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Lateralization of affective processing in the insula

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ABSTRACT

Evidence from electrophysiological and functional neuroimaging studies has suggested strong lateralization of affective processing within the insular cortices; however, little is known about the spatial location of these processes in these regions. Using quantitative meta-analytic methods the laterality of: (1) emotional processing; (2) stimulus valence (positive vs. negative); (3) perception vs. experience of emotion; and (4) sex-differences were assessed using the data from 143 functional magnetic resonance imaging studies. Activation in response to all emotional stimuli occurred in bilateral anterior and mid-insula, and the left posterior insula. Positive emotional stimuli were associated with activation in the left anterior and mid-insula, while negative emotional stimuli activated bilateral anterior and mid-insula. Activation in response to the perception and experience of emotions was highest in bilateral anterior insula, and within the mid and posterior insula it was left lateralized. In males, emotional stimuli predominantly activated the left anterior/mid-insula and right posterior insula, whereas females activated bilateral anterior insula and the left mid and posterior insula. Spatial distinctions observed in emotional processing and its subcategories can provide a comprehensive account of the role of the insular cortices in affect processing, which could aid in understanding deficits seen in psychiatric or developmental disorders.

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Introduction

The insula is an essential brain region for the integration of interoceptive information (sense of the physiological state of the body) and emotional experience (Craig, 2002, 2009). These properties are afforded to the insula through extensive viscerosensory input from the periphery and reciprocal connections with limbic, somatosensory, prefrontal and temporal cortices (Augustine, 1996; Mesulam and Mufson, 1982a, 1982b). The insula processes appetitive and aversive physiological sensations (i.e. thirst, hunger, pain) and the associated emotional arousal that results in the conscious perception of one's affective state (James, 1884; Lange, 1885; Russell, 2003; Schachter and Singer, 1962).

Evidence from electrophysiological studies and hemispheric inactivation procedures has indicated strong lateralization of affective processing within the insula based on autonomic input to this region (Hilz et al., 2001; Oppenheimer et al., 1992). However, inconsistent results have come from lesion studies in patients and findings from functional neuroimaging studies. Meta-analyses of functional imaging data permit the collation of findings across studies and can provide precise spatial localization of affective processing to develop a topographical model of emotional functions within the insula.

Historically, emotional processes were believed to be mediated by the right hemisphere (for review see (Harrington, 1995)). More recent reports with patients and functional neuroimaging studies have indicated that emotional processing is left- or right-lateralized based on stimulus valence (positive/negative emotions) (Davidson et al., 1979; Hellige, 1993; Silberman, 1986), behavior (approach/withdrawal) (Davidson et al., 1990) and/or phenomenal state (perception/experience) (Garrett and Maddock, 2006; Peelen et al., 2010; Zaki and Ochsner, 2011).

Lateralization of emotional processing in the insula has been supported by evidence suggesting differential autonomic inputs (parasympathetic/sympathetic) to this region (Craig, 2005). For example, direct stimulation of the left insula results in changes in parasympathetic functions (Oppenheimer et al., 1992) involving nourishment, safety, positive affect and approach behavior (Craig, 2005), whereas the right insula has been implicated in top-down control of sympathetic-nervous system functioning, which is involved in hunger, survival, negative affect and avoidance behavior.

Support for this stimulus-valence processing scheme has come from functional neuroimaging, but with some discrepancy among the findings (Caria et al., 2010; Phillips et al., 1997; Simmons et al., 2004, 2012; Sprengelmeyer et al., 1998; Wager et al., 2003). For example, functional imaging studies of passionate, maternal and unconditional love showed that these positive stimuli activated the left more than

Abbreviations: ALE, activation likelihood estimate; fMRI, functional magnetic resonance imaging; T, Tesla; AC, accessory gyrus; AS, anterior short insular gyrus; MS, middle short insular gyrus; PS, posterior short insular gyrus; AI, anterior long insular gyrus; PL, posterior long insular gyrus.

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the right insula (for review, see (Ortigue et al., 2010)); however, these results may be influenced by sex as 83% of the studies reviewed tested female participants. In line with the valence hypothesis, the right anterior and mid-insula were activated during negative experiences including motion-induced nausea (Napadow et al., 2012) and viewing intense facial expressions of disgust (Phillips et al., 1997). In contrast, other imaging studies have indicated that the left anterior insula mediates negative stimuli, such as viewing unpleasant visual stimuli (Caria et al., 2010). To determine the effect of valence (positive and negative stimuli) on insular activation was one of the main aims of the current work, with a focus on the hemispheric contributions of anterior, middle and posterior regions.

Previous reports concerning the lateralization of emotional processing in the insula were based largely on results obtained from participants viewing emotional stimuli. Further distinctions can be made in the viewing of emotional stimuli in terms of perceiving or actually experiencing an emotion (Garrett and Maddock, 2006; Kober et al., 2008; Lindquist et al., 2012; Peelen et al., 2010; Zaki and Ochsner, 2011). Individual neuroimaging studies have tested this hypothesis and have suggested some lateralization of processing (Modinos et al., 2011; Wicker et al., 2003). For example, bilateral insular cortex was activated in individuals who smelled disgusting odors (experience), but only the left side was activated when viewing others performing the same act (perception) (Wicker et al., 2003). Few individual neuroimaging studies have contrasted self versus another's emotional experience within the same experimental protocol and therefore the laterality of these processes remains uncertain. In the present work, hemispheric and region-specific (anterior/middle/posterior insula) preferential emotional processing related to self and others was assessed.

Subtle differentiations in self/other emotional processing could have strong clinical relevance. For example, in individuals with autism spectrum disorder (ASD) atypical activity in the insula may underlie deficits in understanding the thoughts and emotions of others (Allman et al., 2005; Silani et al., 2008). Children with ASD were found to activate the right insula when viewing neutral images of themselves as seen in typically-developing children, but they did not activate the right insula when viewing images of others (Uddin et al., 2008). Improved understanding of the localizations of these subtleties of functions in a normative population will greatly facilitate the understanding of findings in clinical populations.

Lastly, further distinctions in emotional processing in the insular cortices may be influenced by the sex of the participants. This line of reasoning comes from several sources such as behavioral evidence suggesting that females are better than males at understanding the emotions of themselves and others (Baron-Cohen and Wheelwright, 2004; Eisenberg and Lennon, 1983). Females demonstrate increased affective arousal or expression of emotion during social interactions (Brody and Hall, 2000), although this may depend on contextual factors (Barrett et al., 1998). Key to emotional competence is the ability to recognize facial expressions; females compared to males have a greater ability to recognize facially expressed emotions, even in instances where stimuli are presented for brief periods (Donges et al., 2012; Hall, 1978; Hall and Matsumoto, 2004; Hoffmann et al., 2010). Several brain-imaging studies have demonstrated differential neural processing in females and males during emotional processing tasks (Cahill, 2006; Derntl et al., 2009; Hofer et al., 2006, 2007). For example, in an fMRI experiment that tested both sexes, only females recruited bilateral insular cortices in conjunction with the amygdalae during the perception of humorous stimuli (Kohn et al., 2011), a finding that the authors attributed to potentially greater emotional-regulation abilities in females. Some evidence also suggests sex-differences in the lateralization of stimulus-valence processing within the insula. An fMRI study examining cognitive modulation of emotion reported activation in the left insula only in females during the perception of aversive stimuli (Koch et al., 2007). Additionally, a recent meta-analysis of 88 studies examining brain activation associated with emotional stimuli reported that females activated the left insula in response to negative emotional stimuli whereas males showed bilateral activation in this region (Stevens and Hamann, 2012). Given these previous findings, we investigated activation in the insula in response to emotional stimuli in males and females separately.

Lateralization of emotional processing in the insular cortices is a fundamental aspect of interpreting the functions of this region; however, no clear consensus on the roles of the left and right insula in emotional processing has been established. Here, using affect-related data from fMRI studies, we explored topographical distinctions of the various aspects of emotional processing (i.e., positive, negative, perception, experience) within the insula and provide normative atlases for these processes in stereotaxic space. The meta-analyses tested: (1) right-insular cortex dominance for global emotional processing, (2) lateralization of stimulus valence (positive vs. negative), (3) perceiving vs. experiencing emotional stimuli and (4) sex differences.

Methods

Article selection and literature search

An initial broad search of the literature was conducted to determine the range of affective-, cognitive-, motor- and sensory-evoked activation in the insula measured using fMRI. The Web of Science (http://www.isiknowledge.com) was searched for articles published between January 1990 and October 2010 using the keywords fMRI and insula. The initial search yielded a total of 1263 articles. The studies were screened for the following inclusion criteria: (1) written in English; (2) fMRI experiment; (3) stereotaxic coordinates; (4) healthy human participant data; and (5) general linear model analyses. Exclusion criteria were: review articles, patient data, connectivity analyses, meta-analyses, case studies, special populations (e.g. savants, psychics), deactivation and pharmacological fMRI. The initial screening resulted in the exclusion of 545 articles (Reviews: 35; Meta-analyses: 14; Case studies: 8; Patients: 86; Special populations: 26; No healthy within-subject analysis: 88; Pharmacological fMRI: 19; Functional connectivity: 10; No coordinates: 191; Not fMRI: 22; Animal studies: 4; Other: 34; Not retrievable: 7; Duplicate study: 1).

A total of 718 studies meeting our criteria underwent full review and the following information was entered into a database: author names, year of publication, number of participants, mean age, Tesla (T) strength of scanner, task description, affect (positive/negative) and contrast(s). Of the 718 studies reporting activation in the insula, the largest single grouping, $n = 143$, used emotional stimuli. The remaining studies reported cognitive-related activation (e.g. language, executive functioning, working memory, reasoning, gambling, time perception, self viewing, reward, mentalizing), or activation in response to somatosensory stimuli (e.g. noxious, tactile) and other perceptual stimuli (e.g. auditory, olfactory, gustatory). Additionally, many studies reported motor-related activity. In the current work, the data from the 143 fMRI studies of emotion were analyzed.

These emotion studies were further categorized according to stimulus valence (positive or negative stimuli) and into perception and experience categories (Table 1 for details). Examples of positive stimuli included images of loved partners and friends or happy faces, whereas negative stimuli/protocols included the induction of feelings of regret, shock avoidance and images of others in pain. Studies were classified as perception or expression using similar criteria as outlined by Wager et al. (2008). The key distinction between the perception and experience categories was the intention of inducing a subjective emotion in the participants in the latter category. The perception category included studies that examined participants who viewed the emotion of others, whereas the experience category included studies with participants who viewed emotional stimuli that elicited a personal emotional experience. For example, studies that asked participants to passively view stimuli or to categorize images (e.g., facial expressions) based on gender were classed as perception. Studies that asked participants to view images of others for whom they had strong feelings (i.e. familiar friendly faces, or enemies) or any studies designed to evoke an affective state, were classified as experience of emotion. Examples of the experience of emotion also included empathy tasks and those examining maternal love. Distinctions between perception and experience of emotions were made based on the instructions to the participants. Even in the instance of viewing aversive stimuli (e.g., a perceived noxious stimuli directed towards a body part or others expressing pain), if participants were not asked to empathize or imagine the pain themselves, the study was categorized as perception. However, if the participants were instructed to empathize and try to feel the emotions portrayed, the studies were classified as experience. In the case of multiple contrasts within a study, a single contrast was selected for each meta-analysis to maintain data independence.

Meta-analytic method

Activation foci reported in MNI coordinates were transformed to Talairach space (Lancaster et al., 2007; Talairach and Tournoux, 1988). Coordinates for activation in response to all emotional stimuli were entered into a single meta-analysis. The data were further subdivided into four separate meta-analyses to examine activation associated with (1) positive and (2) negative emotional stimuli and (3) perceiving and (4) experiencing emotions. Lastly, activation from studies that tested only male or female participants was analyzed in two further distinct meta-analyses.

The activation likelihood estimate (ALE) method (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) was utilized to create probabilistic maps that described the spatial location and extent of activation in the insula in response to emotional stimuli (GingerALE v2.1.1 — http://brainmap.org/ale/). Each activation focus is given equal weighting within the meta-analysis irrespective of the magnitude of the activation or the variance associated with the data. The activation foci were initially converted to probability distributions within a standardized image space. This process involved smoothing the data using a Gaussian blurring kernel, which is a convolution function that acts as a low-pass spatial frequency filter. The size of the kernel's full-width at half maximum (FWHM) was weighted by the sample sizes of the original studies (Eickhoff et al., 2009) to ensure that the results of studies with small sample sizes would not unduly influence the results. The original data collected from the articles were smoothed during the original pre-processing steps; however only the peak foci were utilized in the ALE analyses. Therefore, smoothing the data is a more accurate reflection of the activation foci in that it represents the actual spatial extent of the activation and not just the peak foci. An ALE value was calculated for each voxel in the brain that described the conjunction of the probability distributions. The data were then combined into a three-dimensional volume.

To test the null hypothesis that the ALE values were no different from random noise, data were tested against a null-distribution of ALE values. This procedure involved the selection of a random voxel (with an associated ALE value) from each original experiment, and was repeated 2×10^{10} times. Data were corrected for multiple comparisons using the false discovery rate (FDR) $q = 0.001$ (Laird et al., 2005).

Regional and laterality indices

Hemispheric dominance of affective processing was assessed by calculating laterality indices for each of the thresholded ALE maps (all emotion, positive, negative, experience, perception, male, female). The regions (anterior, mid, posterior) of the insula were manually drawn on a template MRI (Colin1 in Talairach space). The regions were defined based on the anatomy of the insula as outlined by Craig (2009) (see Fig. 1). The insula is comprised of 5–6 gyri (anterior to posterior): (1) accessory gyrus (2) anterior short insular gyrus, (3) middle short insular gyrus (4) posterior short insular gyrus, (5) anterior long insular gyrus and (6) posterior long insular gyrus. Anterior insula was defined as gyri 1 and 2, middle insula included gyri 3 and 4, and posterior insula included gyri 5 and 6. The posterior insula is bordered by the anterior and posterior limiting sulci (Kurth et al., 2010).

The thresholded ALE values within each hemisphere of the insula regions-of-interest were summed. A laterality index was calculated [Right − Left] / [Right + Left] based on the summed values (Seghier, 2008). Hemispheric dominance was set at −0.2/0.2 (left/right) based on the thresholding methods used in previous literature (Deblaere et al., 2004; Springer et al., 1999). A value less than −0.2 was deemed left hemisphere dominant, while a value greater than +0.2 was deemed right hemisphere dominant; values in between were considered bilateral.

The laterality indices were calculated on the ALE maps within each region-of-interest (anterior, mid, posterior). The resulting values reflect right/left differences in the likelihood and spatial extent of the summed ALE values in each anterior, mid, posterior region separately. The laterality indices provide a descriptive illustration of the distribution of activity (based on the probability of activation).

Results

Demographic information

The 143 studies of emotion included 2721 participants (51.6% female), the median of the mean age of the participants was 24.7; 78% of studies reported handedness and tested mainly right-handed individuals (eight of these studies included 1–10 left-handed individuals). For more details on the studies included in the meta-analyses see Table 1.

All emotion

A total of 565 foci were extracted from the 143 experiments reporting activation in the insula in response to emotional stimuli. The stimuli used in the studies included mostly positive and negative stimuli that were presented to the participants in a perceptual manner or were intended to induce an emotional response in the viewer. Thirty-one studies presented positive and 80 studies presented negative stimuli. Nine of the studies used both stimuli types and 23 did not use either. Of these 143 studies, 49 presented perceptual stimuli and 94 studies presented the stimuli with the intention of inducing an emotion (experiential). Lastly, 22 studies tested only female participants, and 15 tested only males.

Activation in response to all emotional stimuli was highest in bilateral anterior insula, and the cluster of activation extended posteriorly to the mid-insula and posterior insula, especially in more inferior regions (Table 2; Fig. 2; see also Suppl. Fig. 1 for more extensive images of the activation in the insula). Laterality indices indicated that within the posterior insula, the left side was more activated by all emotional stimuli. The ALE values in the anterior and mid-insula were comparable in terms of overall value and/or spatial extent and were not lateralized (Fig. 3.).

Positive emotional stimuli

Positive emotional stimuli were associated with 102 foci from 41 experiments (8 involved the perception of emotion, 33 the experience of emotion). The left mid-insula was activated by positive stimuli; the cluster of activation extended anteriorly into the territory of the anterior short insular gyrus. Left dorsal anterior and mid-insula

Table 1
List of studies included in Study 1 (all emotional stimuli).

Study #	Author	Year	*N*	F	Age	Tesla	Task	Sub-category		Contrasts
1	Akitsuki and Decety	2009	26	14	24.4	3	Pain empathy task with social context	Neg	Exp	Pain > no pain
										Self + other > self
										Correlations with hemodynamic response
2	Aleman and Swart	2008	16	8	22.5	3	Emotional face perception task	Neg	Per	Disgust: Women > men
										Male: Disgust male–female
										Female: Contempt male–female
3	Anderson et al.	2003	12	9	22.1	3	Object attentional selection task	Neg	Per	Disgust
4	Bach et al.	2008	16	8	26	3	Emotional prosody processing task	Neg	Per	Emotion > neutral
5	Bartels and Zeki	2000	17	11	24.5	2	Face processing task	Pos	Exp	Pictures of loved partners and friends
6	Bartels and Zeki	2004	20	20	34	2	Face processing task	Pos	Exp	Pictures of own child
7	Baumgartner et al.	2006	9	9	24.78	3	Empathy task	–	Exp	Picture + music > picture
8	Beer et al.	2008	16	8	24.3	1.5	Black–white implicit association test	Neg	Exp	Black faces and unpleasant pictures
								Pos		White faces and pleasant pictures
										Detection of appropriate responses
9	Bermpohl et al.	2006	17	9	21–37	3	Emotional stimuli expectancy and perception task	–	Per	(Emotional > neutral perception) > (emotional > neutral expectancy)
10	Berns et al.	2010	27	14	14.6	3	Music rating task	Pos	Exp	Correlation with likability
										Correlation with popularity
11	Botvinick et al.	2005	12	12	20–30	1.5	Facial emotion task	Neg	Per	Pain > neutral
12	Botzung et al.	2010	23	0	21.45	4	Cued recall task	Pos	Per	Increasing memory confidence on Pos > Neg events
13	Britton et al.	2006	12	6	21.4	3	Affective picture viewing task	Pos	Exp	Emotional faces
										Emotional faces > IAPS pictures
										Happy faces
										Happy faces > happy IAPS pictures
								Neg		Sad faces
										Sad faces > sad IAPS pictures
										Angry faces
										Angry IAPS pictures
										Fearful faces
										Fearful faces > fearful IAPS pictures
14	Britton et al.	2006	12	8	26.7	3	Emotional Stroop task	Pos	Exp	Nonsocial
										Nonsocial positive
15	Britton et al.	2009	12	6	23.6	3	Affective video viewing	Neg	Exp	Phobia-related words > neutral words
16	Brunetti et al.	2008	18	0	24.89	1.5	Affective video viewing	Pos	Exp	Erotic vs. sport visual stimulation
17	Caria et al.	2010	27	NR	NR	NR	Affective picture assessment task	Neg	Exp	Increased activation over time
18	Carr et al.	2003	11	4	29	3	Facial emotions task	–	Per	(Imitation and observation) and (imitation > observation)
19	Cerqueira et al.	2008	11	5	32.4	1.5	Autobiographical recall task	Pos	Exp	Happiness > neutral
										Happiness > irritability
20	Chakrabarti et al.	2006	26	13	23.4	3	Facial emotions task	Neg	Per	Sad > neutral vs. EQ
										Disgust > neutral vs. EQ
21	Chaminade et al.	2010	13	9	29.4	1.5	Facial emotion task	Neg	Per	Disgust
22	Cheng et al.	2010	36	18	23	3	Pain processing perception task	Neg	Per	Pain
23	Chiao et al.	2009	14	14	22.9	NR	Pain empathy task	Neg	Exp	Pain > no pain
24	Chua et al.	2009	29	13	20.2	3	Emotional gambling task	Neg	Exp	Regret > fixation
										Disappointment > fixation
										Regret > disappointment
25	Coen et al.	2009	12	0	26	1.5	Affective music listening; esophageal distensions	Neg	Exp	Painful esophageal stimulation during negative emotional modulation
26	Critchley et al.	2005	15	9	32	1.5	Reaction time task	–	Exp	Heart rate change by viewing emotional face stimuli
										Categorical processing of face expression
										Activity predictive of heart rate acceleration
										Categorical face processing correlated with heart rate acceleration
27	Cunningham et al.	2004	20	NR	NR	3	Good–bad task; abstract–concrete task	Pos	Per	Good–bad = abstract–concrete

28	Cupchik et al.	2009	16	8	NR	1.5	Perceptual esthetics task	–	Per	Pragmatic/esthetic vs. baseline Esthetic vs. baseline
29	Dalton et al.	2005	23	0	20	1.5	Threat-of-shock task	Neg	Exp	Correlation with cardiac contractility to threat of shock Threat > safety Correlation with anxiety in anticipation of shock
30	Davey et al.	2010	20	NR	19.5	3	Likeability rating task	Pos	Exp	Positive feedback > control feedback
31	Decety et al.	2008	17	9	9	3	Pain perception task	Neg	Per	Pain Pain caused by agent
32	Decety et al.	2009	8	NR	17	3	Pain perception task	Neg	Per	Dynamic visual stimuli depicting painful situations
33	Decety et al.	2010	22	11	25.2	3	Pain empathy task	Neg	Exp	Pain Pain > fixation
34	Denson et al.	2009	20	12	18.68	3	Directed rumination task	Neg	Exp	Exposure to interpersonal provocation > fixation Rumination > distraction
35	Di Dio et al.	2007	14	6	24.5	3	Esthetic observation, judgment, and proportion judgment task	Pos	Exp	Canonical and modified images vs. baseline Simple effect observation (C–M)
36	Ehrsson et al.	2007	19	8	19–33	1.5	Threat-of-shock task	Neg	Exp	Threat during ownership > threat during no ownership
37	Eugene et al.	2003	10	10	24.1	1.5	Affective video viewing	Neg	Exp	Sadness (Study 1) Sadness (global analysis)
38	Ferretti et al.	2005	10	0	21–25	1.5	Affective video and picture viewing	Pos	Exp	Erotic vs. sport Regression: Penile turgidity and video clips Onset of erection vs. no erection Sustained erection vs. no erection
39	Fischer et al.	2005	24	12 22	24.7 74.1	1.5	Affective picture viewing	Neg	Per	Older adults Older > younger adults
40	Fischer et al.	2010	24	12 22	24.7 74.1	1.5	Facial emotion task	Neg	Per	Old > young
41	Fitzgerald et al.	2004	12	5	31.2	1.5	Mood induction task	Neg	Exp	Internally-generated disgust
42	Freed et al.	2009	20	16	37.8	1.5	Emotional Stroop task	Neg	Exp	Correlation to attentional bias towards deceased-related words
43	Gizewski et al.	2006	47	25	27.5	1.5	Affective video viewing	Pos	Exp	Related to erotic stimuli: Male/female in luteal phase Male/female in menstrual phase Female in mid-luteal/menstrual phase
44	Goldin et al.	2008	17	17	22.7	3	Affective film viewing, reappraisal, and suppression task	Neg	Exp	Watch-neg > watch-neutral Watch-neg > reappraise; suppress > watch-neg for late component Reappraise > suppress for early component
45	Grabenhorst and Rolls	2009	12	5	27	3	Pleasantness and intensity rating task	Neg	Exp	Correlation with relative unpleasantness of second odor compared to first odor Negative difference vs. positive difference in pleasantness for second odor
46	Gray et al.	2007	12	5	26.1	1.5	Emotional intensity ratings task	Pos	Exp	Emotion (happy/neutral) vs. feedback (T/F) Physiological comparator mismatch: Neutral (asynch > true) vs. emotion (asynch < true)
47	Grosbras and Paus	2006	20	10	28.6	1.5	Emotion perception task	Neg	Per	Neutral face > control Angry face > control Angry hands > neutral hands Angry hand vs. neutral hand andangry face vs. neutral face Angry face vs. neutral face masked by angry face vs. control
48	Gu and Han	2007	10	7	21.6	3	Pain intensity perception task	Neg	Per	Rating painful words vs. counting neutral words Rating painful words vs. counting painful words Conjunction analysis of above two contrasts
49	Gu and Han	2007	12	5	21.9	3	Pain empathy task	Neg	Exp	Rating painful stimuli vs. counting neutral stimuli Rating vs. counting painful stimuli
50	Gundel et al.	2003	8	8	NR	1.5	Grief-related picture/text viewing task	Neg	Exp	Photograph of a deceased relative in picture-word composites
51	Hardin et al.	2009	18	NR	29	3	Wheel-of-fortune task	Pos	Exp	Most extreme positive vs. most extreme negative

(continued on next page)

Table 1 (*continued*)

Study #	Author	Year	*N*	F	Age	Tesla	Task	Sub-category		Contrasts
52	Harrison et al.	2008	24	12	31	3	Mood induction task	Neg	Exp	Sad–neutral recall Neutral recall Sad recall
53	Harrison et al.	2009	14	7	22	1.5	Dynamic papillary exchange task	Neg	Exp	Viewing eyes Change in observed and observer's pupil size Interaction between feedback condition and variance in pupil size
54	Heinzel et al.	2005	13	3	27	1.5	Mood induction task	–	Exp	Parametric modulation by valence
55	Hennenlotter et al.	2004	9	4	37.4	1.5	Facial emotion task	Neg	Per	Disgusted vs. neutral expressions
56	Hennenlotter et al.	2005	12	6	24.5	1.5	Facial emotion task	Pos	Per	Smile-observation (smile-neutral) Smile-execution (move-rest) Smile-neutral and move-rest
57	Herwig et al.	2007	16	10	29.5	1.5	Emotional stimuli expectancy task	Neg	Per	Expectation: negative > neutral Expectation: unknown > neutral Expectation unknown and negative > positive and neutral
58	Herwig et al.	2007	12	12	27.5	1.5	Emotional stimuli expectancy task	Neg	Per	Expectation vs. presentation of unpleasant pictures Conjunction analysis of exp negNneu and exp negNpos
59	Hu et al.	2008	20	0	26.5	1.5	Mood induction task	Pos	Exp	Homosexual males: Sexual arousal in M–M vs. rest Heterosexual males: Sexual arousal in F–M vs. rest
60	Hua et al.	2008	12	6	22	1.5 and 3	Affective tactile stimuli task	–	Exp	Three touch conditions
61	Hutcherson et al.	2005	28	28	18–21	3	Attention and emotion task	Pos	Exp	Amusing vs. neutral: passively viewing, passively rating Amusing films: Emotion rating vs. passive viewing
62	Iaria et al.	2008	20	10	22.8	3	Emotional processing task; orientation task	–	Exp	High emotional susceptibility while performing explicit emotional task
63	Ishai et al.	2004	13	8	23	3	Face working memory task	Neg	Per	Visual perception of faces
64	Jackson et al.	2005	15	7	22	3	Pain empathy task	Neg	Exp	Painful stimuli vs. neutral stimuli
65	Jackson et al.	2006	34	20	29	3	Pain empathy task	Neg	Exp	Pain-related
66	Kaplan et al.	2007	20	10	35.65	3	Face processing task	Neg	Exp	Opposing candidate's face–own candidate's face Correlation: Negative Bush ratings and Bush minus Kerry activity Correlation: Positive Bush ratings and Kerry minus Bush activity
67	Keightley et al.	2003	6	1	23	1.5	Affective picture processing task	–	Per	EP (direct picture) and IF (indirect face) processing
68	Keightley et al.	2007	10	5	27.2	1.5	Facial emotion task	Pos	Per	Happy > other
69	Killgore and Yurgelun-Todd	2007	16	7	11.6	1.5	Facial emotion task	Neg	Per	Negative correlation with Total EQ Negative correlation with adaptability Negative correlation with stress management
70	Kim et al.	2010	28	12	27.4	3	Natural/urban scene picture viewing task	–	Exp	Natural > urban
71	Kim et al.	2006	10	0	52	1.5	Affective video viewing	Pos	Exp	Differential activity in response to sexually explicit and emotionally neutral visual stimuli
72	Kim et al.	2009	14	6	27.5	1.5	Virtual social cognition task	Pos	Exp	Emotional social information processing: Happy vs. control
73	Koelsch et al.	2006	11	5	24.6	3	Affective music listening	Pos	Exp	Pleasant > unpleasant
74	Krendl et al.	2006	22	11	20.7	1.5	Gender discrimination task; affective judgment task	Neg	Exp	Ratings of disgust serving as covariate of interest
75	Kross et al.	2007	20	13	24.5	1.5	Affective picture viewing task	Neg	Per	Rejection > acceptance
76	Kuhn et al.	2010	15	15	20.7	3	Mood induction task	Pos	Exp	Mimicry > antimimicry
77	Kuniecki et al.	2003	16	0	19–25	1.5	Affective picture processing task	Neg Pos	Per	Negative vs. neutral Positive vs. neutral
78	Kurosaki et al.	2006	22	11	24.7	1.5	Affective judgment task	–	Exp	Females: Thin > real
79	Lee et al.	2007	15	14	45.5	1.5	Affective picture viewing task	Neg	Per	Negative picture stimuli
80	Lee et al.	2008	14	7	23.8	3	Emotional expression interference task; the Simon task	–	Per	Interference effect of emotional expression Highest 20% interference effect Lowest 20% interference effect

										Correlation with intensity rating Interference effect of Simon task
81	Lee et al.	2010	18	9	25.8	1.5	Empathy task	–	Exp	Emotional empathy–physical causality
82	Leibenluft et al.	2004	7	7	30	1.5	Face processing task; 1-back repetition detection task	Pos	Exp	Own child vs. familiar child Familiar vs. unfamiliar children Unfamiliar children vs. unfamiliar adults
83	Lemche et al.	2006	12	5	27.25	1.5	Semantic conceptual priming task	Neg	Exp	Stress prime condition only Neutral prime condition only
84	Liu et al.	2010	15	7	21.5	1.5	Affective lexical decision task	–	Exp	Unrelated priming vs. related affective priming
85	Lloyd et al.	2006	14	NR	29	1.5	Threats-to-hand task	Neg	Exp	Painful probe touching rubber hand in Incongruent arm position Painful tactile probe > innocuous tactile probe in Incongruent arm position
86	Longe et al.	2010	17	17	24.71	3	Emotional self-reference task	Pos	Exp	Self-reassurance during threat-to-self scenarios vs. neutral Self-reassurance vs. self-criticism during threat-to-self scenarios
87	Mak et al.	2009	12	12	24	1.5	Affective picture viewing task	Pos	Per	View > regulate
88	Mataix-Cols et al.	2008	37	20	30.7	1.5	Emotional self-reference task	Neg	Exp	Positive correlation with disgust score
89	Meriau et al.	2009	23	23	27.1	1.5	Affective picture viewing task	Neg	Per	Covariation: State negative affect scores during aversive vs. neutral condition Correlation: Skin conductance level during aversive vs. neutral condition
90	Moriguchi et al.	2007	37	30	20.4	1.5	Pain empathy task	Neg	Exp	Painful picture stimuli
91	Najib et al.	2004	9	9	25.9	1.5	Autobiographical recall task	Neg	Exp	Ruminative vs. neutral thought
92	Nielen et al.	2009	23	23	22.5	1.5	Stimulus classification task; surprise recognition task	–	Exp	Interaction effect of valence and arousal
93	Noriuchi et al.	2008	13	13	31.1	1.5	Affective video viewing	–	Exp	Own vs. others
94	O'Doherty et al.	2000	5	NR	NR	3	Satiety reward task	Pos	Exp	Activation with odor
95	Ogino et al.	2007	10	0	26.3	1.5	Pain representation task	Neg	Exp	Pain–rest
96	Pessoa & Padmala	2005	9	6	23	1.5	Near-threshold fear detection task	Neg	Per	Significant choice probabilities
97	Phan et al.	2004	12	6	22.7	3	Emotional salience task	–	Exp	Emotional intensity rating Appraising emotional intensity (valence task) Appraising self-relatedness (association task) Association task > valence task
98	Phan et al.	2004	7	3	34.6	1.5	Affective processing task	Neg	Exp	Aversive > neutral
99	Phillips et al.	1998	6	0	37	1.5	Emotional processing task	Neg	Per	Fear facial expression Disgust vs. fear facial expression Disgust facial expression
100	Phillips et al.	2000	14	NR	31	1.5	Affective picture viewing task	Neg	Exp	Disgusting pictures
101	Phillips et al.	2004	8	0	31.9	1.5	Overt/covert emotional processing task	Neg	Per	Overt expressions of disgust
102	Prehn-Kristensen et al.	2009	28	14	22.1	3	Empathy task	Neg	Exp	Anxiety vs. sport
103	Regenbogen et al.	2010	22	0	25.9	3	Violent game scenario processing task	Neg	Exp	Violent vs. non-violent in real modality Real vs. virtual
104	Rolls et al.	2010	12	5	27	3	Affective decision making task	–	Exp	Pleasantness decide–rate Intensity decide–rate Negative correlation with absolute value of each subject's average difference in pleasantness of each pair of stimuli
105	Royet et al.	2003	28	0	25	1.5	Emotional odor judgment task	Pos, Neg	Exp	Pleasant 1 (P1)–rest (R) Unpleasant 1 (U1)–R P2–R U2–R P1U1P2U2–4R
106	Saarela et al.	2007	30	16	29.5	3	Pain empathy and intensity rating task	Neg	Exp	Provoked-chronic Pain intensity model
107	Sabatini et al.	2009	10	7	23.6	1.5	Overt/covert emotional processing task	Neg	Exp	Angry face associated with painful stimulus vs. angry face masked to neutral

(continued on next page)

Table 1 (*continued*)

Study #	Author	Year	*N*	F	Age	Tesla	Task	Sub-category		Contrasts
108	Sambataro et al.	2006	24	13	26.8	3	Emotion perception task	Neg	Per	Disgust vs. neutral Disgust vs. contempt Disgust
109	Sarinopoulos et al.	2006	43	19	20.12	3	Aversive stimuli task	Neg	Exp	Aversive vs. misleading for expectancy period
110	Sarinopoulos et al.	2010	36	16	20.4	3	Aversive stimuli expectancy task	Neg	Per	Certain aversive cue vs. uncertain cue Neutral pictures following certain neutral cue
111	Schafer et al.	2009	18	18	24.8	3	Affective picture viewing and rating task	Neg	Exp	Disgust > neutral Fear > neutral Correlation: Disgust propensity with activation disgust > neutral Correlation: Trait anxiety with activation fear > neutral Correlation: Anxiety sensitivity with fear > neutral
112	Schafer et al.	2005	40	20	23.93	1.5	Emotion processing task	Neg	Exp	Block design study: Disgust > neutral Disgust > fear Event-related design study: Disgust > neutral Fear > neutral
113	Scharpf et al.	2010	24	NR	25	1.5	Emotion processing task	–	Exp	Emotional > neutral pictures Emotional > neutral sounds Social > non-social pictures Social > non-social sounds Pictures: (emotional/social > emotional/non-social) > (neutral/social > neutral/non-Social) Sounds: (emotional/social > emotional/non-social) > (neutral/social > neutral/non-social)
114	Schienle et al.	2002	12	12	26.3	1.5	Emotion processing task	Neg	Per	Disgust > neutral Fear > neutral
115	Schienle et al.	2005	63	63	27.3	1.5	Mood induction task	Neg	Exp	Regression of activation on disgust sensitivity and trait anxiety
116	Schienle et al.	2008	24	24	22.7	1.5	Affective picture perception and imagery task	Pos, Neg	Exp	Disgust > happiness Imagery > perception Happiness Vividness disgust imagery Vividness happiness imagery Imagery: Disgust > happiness
117	Schroeder et al.	2004	20	10	32.5	1.5	Emotional perception task	Neg	Per	Disgust vs. neutral Disgust vs. surprise
118	Schulz et al.	2009	24	12	26.5	3	Emotional go/no-go task	–	Per	Manipulation of emotional face expression valence Interaction of context preceding response inhibition and emotional face expression
119	Seo et al.	2010	21	0	31.8	3	Affective picture viewing task	Pos	Exp	Erotic vs. happy face
120	Silani et al.	2008	15	2	33.7	1.5	Affective picture processing task	–	Exp	Regression analyses: Toronto Alexithymia Scale Bermond–Vorst Alexithymia Ques. Interpersonal Reactivity Index Internally vs. externally oriented task
121	Simon et al.	2006	17	9	23.1	1.5	Gender discrimination task	Neg	Per	Pain > anger
122	Smith et al.	2005	19	NR	21	1.5	Emotional source memory task	–	Exp	Neutral, negative, and positive source hits vs. correct rejections Emotional vs. neutral source hits
123	Somerville et al.	2010	47	25	18.9	3	Threat-monitoring task	Neg	Exp	Omnibus task > rest

124	Stark et al.	2007	66	22	24.7	1.5	Affective picture rating task	Neg	Exp	Disgust vs. baseline Disgust > fear Disgust > neutral Fear > neutral Disgust > fear
125	Strathearn et al.	2008	28	28	30.2	3	Facial emotion task	–	Exp	Own vs. unknown infant
126	Straube et al.	2004	10	6	25	1.5	Facial emotion task	Neg	Per	Photographs: Angry vs. neutral Intertask difference: Angry vs. neutral
127	Straube et al.	2010	40	20	22.55	1.5	Emotion rating task	Neg	Exp	Threat vs. neutral movie clips
128	Surguladze et al.	2010	9	4	39.7	1.5	Facial gender discrimination task	Neg	Per	Disgust vs. neutral
129	Suslow et al.	2009	51	23	28.5	3	Facial emotion task	Pos, Neg	Per	Masked happy face > neutral Masked sad face > neutral
130	Takahashi et al.	2008	16	8	21.5	1.5	Empathy task	Pos	Exp	Joy > neutral
131	Thielscher and Pessoa	2007	25	15	23	1.5	Facial emotion task	Neg	Per	Fearful vs. disgusted faces
132	Van Dillen et al.	2009	17	13	20	1.5	Affective picture processing task	Neg	Per	Negative pictures Negative > neutral between 5 and 8 s after picture onset Picture valence × task load interaction Low load > high load
133	vandenBos et al.	2009	18	9	19.7	3	Trust reciprocity task	Pos	Exp	Positive correlation with average reciprocity
134	vanderGaag et al.	2007	17	9	23.3	3	Facial emotion task	Neg	Per	Expression imitation vs. rest Emotional vs. neutral execution Execution specificity: Neutral faces Disgust faces Observation of expressions Discrimination of facial expressions Viewing vs. imitations Discrimination > observation Imitation > observation Imitation > discrimination Observation: Pattern > face Discrimination: Pattern > face Direct matching: Emotional vs. neutral Disgust vs. neutral
135	Viinikainen et al.	2010	17	9	23	3	Affective picture viewing task	Pos, Neg	Exp	Positive valence Negative valence U-shaped valence
136	Way et al.	2009	33	NR	21	3	Cyberball social exclusion task	Neg	Exp	Social exclusion vs. inclusion
137	Wicker et al.	2003	14	0	23.5	3	Emotional perception task	Pos, Neg	Per	Disgusting odorant − rest Pleasant odorant − rest Observation of disgust Overlap between observing and feeling disgust
138	Williams et al.	2007	13	8	24	1.5	Facial emotion task	Neg	Per	Disgust vs. neutral 'With arousal' disgust
139	Winston et al.	2002	14	6	23.3	2	Trustworthiness rating task	Pos, Neg	Exp	Untrustworthy vs. trustworthy Trustworthy vs. untrustworthy Explicit vs. implicit
140	Winston et al.	2007	26	13	25.5	1.5	Facial attractiveness judgment task	Pos	Exp	Attractiveness
141	Wright et al.	2004	8	4	23	3	Affective picture viewing task	Neg	Exp	Contamination > neutral Mutilation > neutral
142	Zeki and Romaya	2008	17	7	34.8	1.5	Face processing task	Neg	Exp	Hated faces > neutral faces
143	Zheng et al.	2010	22	14	21.7	3	Affective decision making task	Pos	Exp	Positively framed small group minus negatively framed small group context

List of functional magnetic resonance imaging (fMRI) studies reporting brain activation coordinates in the insula in response to affective stimuli. Abbreviations: *N*, sample size; NR, not reported; Pos = positive; Neg = negative; Per = perception; Exp = experience.

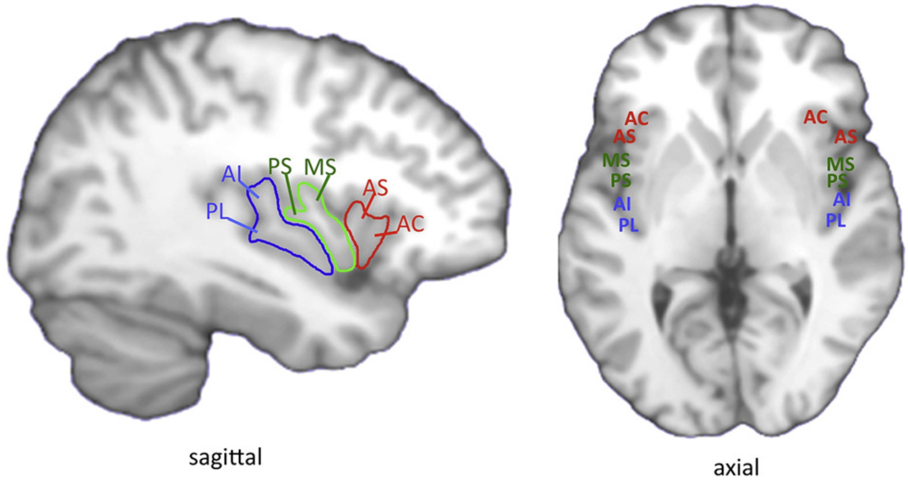

Fig. 1. Anatomy of the insular cortices presented in sagittal (right hemisphere) and axial views. The insula is composed of several gyri that vary based on individual anatomical variability. The anterior insula (red) is comprised of the accessory gyrus (AC) and the anterior short insular gyrus (AS). The mid-insula (green) is composed of the middle short insular gyrus (MS) and the posterior short insular gyrus (PS). The posterior insula (blue) is composed of the anterior long insular gyrus (AI) and the posterior long insular gyrus (PL).

locations were activated by positive stimuli. Activation in the right hemisphere was less extensive (Table 2; Fig. 2; see also Suppl. Fig. 2). The left posterior insula had the lowest activation compared to the other regions in response to positive stimuli. Based on the laterality indices, positive stimuli were left dominant in the anterior and mid-insula (Fig. 3).

Negative emotional stimuli

The ALE maps for negative-emotional stimuli were created from 361 foci from 88 experiments (37 were perceived emotions and 51 were experienced emotions). Data from one study was removed to maintain consistency across studies. Bilateral anterior insula had the

Table 2
Meta-analyses results for all emotional stimuli and sub-categories.

	Side	Insula region	Cluster #	x	y	z	Volume (mm^3)	ALE value	P value
All emotional stimuli	Left	Anterior	1	−34	18	4	10,736	0.21	<0.000001
	Left	Mid		−38	0	−2		0.14	<0.000001
	Left	Mid		−40	−4	8		0.11	<0.000001
	Right	Anterior	2	36	18	2	9120	0.20	<0.000001
	Right	Mid		38	0	4		0.12	<0.000001
Positive	Left	Mid	1	−42	−2	4	2368	0.06	<0.000001
	Left	Anterior		−34	16	0		0.05	<0.000001
	Right	Mid	2	40	−2	4	672	0.05	<0.000001
	Right	Anterior	3	34	12	10	176	0.04	<0.000001
Negative	Left	Anterior	1	−36	18	4	12,776	0.14	<0.000001
	Left	Posterior		−36	−2	−4		0.10	<0.000001
	Left	Mid		−38	−4	10		0.07	<0.000001
	Right	Anterior	2	36	18	2	11,192	0.14	<0.000001
Perception	Left	Anterior	1	−38	14	6	5944	0.06	<0.000001
	Left	Posterior		−34	−4	−4		0.05	<0.000001
	Right	Anterior	2	38	16	0	4560	0.07	<0.000001
	Right	Posterior		32	−2	−8		0.03	<0.000001
	Right	Mid/posterior	3	36	−6	8	792	0.04	<0.000001
Experience	Left	Anterior	1	−34	18	4	6776	0.18	<0.000001
	Left	Mid		−40	4	−2		0.12	<0.000001
	Left	Mid		−40	−4	8		0.09	<0.000001
	Right	Anterior	2	34	20	2	5152	0.14	<0.000001
	Right	Mid		38	2	4		0.10	<0.000001
Male	Left	Anterior/mid	1	−38	4	−2	1232	0.05	<0.000001
	Left	Mid		−38	−2	8		0.04	<0.000001
	Right	Mid	2	36	6	−4	160	0.04	<0.000001
	Right	Mid/posterior	3	38	−4	6	128	0.04	<0.000001
Female	Left	Mid/posterior	1	−40	0	−2	2472	0.04	<0.000001
	Left	Anterior		−34	20	6		0.03	<0.000001
	Right	Anterior	2	38	12	−4	544	0.02	<0.000001

Meta-analyses of activation foci obtained from the insula in response to all emotional stimuli and subcategories. The activation likelihood estimate (ALE) values range from 0 to a possible maximum of 1. Higher values indicate a greater likelihood of activation in response to emotional stimuli. Distinct clusters of voxels with significant likelihood values are listed in order (cluster #) according to their size (largest to smallest). In some instances two or three significant ALE values were located in the same distinct cluster. Coordinates are given in Talairach space (Talairach and Tournoux, 1988). Stereotaxic coordinates are in millimeters and correspond to medial–lateral (x), anterior–posterior (y), and superior–inferior (z) directions. The directions are relative to midline, anterior commissure, and commissural line, respectively (positive values = right-sided [medial–lateral or x], anterior [y] and superior [z]). Abbreviations: mm = millimeters; ALE = activation likelihood estimate.

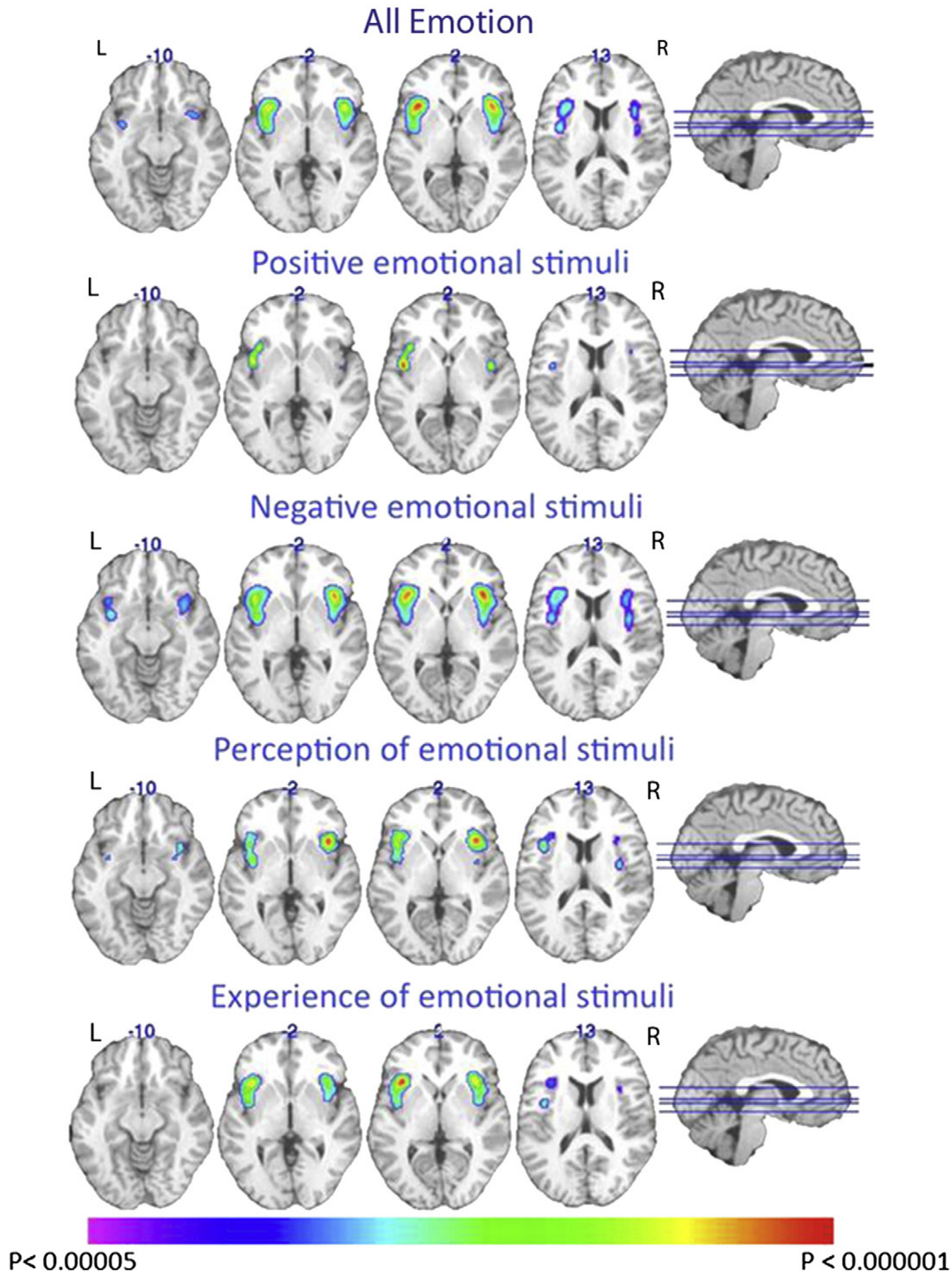

Fig. 2. Activation likelihood estimate (ALE) maps for all emotional stimuli, positive and negative emotional stimuli, and perceiving and experiencing emotions. Coordinates are in Talairach space (Talairach and Tournoux, 1988). Left = left hemisphere. Multiple comparisons were controlled for using the FDR (q = 0.001).

greatest activation in response to negative stimuli; the cluster of ALE values extended to the mid and posterior insula, bilaterally (Table 2; Fig. 2; see also Suppl. Fig. 3). Activation in response to negative stimuli was located in the anterior insula and was ventral to that seen for positive stimuli. Although there was a trend towards left-sided dominance, activation was bilateral for all regions of the insula in response to negative stimuli (Fig. 3).

Compared to positive-emotional stimuli, a larger number of studies contained negative-emotional stimuli, and much of the activation associated with negative stimuli overlapped with that of the positive stimuli in the anterior and mid regions of the insula. This difference may have unduly influenced the effects related to valence. Therefore, two subsequent meta-analyses were performed with data from 40 negative-emotion studies (175 foci; 5 used perceptual and 26 used experiential stimuli, 9 used both types of stimuli and provide separate contrasts) and 40 positive-emotion studies (101 foci; 4 used perceptual and 27 used experiential stimuli, 9 used both stimulus types; see Suppl. Table 1 for details). Results were comparable to those seen in the previous meta-analyses with the full datasets included, providing additional confidence for the methodology and the findings. Positive stimuli were

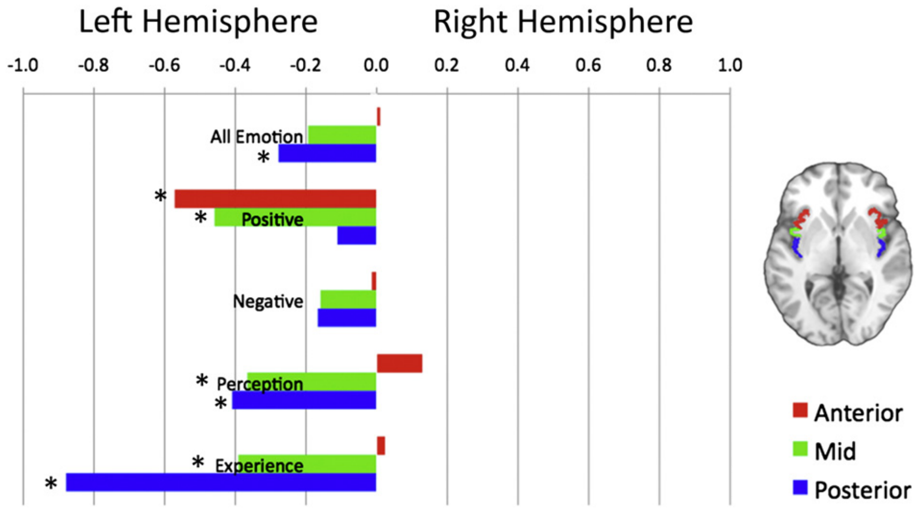

Fig. 3. Laterality indices for the anterior, mid, and posterior insula. * = laterality values that exceeded the criteria for dominance (−0.2/0.2).

associated with activation in the bilateral mid and anterior insula, with activation in the left hemisphere extending into the territory of the posterior insula. Negative stimuli activated bilateral anterior and posterior insula and also the right mid insula (Suppl. Fig. 4; Suppl. Table 2).

Laterality indices were similar to those seen for the positive-emotional stimuli in the original analyses (above), as they activated the left anterior (LI = −1.0) and mid insula (LI = −0.46), but showed no hemispheric dominance in the posterior insula (LI = −0.11).

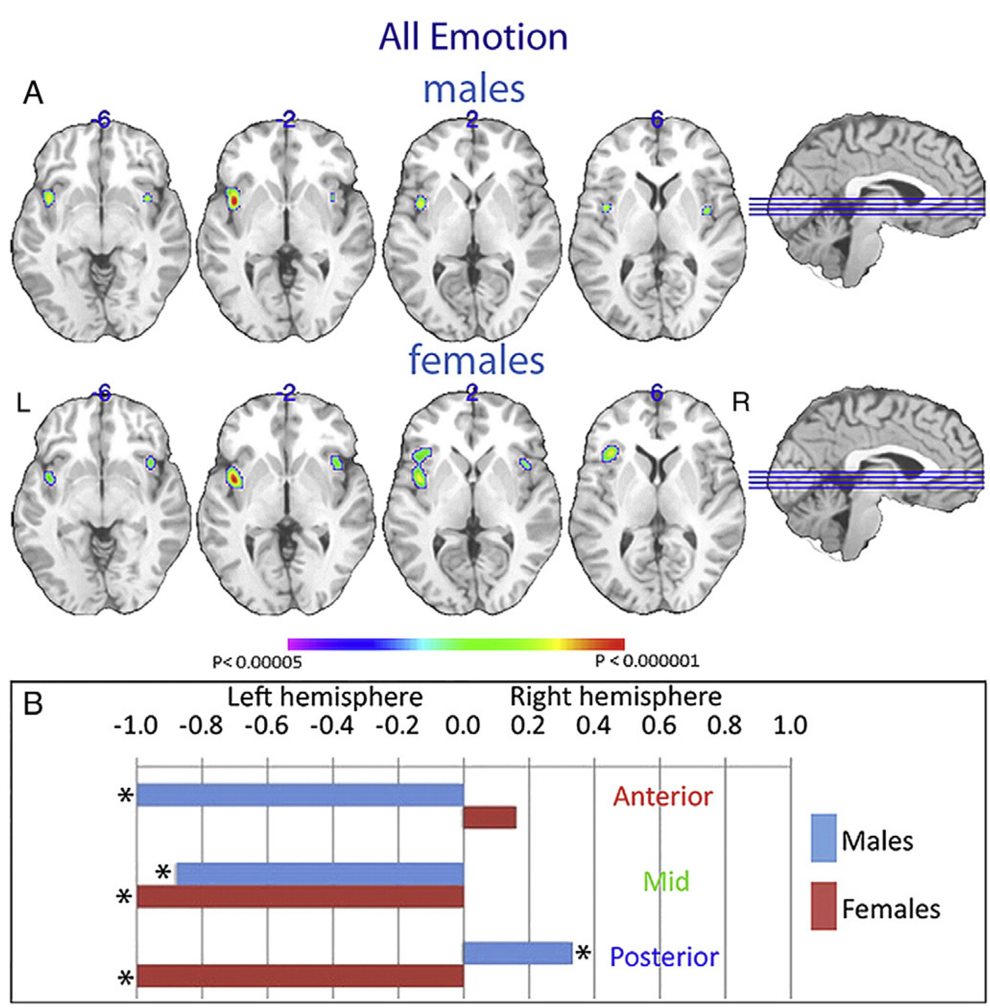

Fig. 4. A: Activation likelihood estimate (ALE) maps for activation in response to emotional stimuli viewed by males and females. Coordinates are in Talairach space (Talairach and Tournoux, 1988). Left = left hemisphere. Multiple comparisons were controlled for using the FDR (q = 0.001). B: separate laterality indices for activation in the anterior, mid and posterior insula in males (blue) and females (red). * = laterality values that exceeded the criteria for dominance (−0.2/0.2).

Negative-emotional stimuli did show hemispheric dominance for activating the left mid (LI = −0.84) and posterior insula (LI = −1.0), but not the anterior insula (LI = 0.11).

Perception of emotion in others

The database contained 171 foci from 49 experiments (35 used negative stimuli, 5 used positive stimuli, 3 used both types of affective stimuli and 6 were unspecified) that examined activation in response to the perception of emotion in others. These stimuli activated bilateral anterior insula, with the greatest activation located in the right anterior insula, but a large cluster of activation was located in the dorsal portion left insula (Table 2; Fig. 2; Suppl. Fig. 5). A separate cluster in the right mid-insula was also apparent for these stimuli. Less activation was observed in the left compared to the right posterior insula. Laterality analyses confirmed greater left-hemisphere dominance for the mid and posterior insula in response to the perception of emotions.

Experience of emotion

The experience of emotion was associated with 399 foci from a total of 94 studies (31 used positive stimuli, 47 negative stimuli, and 16 unspecified emotional stimuli). Bilateral anterior insula had the greatest activation in response to these types of stimuli with the peak occurring in the left hemisphere, more ventral than that seen for the perception of emotional stimuli (Table 2; Fig. 2; Suppl. Fig. 6). The cluster of activation extended to the mid and posterior insula. No overlap in activation was observed with that of the perception of emotional stimuli in the right mid insula. The laterality indices revealed greater left hemisphere dominance for the mid and posterior insula, indicating that the right mid and posterior insula were activated less than their equivalent, contralateral regions in response to the experience of emotions.

Sex-differences in emotional processing

In two final meta-analyses, the influence of the sex of the participants on activation in the insula in response to all emotional stimuli was explored. Within the main meta-analysis for all emotional stimuli 15 studies tested only male participants and 22 tested only females. Of these studies, 6 used positive and 11 used negative stimuli (one study included both stimulus types in separate contrasts). 5 studies used emotional stimuli that were perceived by the participants and 17 used stimuli aimed at evoking an emotional response.

Seventeen of the 22 studies that tested only female participants were included in the analysis. Four studies were excluded as they included contrasts for perception or experience of emotion, but did not include aspects of stimulus valence. To maintain better consistency with the meta-analysis of the male studies, one study with females was excluded due to its large number of participants. Of the 15 studies that included only male participants, 9 used positive and 6 used negative stimuli (within these studies three used both stimulus types). Five studies used perceptual–emotional stimuli, while 10 utilized experiential–emotional stimuli.

In females, activation in response to emotional stimuli was localized to bilateral anterior insula, which extended to the mid and posterior insula on the left side (Table 2; Fig. 4A; Suppl. Fig. 7). In comparison, males activated left anterior/mid insula and the right posterior insula. Males also weakly activated a small portion of the right mid insula. Activation overlapped for both male and female participants in the left mid and anterior insula and the right ventral anterior insula. Laterality indices revealed that males activated the left anterior insula more than the right side compared to females who showed bilateral activation in this region (Fig. 4B; Suppl. Fig. 8). For both males and females the mid insula was activated on the left side more than on the right. The posterior insula was left dominant for females and right dominant for males.

Discussion

Through meta-analyses of existing functional neuroimaging data, the spatial location and extent of activation in the insula associated with affective processing were assessed. Four key results were found:

(a) Activation in response to all emotional stimuli occurred bilaterally in the anterior and mid-insula extending to the posterior insula. Laterality indices revealed that within the posterior insula the left side was activated more than the right.
(b) Positive emotional stimuli showed left-hemisphere dominance in the anterior and mid-insula, whereas the posterior insula was activated bilaterally. Negative stimuli activated bilateral anterior, mid and posterior insula. Strong laterality differences elicited by positive and negative stimuli are not supported by these results.
(c) Perceiving emotions in others activated bilateral anterior and mid-insula, with the greatest activation occurring in the right anterior insula. The experience of emotion showed the greatest activation in the left anterior insula. Laterality analyses revealed that both types of stimuli activated the left mid and posterior insula.
(d) Male and female participants activated the left mid and right ventral anterior insula in response to all emotional stimuli. Males processed emotional stimuli predominantly in the left anterior/mid-insula and the right posterior insula, whereas females activated bilateral anterior insula and left mid/posterior insula.

This topographical map of emotional processing in the insula may reflect the integration of afferent and efferent projections to and from this region that is associated with homeostatic regulation and higher-order cognitive processing. Projections from frontal and limbic cortices terminate in the anterior portion of the insula, whereas viscerosensory input is represented in more posterior regions, which is then forwarded anteriorly (Craig, 2009). The re-representation of viscerosensory input in the insula, combined with connections to and from the frontal and limbic cortices, may contribute to the neural bases of experiencing and perceiving both positive and negative emotions in the insular cortices.

The posterior to anterior representation of emotional processing could indicate that an initial affective response is triggered by viscerosensory input to the posterior/mid-insula (primarily to the left hemisphere), whereas anterior portions of the insula mediate more complex recognition and self-awareness processes. This organization is likely facilitated by the connections of the insula with the amygdalae, that enable the projection of information from all sensory domains (somatosensation, audition, gustation, olfaction, vision) to the limbic system (Mesulam and Mufson, 1982b). With an emphasis on laterality indices, we elaborate on these hypotheses by discussing the influence of stimulus valence, phenomenal state and sex on emotional processing in the insula.

Emotional processing

The entire insula was activated by all emotional stimuli, but with the greatest activation in bilateral anterior regions. The extent of activation included the territory of the mid and posterior insula. Laterality indices showed that within the posterior insula, the left hemisphere was activated more than the right. The significance of greater left-sided activity within the mid and posterior insula remains uncertain. However, this may be a result of greater viscerosensory input to the left hemisphere via afferent projections from the ventromedial nucleus that mediates vagal nerve input (Craig and Zhang, 2006).

Our results suggest a posterior-to-anterior processing of emotion that is initiated by viscerosensory input to predominantly the left posterior insula that is then processed by the mid and anterior insula. Findings are consistent with the James–Lange (James, 1884; Lange, 1885) theory of emotion whereby the initial reaction to a change in one's physiological state (i.e. increase in heart rate) is relayed to the thalamus and insula, and through re-representations of viscerosensory input, this culminates in the experience of an emotional state. Our results are also in agreement with the work of Craig (2011) whereby awareness of feeling states is initiated by sensory inputs to the posterior insula and through increasing homeostatic processing in the mid insula, the information is relayed to more anterior regions that are the center of saliency processing. In line with our findings is the work of Menon and Uddin (2010) who proposed that the insula, through expansive connections with brain regions implicated in attention, working memory and movement, are essential for processing salient environmental stimuli and are involved in bottom-up (sensory input) and more top-down processes to centrally manage responses to salient events.

An earlier meta-analysis of functional neuroimaging data tested for right-hemisphere dominance of emotional processing by comparing data obtained from either entire hemisphere (Wager et al., 2003); little evidence for hemispheric asymmetry of emotional processing was detected. The authors suggested that specific regions of the brain were more likely to show lateralization effects. The results of the current work demonstrate that the insula, an essential brain region involved in emotional processing, showed mixed hemispheric dominance when segregated into regions. The lack of lateralization observed in the Wager et al. (2003) study may be due to their broad categorization of emotion as an affective category. Our categories consisted of all emotional stimuli, positive, negative, perceived and experienced emotion. One of our goals was to distinguish these sub-divisions of emotional processing and identify their representation in the insular cortices.

The regions of the anterior insula with the greatest activation in response to emotional stimuli were in the territory of the dorsal anterior short insular gyrus. Our findings are in agreement with a meta-analysis of 13 different functions of the insula (Kurth et al., 2010) that also showed social–emotional functions occupying the anterior insular cortices. The anterior regions of the insula have agranular and dysgranular subfields and have reciprocal connections with frontal cognitive, motor association, and limbic cortices (lateral and ventromedial prefrontal cortex, supplementary motor area, cingulate cortex, entorhinal cortex and the periamygdaloid complex) (Aggleton et al., 1980; Augustine, 1996; Cauda et al., 2011; Cerliani et al., 2012; Cloutman et al., 2012; Hoistad and Barbas, 2008; Mesulam and Mufson, 1982b; Preuss and Goldman-Rakic, 1989; Van De Werd and Uylings, 2008). The emotional tasks included in the meta-analyses may have also recruited these higher-order cognitive brain regions. Although, insular connectivity with these brain regions was not tested, future studies could combine multimodal-imaging and analysis techniques to verify, for instance, whether the anterior insula and prefrontal areas bring about conscious awareness of affective states and test connectivity in relation to hemispheric asymmetry.

Positive and negative emotional stimuli

Positive stimuli activated the left anterior and mid-insula more than their counterparts on the right side, which was confirmed by laterality analyses. Negative emotional stimuli activated bilateral anterior insula. The mid and posterior insula were also activated by these stimuli. Much of the activation for both stimulus types overlapped, indicating that similar neural processes subserve the experience and perception of positive and negative stimuli. However, additional information gained from the laterality-indices analyses based on a subset of the negative-emotional studies, indicated left-sided activation in the mid and posterior insula. Overall, these findings do not provide support for mutually exclusive valence hypothesis (positive/negative stimuli processed in left/right hemispheres, respectively). These results may reflect our experimental design in which we included all positive and negative emotions. It may be that stronger emotions may preferentially activate one hemisphere; for example, maternal love may be exclusively associated with left insular activation. Future work in this area could explore laterality effects with modulation of emotional salience.

The physiological basis of lateralization of affective processing has been suggested to arise from differences in autonomic input to the insular cortices. A specialized spinothalamic cortical pathway has been suggested to transmit the physiological state of the body to the insula (Craig, 2002). Our data suggest that in terms of valence, positive and negative emotions engage bilateral insula. However, positive stimuli activated the left anterior and mid insula more than the right. This discrepancy may reflect that during some approach/pleasant or withdrawal/unpleasant behaviors, there is coactivation of both branches of the autonomic nervous system within the framework of an opponent control system. Valence processing is complex and is mediated by a number of brain areas in addition to the insula, including the anterior cingulate, the prefrontal and the posterior parietal cortices and the amygdalae (Britton et al., 2006; Mitterschiffthaler et al., 2007; Schulz et al., 2009; Straube et al., 2011; Vrticka et al., 2011). As well as emotion being mediated by physiological input, it also involves appraisal processes and differential emotional-related activity that would be influenced by cognition–emotion interactions.

Consistent with our findings, lesion studies also report results contrary to the left/right, positive/negative valence organization of the insula (Berthier et al., 1988; Calder et al., 2000; Gilmore et al., 1992; Greenspan et al., 1999; Naqvi et al., 2007). For example, Calder et al. (2000) found that a lesion to the left mid and posterior insula resulted in impaired disgust recognition more than other facial and vocal expressions of emotion (fear, happiness, surprise, anger, contempt, sadness). Other investigators have explored affective processing in patients with unilateral lesions to the insula and did not report asymmetries, or had too few patients to make statistical comparisons (Berthier et al., 1988; Greenspan et al., 1999; Naqvi et al., 2007).

Perception and experience of emotional stimuli

Activation in response to the perception and experience of emotions was found largely to overlap in the insula, except for the right mid insula that was uniquely associated with perception. Additionally, both types of protocols showed preferential activation of the left mid and posterior insular cortices, a finding that suggests that similar mechanisms within the insula mediate both types of processing. Based on the laterality indices within the posterior insula, the left hemisphere showed the greatest activation in response to the experience of emotion. This finding may be due to a greater parasympathetic response produced during the actual experience of emotions compared to more passive perception of an emotional expression (Levenson, 2003). In turn, this may result in a greater parasympathetic-mediated orienting response leading to changes in heart-rate variability. The greater left-sided activation in response to experienced emotions may reflect the proposed asymmetry of parasympathetic inputs to the left mid insula (Craig, 2005).

Greater activation in response to experienced-emotional, compared to that seen for perceived-emotional events, may also reflect the insula's role as a salience detector (Menon and Uddin, 2010; Seeley et al., 2007). As the insula is a central hub for physiological, sensory, motor, cognitive and affective processes, it serves as an interface among many different cortical and subcortical regions, making the insula essential for attention and working memory functions

(Augustine, 1996). Therefore, the activation in the insula, particularly in more anterior regions, may be associated with the highly salient and attention-orienting nature of emotional experiences.

Sex-differences in insular activation in response to emotional stimuli

Females and males showed both common and differential activation in response to all emotional stimuli within the insular cortices. Males showed preferential activity in the left anterior insula, whereas the females exhibited bilateral activity in this region. Females and males activated the left mid insula more than the right. The activation in the posterior insula occurred in the left hemisphere in females and in the right hemisphere in males.

In a recent meta-analysis exploring sex-differences in brain activation of emotional processing, females activated the left amygdala more than males in response to negative emotional stimuli (Stevens and Hamann, 2012). Both men and women activated the right anterior insula in response to negative emotions and the left anterior insula in response to positive emotions. Additionally, females showed greater activation than males in the left hippocampus irrespective of stimulus valence. As these regions have a strong role in affective processing and memory, the authors suggested a greater capacity for women to remember emotional events. In the current study, greater left-sided activity in the mid/posterior insula was seen in females. Similarities in function related to sex differences and emotional valence in the insula certainly warrant future investigations given the dense connections these regions have with medial temporal lobe structures (Cerliani et al., 2012; Mesulam and Mufson, 1982b).

Differential activation within the insula for females and males may also represent neural processing strategies for understanding and evaluating emotions (Baron-Cohen and Wheelwright, 2004; Eisenberg and Lennon, 1983). For example, in addition to identifying the emotion, compared to males, females may engage more in cognitive processing that mediates the appraisal of emotional stimuli. The supplementary cognitive evaluation of emotion may be aided by the connection of the anterior insular cortex with the left ventrolateral prefrontal cortex, a region implicated in emotional regulation (Herwig et al., 2010). Our data give additional support to the hypothesis that differential processing strategies of females and males implicate higher-order cognitive mechanisms.

Other factors influencing lateralization of activity in response to emotional stimuli

The purpose of these meta-analyses was to assess activity in the insula in response to emotional stimuli with a particular focus on stimulus valence, experiencing vs. perceiving emotions and sex differences. The literature was searched for fMRI articles reporting activation foci in the insula in response to emotional stimuli. This search and subsequent meta-analyses were designed to review the role of the insula in affective processing and did not consider other modulating factors such as expectancy effects (Stafford and Brandaro, 2010), personality (Iaria et al., 2008) or handedness (McFarland and Kennison, 1989). The limited number of studies that have considered these factors did not permit their subcategorization and analysis with meta-analytic techniques. The goal of the current study was to perform a detailed analysis of the insula in response to a comparatively broader emotional experience. As such, future work exploring differences in relation to the stimuli and the characteristics of the observers is warranted as more data become available.

Summary and conclusions

By performing meta-analyses of activation in the insula in response to emotional stimuli, we showed that this complex brain structure has a strong role in global-emotional processing and awareness. All emotional stimuli, and the subcategories, activated the anterior and mid-insula more than the posterior insula and exhibited hemispheric asymmetries as a function of the three insular sections (anterior, mid and posterior). Our results suggest a posterior-to-anterior processing scheme whereby sensory information is represented in the posterior insula and more complex processing of the emotional state is achieved in anterior regions. The current study contributes to a better understanding of the neural correlates of emotional processes and in turn could help identify specific deficits seen in neurodevelopmental disorders or as a result of neurovascular insults.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.04.014.

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