A selective role for right insula—basal ganglia circuits in appetitive stimulus processing

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Hemispheric lateralization of hedonic evaluation (‘liking’) and incentive motivation (‘wanting’) in neural networks connecting the basal ganglia and insula (BG-I) in humans was examined. Participants with brain damage restricted to the BG-I of the right (n = 5) or left (n = 5) hemisphere, and 26 healthy participants matched on age, sex and intelligence quotient were tested on positively and negatively valenced pictures drawn from varied stimulus categories (Vijayaraghavan et al., 2008). Liking was assessed with explicit ratings of pleasantness using a nine-point Likert scale. Wanting was quantified as the amount of work (via repeated keypresses) that participants expended to increase (approach) or decrease (withdraw) viewing time. Right-lesion patients showed abnormally low viewing times and liking ratings for positive images. For a subset of positive images depicting sexual content, right-lesion patients exhibited active withdrawal, while the other two groups approached such stimuli. These results suggest that the right basal ganglia–insula complex plays a greater role than the left in supporting hedonic evaluation and motivational approach to positively valenced stimuli. The finding that active avoidance of stimuli that were not ‘liked’ was spared in both right- and left-sided lesion subjects suggests that unilateral damage to insula/basal ganglia circuits may not be sufficient to affect general incentive motivation independent of preference.

Keywords: insula; basal ganglia; emotion; incentive motivation; hedonic evaluation

The insular–striatal–pallidal–thalamic–insula circuit (Chikama et al., 1997; Wright and Groenewegen, 1996) plays a critical role in hedonic (‘liking’ or preference) and incentive (‘wanting’) components of motivation (Balleine and Dickinson, 2000; Berridge and Robinson, 2003). Damage to this circuit in humans leads to emotional blunting and apathy (Bhatia and Marsden, 1994; Manes et al., 1999), especially if damage is bilateral (Vijayaraghavan et al., 2008). Neuroimaging studies have shown involvement of regions of this circuit during preference judgments of and approach-withdrawal behavior in response to stimuli portraying humans ranging from facial expressions to stimuli of sexual nature (Phillips et al., 1997; Stolru et al., 1999; Redoute et al., 2000; Aharon et al., 2001; Arnow et al., 2002; Karama et al., 2002; Stolru et al., 2003; Ferretti et al., 2005; Redoute et al., 2005; Moulier et al., 2006; Schiffer et al., 2008; Walter et al., 2008) and inanimated objects including foods (Small et al., 2001; Schienle et al., 2002; Beaver et al., 2006; Calder et al., 2007).

Although it is known that basal ganglia and insula (BG-I) are involved in hedonic evaluation and incentive motivation, it is unclear whether left and right hemispheres support unique aspects of these processes. Anecdotally, a patient with a left hemisphere tumor and subsequent lesion that included the posterior insula was reported to have odd and extreme taste preferences (Pritchard et al., 1999). Another individual ‘reported heightened taste intensity that resulted in visually appealing and previously familiar food tasting intensely unpleasant and unfamiliar’ immediately following a left insular stroke (Mak et al., 2005). Another study found decreased ‘urges’ and ‘cravings’ to smoke in previously nicotine-addicted individuals following unilateral insula damage, with possibly stronger effects in the right hemisphere (Naqvi et al., 2007). Thus, the critical role of left vs right lateralized insular/basal ganglia circuits for hedonic evaluation and motivation needs further examination.

The main focus of this research was testing the effects of lateralized damage to basal ganglia and adjacent insula on hedonic preference, incentive motivation and the typical positive relationship between the two using the paradigm developed by Aharon et al. (2001; Vijayaraghavan et al., 2008). To assess hedonic preference, participants were asked to rate pleasantness on a nine-point Likert scale with very unpleasant (1) and very pleasant (9) as anchors. To assess incentive motivation, participants were given the opportunity to increase or decrease viewing time of the images via repeated keypresses (if the subject did nothing, the image would stay on the screen for a fixed duration of 9 s).

The stimuli in this study included positive (e.g. sexual) and negative (e.g. violent) images depicting humans and positive (e.g. appetitive) and negative (e.g. disgusting) images depicting foods/objects. These were chosen because neuroimaging data suggest that BG-I participate in the appraisal of positive and negative images of humans (Phillips et al., 1997; Stolru et al., 1999; Redoute et al., 2000; Aharon et al., 2001; Arnow et al., 2002; Karama et al., 2002; Stolru et al., 2003; Ferretti et al., 2005; Redoute et al., 2005; Moulier et al., 2006; Schiffer et al., 2008; Walter et al., 2008) as well as foods and objects (Small et al., 2001; Schienle et al., 2002; Beaver et al., 2006; Calder et al., 2007). Although on the one hand, neuroimaging studies have provided information on the participation of BG-I in the appraisal of emotionally charged human and non-human stimuli, on the other hand a neuroimaging approach cannot establish a critical role of these brain regions in emotional appraisal. This important issue was addressed by examining the effect of damage to insula and basal ganglia.
on behavioral responses to stimuli similar to those used in neuroimaging studies (e.g. Aharon et al., 2001; Beaver et al., 2006).

METHODS

Participants

Eighty-two subjects with a history of damage to the insula, basal ganglia and/or connecting white matter tracts (insula-striatal circuits) were identified from the Patient Registry in the Division of Cognitive Neuroscience at the University of Iowa. Exclusion criteria were as follows: bilateral lesions, visual, motor or cognitive deficits impairing task performance (e.g. apraxia, amnesia and aphasia), history of psychiatric disorders or other neurological disorders affecting the basal ganglia (including Huntington’s disease and Parkinson’s disease), Mini-Mental State Examination (Folstein et al., 1975) score 26 or lower. After applying these stringent criteria, 10 subjects (5 right and 5 left, 6 men) with stable lesions (at least 1 year after onset of brain damage) limited to unilateral cerebrovascular damage to the insula, basal ganglia and/or connecting white matter tracts were found to be eligible to participate in the study.

Twenty-six individuals (13 women) with no history of neurological or psychiatric disorders, matched for age, sex and general intelligence, were chosen as healthy comparison participants. Of them, 13 participants were recruited from a registry in the Division of Cognitive Neuroscience at the University of Iowa. The remaining 13 participants were recruited via advertisements in the Department of Psychiatry at the University of Iowa. Informed written consent was obtained from all subjects in accordance with guidelines of the Institutional Review Board of the University of Iowa Hospitals and Clinics.

Anatomy

Figure 1 shows representative coronal T2-weighted structural magnetic resonance images for each subject along with a description of the lesion (see legend). A consensus opinion about the location of the lesion was obtained from three experts: a neuroanatomist (M.C.), a psychiatrist with extensive training in neuroimaging (S.P.) and a neurologist/neuroimaging expert (Dr T. Grabowski). The following landmarks were used to define the boundaries of the insula: the limen insulae, which separates the antero-basal insula from the anterior perforated substance; the circular sulcus, which separates the insula from the fronto-orbital, fronto-parietal and temporal opercula; and the central insular sulcus, which divides the insula into anterior and posterior regions (Augustine, 1996; Shelley and Trimble, 2004).

Neuropsychological function

General intelligence was measured using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Visual perception was assessed using the Judgment of Line Orientation Test (Benton Scale of Intelligence (Wechsler, 1999)). Visual perception was assessed using the Judgment of Line Orientation Test (Benton Scale of Intelligence (Wechsler, 1999)). Neuropsychological function

Baseline motor function

In order to assess baseline motor functioning for each individual participant, 20 neutral stimuli (10 red squares and 10 blue squares) were presented randomly on a computer screen, followed 3 s later by a bar with a slider indicating remaining viewing time of the stimulus. Participants were instructed to increase viewing time when a red square appeared and decreased viewing time when a blue square appeared, and to do so by pressing pairs of pre-assigned keys (QW and NM counterbalanced across participants). This task served as practice for the motivation task (see subsequent sections) and also provided a baseline measure of motor ability. This motor task was always performed before the subsequent motivation task.

Approach/withdrawal and hedonic appreciation

Each participant viewed 36 sets of stimuli, 18 pleasant and 18 unpleasant. Each stimulus was a montage of three pictures from the International Affective Picture Series (Lang et al., 1997) and other sources and included three congruent pictures depicting items or persons judged by healthy male and female volunteers as strongly liked (e.g. attractive people—some with a sexual perspective but never offensive and appetitive foods) or strongly disliked (e.g. images of dirty toilets and persons carrying weapons; Figure 2) (see Vijayaraghavan et al., 2008 for further details and stimuli development). In order to have an entirely empirical approach to stimulus category-level analysis, stimuli were not grouped in a priori categories for the analysis (for an alternative approach, see Vijayaraghavan et al., 2008).

The stimuli were presented randomly on a computer screen using the multimedia program Authorware (Macromedia). A bar with a slider indicating remaining viewing time appeared 3 s after stimulus onset. Participants could either increase (maximum 16 s) or decrease viewing time of the stimulus by continuously pressing pairs of pre-assigned keys (QW and NM, counterbalanced across participants) on a standard computer keyboard. The stimulus remained on the screen for 9 s if no response was given (baseline viewing time). Increasing numbers of key presses were required to both increase and decrease viewing time as time passed (for further details see Aharon et al., 2001). Immediately after the stimulus offset, subjects provided ratings of pleasantness (‘How pleasant was this picture?’ −1 = very unpleasant, −5 = neutral, −9 = very pleasant) and arousal (‘How arousing was this picture?’ −1 = not at all, −5 = neutral, −9 = very much) using a nine-point Likert scale. The inter-trial interval was 3 s.

Statistical analysis

All analyses were carried out separately for positively and negatively valenced stimuli. Kruskal-Wallis (K-W) statistics were computed to examine the effects of group (right-lesion group, left-lesion group and healthy comparison group) on baseline motor function, arousal and viewing time. Post hoc tests were Bonferroni corrected for multiple comparisons. The strength of association between viewing time and ratings of pleasantness as a function of group was examined using Fisher-transformed Spearman’s correlations.

RESULTS

Neuropsychological functioning

Group cognitive data are shown in Table 1. Significant group effects were found for Full Scale and Performance IQ and for facial recognition (Table 1). As expected, both lesion groups were different from healthy comparison subjects (but not different from each other) on general and visual spatial intelligence. The group effect on verbal intelligence was not statistically significant. Right-lesioned participants were different from healthy comparison subjects on facial recognition, but lesion groups were not different from each other. Measures of cognitive function for both lesion groups were within 1.5 standard deviations (s.d.) of the mean of healthy subjects (one exception: face recognition for right-lesion subjects was 1.77 s.d. below that of healthy subjects) and never in the impaired range. Mean BDI scores were 5.43 (s.d. = 2.76) for the left-sided lesion group and 8.5 (s.d. = 3.15) for the right-lesion group, well below the cut-off of 13 for clinical depression (Beck et al., 1966).
Baseline motor function
In order to assess baseline motor function in the context of repeated keypresses, participants were instructed to press as fast as possible either the increase time or decrease time keys in order to increase or decrease viewing duration. Healthy comparison participants, left-lesioned subjects and right-lesioned subjects did not differ in their ability to maximally increase total viewing time [14.3 s (s.d. = 1.2); 14.5 (s.d. = 1.1); 14.1 (s.d. = 1.1), respectively; K-W statistic = 0.84, df = 2, P = 0.66] or maximally decrease total viewing time [5.1 s (s.d. = 0.8); 5.3 (s.d. = 1.0); 4.9 (s.d. = 0.8), respectively; K-W statistic = 0.19, df = 2, P = 0.91].

Arousal
Mean arousal ratings were not significantly different between healthy volunteers, left-lesioned subjects and right-lesioned subjects for either positive stimuli [5.4 (s.d. = 1.4); 6.0 (s.d. = 2.0) and 4.8 (s.d. = 1.9),...
To further examine these two alternatives, the mean absolute deviation from the baseline viewing time of 9 s for each participant was calculated (Figure 4). Given that the stimulus remained on the screen for 9 s if the participant did nothing, the mean absolute value of the difference from 9 s provides a measure of how much each participant actually worked to increase or decrease viewing time. Mean viewing time deviation did not differ between healthy comparison, left-lesioned and right-lesioned participants (4.1 s (s.d. = 1.6), 4.5 s (s.d. = 2.1) and 2.8 s (s.d. = 1.6), respectively; K-W statistics = 3.48, df = 2, P = 0.18), indicating that poor incentive motivation was not a strong determinant of the group differences in viewing time. One subject in the right-lesioned group (of 5) and one healthy control participant (of 26) rarely changed their viewing time from the baseline duration of 9 s. When these subjects were excluded, the mean deviation for the right-lesioned group increased to 3.4 s (s.d. = 0.7) and for the healthy group was 4.2 s (s.d. = 1.4; K-W statistics = 1.58, df = 2, P = 0.45).

Next, the extent to which the group effect on viewing time was driven by active key pressing to reduce viewing time (i.e. withdrawal) was examined by comparing across groups the proportions of positive stimuli with reduced viewing time (i.e. <9 s baseline) for each individual. The percentage of positive stimuli with viewing time below baseline was 43% (s.d. = 29%) for right-lesioned, 9% (s.d. = 11%) for left-lesion and 6% (s.d. = 10%) for healthy comparison participants (K-W statistics = 8.17, df = 2, P = 0.017). Taken together, these findings suggest that the lower viewing time for positive stimuli measured across right-lesioned participants (mean 9.3 s, s.d. = 0.8) relative to other comparison groups [left-lesion = 12.9 s (s.d. = 2.0); healthy controls = 12.8 s (s.d. = 1.6)] was more strongly determined by active withdrawal from positive stimuli as opposed to poor incentive motivation.

To confirm this observation, the degree to which stimuli eliciting shorter viewing times were also liked (or disliked) by right-lesioned subjects was determined. Among right-lesioned participants, mean pleasantness rating for positive stimuli with viewing times shorter than 9 s was 5.6 (s.d. = 0.9), whereas mean rating of pleasantness for the rest of the stimuli was 6.7 (s.d. = 1.7), indicating that subjects with right-side lesion actively withdrew from stimuli whose pleasantness they did not rate as high as the stimuli they responded neutrally toward or actively approached.

**Categories of actively avoided stimuli**

This examination aimed at establishing if a specific category of stimuli was actively avoided by right-lesioned participants. **Actively avoided stimuli** were defined as stimuli that received a reduction in viewing possibility would be consistent with reduced motivation, the latter would suggest the opposite (i.e. motivation intact but preferences altered).
time by the majority (at least 3 of 5) of right-lesioned participants. Five (83%) of six stimuli actively avoided by right-lesioned participants were human (and sexual) in nature, as opposed to food or objects. The single non-sexual stimulus depicted either jewelry or fancy cars, depending on the sex of the rater. To attain independent confirmation of this observation, 10 healthy volunteers (not part of this study sample, five women, Caltech students or workers) rated all 18 positive stimuli for sexual content using a nine-point Likert scale. The stimuli right-lesioned patients actively withdrew from were rated as having a mean sexual context of 5.95 (s.d. = 1.4) \( t(16) = 3.5, P = 0.0025 \).

**Negative-valence stimuli**

**Preference and viewing time**

There were no group differences on ratings of pleasantness (K-W statistic = 3.19; df = 2, \( P = 0.2 \)) or viewing time (K-W statistic = 2.5; df = 2, \( P = 0.3 \); Table 2). Based on these results, no further analyses were computed.

**DISCUSSION**

This study was carried out to examine whether lateralized insular/basal ganglia complex lesions affect hedonic evaluation, incentive motivation or the relationship between the two. Dependence of significant group effects on specific stimulus categories was also examined. Although there were no significant group effects for negative stimuli, subjects with damage to right insular–basal ganglia circuits showed reduced preference and viewing time for positive stimuli, as compared with both the left-lesioned group and healthy volunteers. Shorter average viewing time for positive stimuli among the right-lesioned participants may have originated either from poor incentive motivation to approach or alternatively from active withdrawal. Analyses showed that right-lesioned subjects did not have a general reduction in motivation to approach positive stimuli, but withdrew from those positive stimuli to which they gave lower pleasantness ratings. Stimulus-level analyses showed that this reduced preference (and viewing time) for positive stimuli was, in large part, determined by negative responses to stimuli depicting humans and having sexual content. Right-side lesion participants gave lower ratings and actively withdrew from such stimuli. This behavior was not observed in either the healthy comparison or the left-lesioned group. In addition, the typical positive relationship between hedonic evaluation and incentive motivation was preserved (i.e. right-lesioned participants were not motivated to work for stimuli that they did not like, and vice versa). These findings could not be explained by group differences in either motor ability or ratings of arousal.

While an individual’s ‘liking’ of a given stimulus may reasonably be expected to be closely related to the amount of work (i.e. ‘wanting’) the individual is willing to undertake to obtain that stimulus, empirical research has shown that liking and wanting may be—at least under experimental conditions—dissociated (Berridge and Robinson, 2003). Wanting has been shown to depend on the core of the nucleus accumbens dopaminergic activity; in contrast, liking depends on the shell of the nucleus accumbens and is less dependent on dopaminergic activity (reviewed in Berridge and Robinson, 2003). The task used in this study is based on the task in Aharon et al. (2001), an influential research that showed a behavioral dissociation between liking and wanting in humans. Men reduced viewing time of faces of men they rated as attractive (i.e. they did not ‘want’ to see what they ‘liked’; Aharon et al., 2001). That study also showed a relationship between wanting and neural activity in the nucleus accumbens, and based on the overall results of that work, this study sought to determine if...
lesions of the basal ganglia/insula complex might result in a liking/wanting dissociation and whether the side of the lesion played a role.

The findings in the present study are particularly relevant in light of two recent studies showing that bilateral basal ganglia damage is associated with reduced incentive motivation (Schmidt et al., 2008; Vijayaraghavan et al., 2008). Hence, the extant lesion literature and this study suggest that unilateral damage to insula/basal ganglia circuits may not be sufficient to alter incentive motivation independent of preference. These conclusions are consistent with the observation that active avoidance in response to negative stimuli in both right- and left-side lesion subjects was unaltered, arguing against a general loss of motivation following unilateral damage to insular/basal ganglia circuits.

Other limitations of this study should be kept in mind. The left-sided lesions were smaller than right-sided lesions. The stringent study criteria (see Methods section) have reasonably led to exclusion of some patients with larger left-sided lesions due to associated impaired language comprehension and/or aphasia, which would have reduced full participation in the tasks. Although the possibility stands that lateralized differences were related to differing lesion sizes, examination of individual responses showed that the person with the smallest right-sided lesion (R2; see Figures 1 and 3) showed responses similar to all other right-sided lesion subjects and different from both healthy volunteers and participants with left-sided lesions. In addition, all of the left-sided lesion participants’ behavior resembled the behavior of healthy volunteers much more closely than any right-sided participant (Figure 3). In addition, conclusions from negative stimuli data may need to be mitigated based on likelihood of floor effects. The role of the insula/basal ganglia complex in evaluating negative stimuli should be investigated further. Nonetheless, both lesion groups gave low preference ratings and actively avoided negative stimuli, suggesting that hedonic evaluation of and incentive motivation for negative stimuli remained coarsely intact. The findings in this study apply to individuals with stroke of the basal ganglia/insula circuit who are not cognitively impaired, have no psychiatric diagnosis and depression severity below the most liberal clinical cutoff.

This study did not find evidence of a pure incentive-motivational impairment following unilateral right-sided (or left-sided) lesion to the insular–basal ganglia complex. Although unilateral damage to right insular–striatal circuits did not induce a generalized dysfunction of approach–withdrawal behavior, there were preference alterations that were strongly dependent on both stimulus valence and content. Right-lesioned participants were motivated to avoid negative stimuli, as well as positive stimuli that they found less pleasant (i.e. sexual stimuli), and approached positive stimuli that they found more pleasant (i.e. appetitive foods and coveted objects).

Right-side lesion participants’ altered response (reduced pleasantness ratings following by active withdrawal) to stimuli portraying humans in sexually charged (albeit not graphic or offensive) poses was perhaps the most surprising finding. Neuroimaging studies carried out while participants viewed sexually laden stimuli for the purpose of sexual stimulation may help in the interpretation of this result. These studies have consistently shown increased activity in the head of the caudate nucleus (Stoleru et al., 1999; Redoute et al., 2000; Arnow et al., 2002; Karama et al., 2002; Stoleru et al., 2003; Ferretti et al., 2005; Redoute et al., 2005; Moulier et al., 2006; Schiffer et al., 2008; Walter et al., 2008) among other regions (e.g. hypothalamus) in association with physiological changes related to sexual pleasure. As components of the circuit activated during sexual visual stimulation, the head of the caudate may subserve the evaluation and feed back of personal (including sexual) acts (Lau and Glimcher, 2007; Tricomi and Fiez, 2008), whereas the insula may monitor the internal state of the body in response to sexually laden stimuli (Craig 2002; Saper, 2002). Both of these functions have been posited to be critical for appraisal of the emotional content of environmental stimuli (Damasio, 1999) and their failure following focal damage may induce loss of appreciation for sexually laden stimuli. It is less clear why sexually laden stimuli and not other appetitive stimuli were prevalently responsible for the effect shown in this study. Further insights on this important issue may come from research examining whether damage to basal ganglia/insula circuits reduces also sexual desire (Prause et al., 2008).

Active withdrawal from pleasant stimuli following basal ganglia damage is not new in the literature. Using the same paradigm used in this study, Vijayaraghavan et al. (2008) showed that bilateral globus pallidus damage led to withdrawal from pictures of appetizing foods (similar to food aversion in rats with ventral pallidal lesions; Cromwell and Berridge, 1993). In contrast with the extensive literature associating the processing of disgust with insular–striatal circuits (Calder et al., 2001), an effect of lateralized insular–striatal damage on incentive motivation or hedonic evaluation of disgusting stimuli was not found. Processing of disgust may have been preserved because left-sided lesions did not include the anterior most portion of the insula, or because other brain structures, such as the orbitofrontal cortex or the amygdala took on a compensatory role (Schenle et al., 2002; Buchanan et al., 2004). Alternatively, exclusion of patients with significant depression may explain failure to show a significant effect on disgust (Paradiso et al., 2012).

In sum, this study findings clarify the role of the right insular–striatal circuit in mediating hedonic preference and incentive motivation. Surprisingly, there were no pure motivational changes, and the relationship between incentive motivation and preference remained intact. Stimuli of sexual nature were found to be particularly aversive by patients with right-sided lesions. These results may have relevance for the assessment and treatment of neuropsychiatric disorders characterized, in part, by insula/basal ganglia complex dysfunction including Huntington’s and Parkinson’s disease and depression (reviewed in Paradiso et al., 2012).

REFERENCES


