceptions: e.g., (Mayberg et al., 1994)], perhaps because of the greater attention paid to the location of direct stroke damage (Robinson, 2006). Brain activity during processing of neutral stimuli showed a positive association with depression severity in the amygdala and mesial prefrontal cortex and indirect in dorsal lateral prefrontal cortex. These findings are strongly consistent with network changes widely reported in idiopathic depression (Baxter et al., 1985; Baxter et al., 1989; Martinot et al., 1990; Drevets, 1999, 2001; Mayberg, 2002), and suggests that brain activity occurring as a result of LBG damage during processing of neutral material may explain why damage to this brain region is so frequently associated with depression.

The basal ganglia have been posited to be central components of 5 networks (loops) subserving movement (including ocular), cognition, and emotion (Alexander et al., 1986). Brain activity changes occurring in LBG damage participants were consistent with classical animal and recent probabilistic diffusion tractography studies in humans. Regions of the caudate nucleus (dorsal posterior and ventral anterior respectively) are topographically connected to dorsal lateral and ventral prefrontal cortex (Yeterian and Pandya, 1991; Leh et al., 2007). The caudate nucleus is also connected to middle and inferior temporal gyrus, and both caudate and putamen are connected to the cerebellum (Leh et al., 2007). Nuclei of the basal ganglia (i.e., ventral striatum) are also connected to the anterior cingulate cortex (Alexander et al., 1986) widely viewed as the *trait d'union* between motor and limbic/paralimbic areas including amygdala, entorhinal and insular cortex subserving reward, emotion, and motivation (Tisch et al., 2004).

Notably, several changes in brain activity occurred contralaterally from the side of damage and included areas (e.g., primary visual cortex) not immediately predicted based on

structural magnetic resonance imaging connectivity studies (Leh et al., 2007) or classic animal hodology studies (Alexander et al., 1986). Some remote changes may be ascribed to the fact that some LBG participants had some damage to white matter tracts (e.g., external capsule, corpus callosum). Studying subjects with basal ganglia damage restricted to the gray matter should be able to determine whether distant activity changes may occur exclusively due to disruption of the integrative nature of pathways including the basal ganglia and the "...cross-talk between systems at the edges of functional domains" (Haber, 2010). The time course of functional changes following focal brain damage would constitute fascinating information because distant changes may result from compensation for lost function occurring over time perhaps with the contribution of rehabilitation measures.

Nonetheless many alterations in brain activity occurring as a consequence of damage to the LBG correspond closely to hodology studies. LBG stroke subjects showed changes in activity in brain regions known to subserve emotion experience and awareness including mesial prefrontal cortex, cingulate gyrus, and insula (Craig, 2009; Etkin et al., 2011). Many of these regions showed elevated brain activity in conjunction with blunted emotion experience. While somewhat unexpected, this finding is consistent with the well-known observation that brain areas may initially show higher activity in the face of reduced function [for an example referring to Mild Cognitive Impairment (MCI) see (Dickerson et al., 2004)]. This phenomenon is also observed in the normal aging brain showing a dissociation between relatively higher activity in some regions (e.g. frontal lobes) and reduced occipital lobe function (secondary to older age sensory decline) across differing cognitive tasks (Cabeza et al., 2004). This may be an initial attempt to recruit the support of additional neural networks to help prevent loss of function. Higher activity may linger for some time upon decline of function.

The right retrosplenial cingulate showed higher activity in response to negative stimuli, consistent with its role in psychiatric disorders accompanied by abnormalities in emotional functioning (including depression) (Maddock, 1999). High activity was also observed in the right entorhinal cortex irrespective of emotional valence consistent with its role in motivated attention (Coutureau and Di Scala, 2009). Activity changes in the right hemisphere may help explain some cognitive and psychiatric manifestations of LBG damage such as high alexithymia scores, generally expected to be elevated after right hemisphere damage (Spalletta et al., 2001) (but consistent with activity changes in right anterior cingulate cortex) (Paradiso et al., 2008), and their association with lower disgust and anger response. Visual neglect, generally attributed to damage in the right hemisphere (Vallar and Perani, 1986; Halligan and Marshall, 1998b; Heilman et al., 2003; Mort et al., 2003) including the right insula (Manes et al., 1999), was also plausibly another consequence of low right hemisphere activity following LBG stroke.

Several cerebellar regions showed lower activity irrespective of valence while the experiment required no movement. Specific functions of the cerebellum in emotion remain partially elusive, (Parvizi et al., 2001; Dum and Strick, 2003) although a number of studies have revealed increased cerebellar activity during emotion tasks (George et al., 1993; Paradiso et al., 1997; Reiman et al., 1997; Paradiso et al., 2003) while lesion studies show deficits in emotional experience (Turner et al., 2007).

Finally, lower activity was shown in primary visual and association cortices among LBG subjects. These regions have been shown to respond to affective visual stimuli (Fredrikson et al., 1993; Lang et al., 1998) perhaps due to re-entrant processing by distant subcortical limbic structures including the anterior cingulate and amygdala to enhance sensory and experiential processing (Lang et al., 1998; Bradley et al., 2003).

4.6 Conclusions

LBG damage is associated with depression and with blunted pleasant and unpleasant experience in response to social stimuli. The data herein presented suggest that depression may play an important role in the alteration of emotional experience that follows LBG damage. Depression may contribute to altering emotional experience via remote changes in the activity of fronto-limbic structures, and in brain regions subserving emotional awareness.

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Figure 1.

MRI scans (T1 or T2 where indicated) showing the lesion location of LBG subjects (arrows). Slice orientation was chosen based on ability to display the damage. Orientation follows radiological convention. For full description of damaged structures see Table 3.

Figure 2.

MR images showing the lesion location (arrows) in SDC participants. Slice orientation (axial vs. coronal) was chosen based on ability to display the damage. Orientation follows radiological convention.

Figure 3.

Axial view of thresholded depression baseline brain activity correlation map among LBG damage and NSNDH participants (overlaid onto an average of their MRI scans) showing positive correlation including the right amygdala (red arrow, $\rho=.73$, $p=.005$) and negative correlation including the left frontal polar and dorsal lateral prefrontal cortex (white arrow, $\rho=-.60$, $p=.008$). Image follows radiological convention (right side of brain is on the left). Color pallet (right aspect of the Figure) indicates the strength of the correlations (ρ values).

TABLE 1

Demographic, psychopathological, social and physical functioning data

	LBG		NSNDH		SDC		LBG/NSNDH contrast		LBG/SDC contrast	
	Mean	SD	Mean	SD	Mean	SD	Mann-Whitney U	p-value	Mann-Whitney U	p-value
Demographic										
Age, years	67.5	9.4	65.5	6.3	67.00	7.0	21.0	0.155	23.50	0.479
Education, years	12.0	0.0	15.6	4.1	12.60	2.7	10.0	0.083	18.00	0.741
Functioning										
GAF	69.3	12.6	83.3	7.7	73.8	10.9	12.5	0.021	25.50	0.615
JHFI	4.2	2.3	0.0	0.0	3.70	2.1	6.0	0.000	25.50	0.622
FIM	62.8	6.8	71.3	1.2	60.88	7.9	3.0	0.001	24.50	0.551
SFE	0.1	0.1	0.1	0.1	0.09	0.1	23.0	0.221	28.00	0.828
STC	3.3	1.4	2.5	0.9	3.5	1.8	23.0	0.197	29.00	0.912
Psychopathological										
HamD	16.0	6.8	3.8	2.7	15.50	9.5	4.5	0.003	27.50	0.786
HamA	13.0	6.6	6.8	5.2	12.70	6.2	15.5	0.054	29.00	0.913
TAS-20	56.8	5.9	41.6	9.8	53.20	8.1	4.0	0.008	15.50	0.243
TAS-F1	14.7	4.2	9.7	3.3	13.73	3.8	7.0	0.020	21.00	0.624
TAS-F2	13.2	1.8	10.1	2.1	13.19	2.4	5.0	0.011	22.00	0.713
TAS-F3	13.3	1.0	10.6	1.9	12.66	1.8	3.0	0.006	20.00	0.540

Legend:

LBG: Left basal ganglia damage group

NSNDH: Non-stroke, non-depressed healthy volunteer group

SDC: Stroke Damage Comparison group

GAF: Global Assessment of Functioning

JHFI: Johns Hopkins Functioning Inventory

FIM: Functional Independence Measure

SFE: Social Functioning Exam

STC: Social Ties Checklist

HamD: Hamilton Depression Scale

- HamA: Hamilton Anxiety Scale
- TAS-20 Toronto Alexithymia Scale – 20 items
- TAS-F1: Factor Representing/Difficulty Identifying Feelings
- TAS-F2: Factor Representing/Difficulty Describing Feelings
- TAS-F3: Factor Representing/Externally-oriented Thinking

TABLE 2

Cognitive functioning

	LBG		NSNDH		SDC		LBG/NSNDH contrast		LBG/SDC contrast	
	Mean	SD	Mean	SD	Mean	SD	Mann-Whitney U	p-value	Mann-Whitney U	p-value
General Intelligence										
WAIS-R VIQ	94.4	16.9	110.8	14.2	93.00	13.29	14.0	0.125	16.00	0.385
WAIS-R PIQ	105.4	28.1	121.7	21.1	94.78	16.56	17.0	0.234	15.00	0.317
WAIS-R FIQ	104.2	32.6	118.1	20.0	93.33	14.99	20.0	0.395	15.00	0.315
NART	104.8	8.3	115.0	11.4	104.2	7.21	13.0	0.100	23.00	0.806
Executive Functions										
WCST PE	18.8	6.3	8.5	5.3	19.20	14.72	4.0	0.007	17.50	0.356
MAE COWA	19.4	9.9	32.7	10.9	22.80	9.37	10.5	0.054	19.00	0.461
Language										
Boston Naming Test	26.0	9.1	27.1	3.0	23.10	5.51	10.0	0.044	22.50	0.758
Token Test	36.8	2.8	42.3	1.7	39.60	5.15	1.5	0.006	9.50	0.136
Visuospatial Cognition										
RCFT-Copy	23.8	8.3	26.6	6.2	22.80	4.91	23.5	0.650	19.50	0.500
Benton Facial Recognition	41.6	4.8	44.6	3.4	43.10	4.82	15.5	0.164	19.50	0.496
Line Bisection/20mm	10.5	0.4	9.6	0.5	9.79	0.75	4.0	0.010	9.00	0.046
Line Bisection/40mm	20.9	1.7	19.3	0.7	19.93	0.72	9.0	0.049	14.50	0.198
Line Bisection/60mm	31.9	3.0	28.9	1.2	30.29	1.56	7.0	0.027	14.00	0.178
Visual Memory										
RCFT-Immediate	11.1	6.0	12.5	3.3	11.10	6.40	25.5	0.820	23.50	0.854
RCFT-Delayed	10.7	4.9	11.5	3.8	10.30	6.05	24.5	0.734	22.50	0.759
BV-Total	27.0	8.7	29.5	2.4	26.11	5.35	20.0	0.786	13.50	0.480
Attention										
Digit Span	10.2	4.7	14.5	3.0	13.50	4.50	13.0	0.099	17.50	0.480
Motor										
Finger Tapping, Dominant Hand	19.9	10.7	42.0	8.6	31.50	14.33	0.0	0.011	10.00	0.398
Finger Tapping, Non-dominant Hand	34.6	15.3	38.5	7.4	34.34	9.07	24.5	0.953	14.50	0.626

Legend:

LBG: Left basal ganglia damage group

NSNDH: Non-stroke, non-depressed healthy volunteer group

SDC: Stroke Damage Comparison group

WAIS-R-VIQ: Wechsler Adult Intelligence Scale Verbal Intelligence Quotient

WAIS-R-PIQ: Wechsler Adult Intelligence Scale Performance Intelligence Quotient

WAIS-R-FIQ: Wechsler Adult Intelligence Scale Full scale Intelligence Quotient

RCFT: Rey-Osterreith Complex Figure Test

Token Test: Multilingual Aphasia Exam Token Test

BV: Benton Visual Retention Test

WCST PE: Wisconsin Card Sorting Test Perseverative Errors

NART: Adult North American Reading Test WAIS-R Equivalency

MAE COWA: Multilingual Aphasia Exam Controlled Oral Word Association

TABLE 3

Structures involved by damage in each patient with LBG stroke

Lesion Description	
LBG Subject 1	The lesion lies lateral and posterior to the left genu of the corpus callosum (CC) and lateral to the left caudate head, the most affected structures at the level of the anterior commissure being the external capsule and claustrum with the caudate head progressively more involved moving dorsally. A hyperintense area appearing in the region of the left putamen and globus pallidus and overlapping the lesion area indicates calcification. Moving posteriorly the caudate head and body are increasingly involved, as does the putamen and neighboring anterior limb of the internal capsule. No ventral striatum damage.
LBG Subject 2	Ventrally, beginning approximately at an axial level through the anterior commissure, the lesion is localized to the left putamen, with damage encompassing a majority of the structure as well as the nearby external capsule. The left globus pallidus externa appears involved. Progressing dorsally and posteriorly, the left caudate becomes increasingly involved. Posteriorly, in a coronal section through the anterior commissure, the lesion encompasses the left ventral putamen. No damage to the ventral striatum.
LBG Subject 3	Small, distinct lacunar-type lesions, with damage localized to regions of the left putamen and caudate nucleus – both lesions appearing in the same coronal plane at the posterior edge of the genu of the CC. Additional distinct lesions appear more posteriorly in the left mediodorsal thalamus. No ventral striatum damage.
LBG Subject 4	The lesion is primarily localized to the left putamen and portions of the globus pallidus. The anterior-most aspect of the lesion resides in the ventral putamen and globus pallidus externa. The caudate head becomes increasingly atrophied progressing posteriorly, resulting in enlargement of the lateral ventricle and clear damage to the bordering anterior limb of the internal capsule, uncinate fasciculus and claustrum. No ventral striatum damage.
LBG Subject 5	The lesions are lacunar in the left lateral putamen in the caudate head. An additional lesion in the left globus pallidus is more dorsal. The corpus callosum is reduced overall in this patient, who also shows evidence of a cavum septum pellucidum. No ventral striatum damage.
LBG Subject 6	The lesion appears ventrally as a lacunar lesion in the left putamen with major atrophy of the caudate head in the same horizontal plane, at a level just below the inferior edge of the splenium of CC. No ventral striatum damage is apparent.

TABLE 4

Structural imaging

	LBG		NSNDH		Mann-Whitney U	p-value
	Mean	SD	Mean	SD		
Total Brain Volume	1095.6	94.0	1275.4	124.6	8	0.009
Total White Matter	393.3	48.1	518.9	66.9	3	0.002
Total Gray Matter	702.3	77.8	756.5	70.3	25	0.303
Total CSF	261.9	131.5	190.3	100.4	24	0.261
White Matter Lesions						
<i>Frontal</i>						
Left	1.16	0.9	0.50	0.5	21	0.11
Right	0.5	0.5	0.16	0.4	24	0.15
<i>Parieto-Occipital</i>						
Left	0.5	0.8	0.16	0.4	29	0.37
Right	0.5	0.8	0.16	0.4	29	0.37
<i>Temporal</i>						
Left	0.33	0.8	0	0	30	0.16
Right	0.33	0.8	0	0	30	0.16
<i>Basal Ganglia</i>						
Left	N/A	N/A	0.33	0.8		
Right	0	0	0.33	0.8	30	0.30

LBG = Left basal ganglia damage group

NSNDH = Non-stroke, non-depressed healthy volunteer group

TABLE 5

Evoked emotions in healthy volunteers

Experienced Emotion	NSNDH	
	Z*	p-value*
<i>Positive Stimuli/Facial Expressions</i>		
Amusement	-2.80	0.005
Happiness	-2.95	0.003
<i>Negative Stimuli/Facial Expressions</i>		
Fear	-2.81	0.005
Disgust	-3.08	0.002
Anger	-2.94	0.003
<i>Positive Stimuli/Scenes, Objects</i>		
Amusement	-1.87	0.061
Happiness	-2.53	0.011
<i>Negative Stimuli/Scenes, Objects</i>		
Fear	-2.85	0.004
Anger	-2.94	0.003
Disgust	-2.67	0.007

Note: Emotion experience change from baseline (neutral) condition among non-stroke, non-depressed healthy volunteers (NSNDH).

TABLE 6

Emotions evoked by stimuli including facial expression

Experienced Emotion	Affective Stimuli	LBG		NSNDH		SDC	
		Mean	SD	Mean	SD	Mean	SD
Positive							
Amusement	Neutral	2.2	2.23	3.4	2.61	2.3	2.95
	Positive *	5.5	1.64	7.9	2.11	4.4	1.96
Happiness	Neutral	4.2	2.32	5.2	1.59	3.1	3.41
	Positive	7.3	1.97	8.8	1.19	6.1	2.28
Negative							
Fear	Neutral	0.3	0.82	0.5	0.90	0.6	1.08
	Negative	5.3	1.86	6.0	3.64	2.8	3.29
Disgust	Neutral	0.5	1.22	0.8	0.54	1.0	1.15
	Negative *	6.2	3.31	8.6	1.83	6.1	3.45
Anger	Neutral	0.7	1.03	0.6	1.24	0.7	0.95
	Negative	6.3	3.44	7.5	3.34	4.4	4.17

* LBG vs. NSNDH contrasts $p < .05$

LBG = Left basal ganglia damage group

NSNDH = Non-stroke, non-depressed healthy volunteer group

SDC = Stroke Damage Comparison group

TABLE 7

Brain activity changes in LBG subjects vs healthy volunteers in response to emotion-evoking facial expression stimuli

Region/Broadmann's Area		Talairach Coordinates (mm)			Volume			
	Hemisphere (based on t max)	BA	X	Y	Z	cc	Voxels	t (max)
Regions with Decreased Activity in Response to Positive Stimuli								
Posterior Cingulate	L/R	31	5	-43	29	0.2	109	-2.9
Primary Visual Cortex	L	17	-17	-89	6	0.1	53	-3.0
Cerebellum	R	-	15	-44	-12	0.1	60	-2.8
Regions with Increased Activity in Response to Positive Stimuli								
Frontopolar Area (Medial/Superior Frontal Gyrus)	L/R	10	5	67	9	1.0	445	3.6
Anterior Cingulate, Medial Frontal Gyrus	R	10, 32	5	42	10	0.2	98	2.9
Ventral lateral prefrontal cortex (Pars Orbitalis, Inferior Frontal Gyrus)	R	44, 45	60	16	10	0.1	61	3.0
Insula, Inferior Frontal Gyrus	R	45	39	-14	18	0.2	70	2.9
Amygdala/Entorhinal Cortex	R	38	14	-8	-19	0.6	265	3.5
Pons		-	-4	-33	-24	0.7	329	3.8
Cerebellum	L	-	-30	-62	-36	0.5	226	3.8
Cerebellum	L	-	-34	-72	-18	0.3	143	3.0
Regions with Decreased Activity in Response to Negative Stimuli								
Frontopolar Area, Superior Frontal Gyrus	R	10	28	63	0	0.1	65	-2.7
Fusiform Gyrus	R	19	35	-70	-6	0.1	57	-2.8
Primary Visual Cortex	R	17	2	-87	3	0.7	338	-3.5
Cerebellar	R	-	28	-64	-14	0.2	71	-2.9
Cerebellar	R	-	12	-44	-12	0.1	54	-2.9
Regions with Increased Activity in Response to Negative Stimuli								
Entorhinal Cortex	R	34, 38	13	-9	-19	0.7	320	3.5
Posterior Cingulate Gyrus	R	31	25	-52	12	0.2	108	3.4

Note: Laterality is based on the location of the t max for the region of activity change. For full extent (e.g., extension to contralateral hemisphere) of region of activity change consult text.