Behavioural Brain Research 288 (2015) 11–19

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Hemispheric specialization in affective responses, cerebral dominance for language, and handedness
Lateralization of emotion, language, and dexterity

Elsa Yolanda Costanzo[a,b,d], Mirta Villarreal[a,c,g], Lucas Javier Drucaroff[a,b,c], Manuel Ortiz-Villafañe[a,b], Mariana Nair Castro[a,b,c,d], Micaela Goldschmidt[a,b], Agustina Edith Wainsztein[a,b], María Soledad Ladrón-de-Guevara[a,b,c], Carlos Romero[a], Luis Ignacio Brusco[c,e], Joan A. Camprodon[h], Charles Nemeroff[f], Salvador Martín Guinjoan[a,b,c,d,*]

[a] FLENI Psychiatry and Neuroimaging, Buenos Aires, Argentina
[b] Department of Mental Health (FLENI Teaching Unit), University of Buenos Aires School of Medicine, Buenos Aires, Argentina
[c] Argentine National Council of Scientific and Technological Research (CONICET), Argentina
[d] Department of Neurophysiology, University of Buenos Aires School of Psychology, Buenos Aires, Argentina
[e] Center for Neuropsychiatry and Behavioral Neurology (CENECON), Hospital de Clínicas "José de San Martín", Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina
[f] Department of Psychiatry and Behavioral Sciences, Leonard M. Miller School of Medicine, University of Miami, Coral Gables, FL, United States
[g] Department of Physics, University of Buenos Aires School of Science, Buenos Aires, Argentina
[h] Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

HIGHLIGHTS

- Hemispheric specialization in affective response seems to be related to language processing and motor preference.
- Lateralization in allocortical limbic areas shows specificity for emotion valence.
- Left amygdala activation is preeminent depending on emotional salience.
- Lateralization in mood regulation is defined better in right-handed than in non right-handed persons.

ARTICLE INFO

Article history:
Received 26 February 2015
Received in revised form 31 March 2015
Accepted 4 April 2015
Available online 13 April 2015

Keywords:
Emotion
Lateralization
fMRI
Amygdala
Subgenual cingulate
Anterior insula

ABSTRACT

Hemispheric specialization in affective responses has received little attention in the literature. This is a fundamental variable to understand circuit dynamics of networks subserving emotion. In this study we put to test a modified "valence" hypothesis of emotion processing, considering that sadness and happiness are processed by each hemisphere in relation to dominance for language and handedness. Mood induction and language activation during functional magnetic resonance imaging (fMRI) were used in 20 right-handed and 20 nonright-handed subjects, focusing on interconnected regions known to play critical roles in affective responses: subgenual cingulate cortex, amygdala, and anterior insular cortex. We observed a consistent relationship between lateralization of affective processing, motor dexterity, and language in individuals with clear right-handedness. Sadness induces a greater activation of right-hemisphere cortical structures in right-handed, left-dominant individuals, which is not evident in nonright-handed subjects who show no consistent hemispheric dominance for language. In anterior insula, right-handed individuals displayed reciprocal activation of either hemisphere depending upon mood valence, whereas amygdala activation was predominantly left-sided regardless of mood valence. Nonright-handed individuals exhibited less consistent brain lateralization of affective processing regardless of language and motor dexterity lateralization. In contrast with traditional views on emotion processing lateralization, hemispheric specialization in affective responses is not a unitary process but is specific to the brain structure being activated.

* Corresponding author at: Department of Mental Health (FLENI), University of Buenos Aires School of Medicine, Montañeses 23258th floor, C1428AQK Buenos Aires, Argentina. Tel.: +54 1157773200x2824; fax: +54 1157773209.
E-mail addresses: sguinjoan@fleni.org.ar, sguinjoan@hotmail.com (S.M. Guinjoan).

http://dx.doi.org/10.1016/j.bbr.2015.04.006
0166-4328/

1. Introduction

Lateralization of brain functions is ubiquitous in vertebrates [1,2] contradicting the long-held belief that only *Homo sapiens* display significant hemispheric asymmetry [3]. This view was probably based on the fact that structural and functional asymmetry in the brain was initially defined for language-related areas [3–5]. With the discovery that brain functions other than language display lateralization in different species, e.g. singing [6] and visual specialization [7] in different avian species, a series of theories eventually emerged in relation to hemispheric specialization of different functions, including emotion processing. Two main theories evolved in relation to lateralization of emotion processing in the human brain. The "right hemisphere" hypothesis postulates that the right hemisphere is the main responsible for the processing of emotion, regardless of its positive or negative nature [8]. The "valence" theory [9] proposes that lateralization depends on the type of emotion; in this view, happiness and other affiliative emotions are processed predominantly by the left hemisphere and sadness is processed by the right hemisphere. In the present study we put to test a modified "valence" hypothesis of emotion processing lateralization, considering dominance for language and handedness rather than the actual side of the brain, in subjects with evidence for varying degrees of brain lateralization (i.e., right- and nonright-handed); such hypothesis considers motor preference, language, and emotion processing part of a general hemispheric specialization phenomenon.

To test this hypothesis, we used paradigms of affective response and language activation during functional magnetic resonance imaging (fMRI) in right- and nonright-handed persons. Although we set out to explore whole-brain effects of induced sadness and happiness, we also focused on interconnected regions previously shown to play critical roles in emotion regulation, namely, subgenual cingulate cortex, amygdala, and anterior insular cortex. The circuit connecting subgenual cingulum and amygdala is involved in emotional processing and social abilities in healthy conditions [10–12] and in major depression [13] leading to the hypothesis that variation in amygdala-subgenual cingulate circuitry is the origin of emotional and social deficits characteristic of it [13,14]. The amygdala is also pivotal in circuits modulating anxiety and fear [15,16]. In turn, insular cortex has been posited to be critical in the regulation of visceral activity, which is linked to emotional behavior, and in psychosis [17]. Thus, we used those areas as hypothesis-driven regions of interest (ROIs) in the present study.

2. Materials and methods

2.1. Participants

All participants were assessed at the Cognitive Neurology Section and the Psychiatry Department at FLENI Hospital, Buenos Aires. A total of 20 right-handed subjects (11 females, age 25.9 ± 5.6 years) and 20 non-right handed subjects (12 females, age 29.2 ± 9.7 years) participated in this study. Subjects were volunteers who did not receive financial compensation. Participants had no lifetime DSM-IV-TR diagnoses, and no first-degree relatives with schizophrenia, bipolar disorder, or depression as per their report. Participants were free from medications and chronic medical disorders including diabetes, major neurological and cardiovascular disorders per their self-report. They provided written informed consent as approved by the local bioethics committee, and in accordance with the ethical standards set by the 1964 Declaration of Helsinki.

2.2. Affective response measures

Subjects were also assessed for depression symptom severity with the Hamilton Depression Rating Scale [18] and for anxiety symptom severity with the Hamilton Anxiety Rating Scale [19] prior to fMRI scanning.

2.3. fMRI stimuli

FACES: subjects participated in a standardized affective response procedure, described in greater detail elsewhere [20]. fMRI data were acquired for two different affective conditions (happiness and sadness). Briefly, preceding the experimental conditions, subjects were shown a single slide with instruction on the task. Participants were told in Spanish: "During this task, I would like you to try to become happy [or sad] helping yourself with the faces showing such emotion". Subjects viewed the stimuli at their own pace and moved on to the next face with the aid of a response device by pressing two buttons simultaneously with the 2nd and 3rd fingers of the right hand. The mean time the subject spent looking at each picture in each condition was registered as "time to induce emotion".

In a debriefing session immediately after scanning, they were asked to complete self-assessment manikins (SAM) [21] on both arousal and valence associated with sad and happy faces. The SAM is a non-verbal pictorial assessment technique which can directly measure valence and arousal associated with a person's affective reaction to a wide variety of stimuli. It is later scored in a 9 point scale. Higher values for valence (picture of a smiling manikin) indicate happy affective reactions for a specific set of stimulus, whereas lower scores indicate sad reactions to them. Paired samples t test was used to compare valence of emotion induction for sad and happy stimulus in each group.

2.3.1. Block design of the affective response paradigm

Experimental design consisted of 2 sessions, one for sad responses and one for happy responses. Each session consisted of 3 blocks of task condition (sad [happy] faces) alternated with 3 blocks of baseline (fixation cross) of 60 s each block.

LANGUAGE: we used a category fluency paradigm to ascertain activation of language areas in individual participants. Subjects were shown a certain category in the screen (e.g., countries, colors, body parts) and asked to mention as many items in the category as possible. The paradigm consisted of 7 blocks of 30 s category fluency task alternating with 7 blocks of 20 s rest, for a total duration of approximately 6 min.

2.4. fMRI data acquisition

MRI data were acquired on a 3 T GE HDx scanner with an 8 channel head coil. Change in blood-oxygenation–level-dependent (BOLD) T2* signal was measured using a gradient echo-planar imaging (EPI) sequence. Thirty contiguous slices were obtained in the AC-PC plane (TR: 2 s, TE: 30 ms, flip angle: 90°, FOV: 24 cm, 64 × 64 pixels per inch matrix, voxel size = 3.75 × 3.75 × 4). A structural MRI was acquired with the T1-weighted 3D fast SPGR-IR sequence (120 slices, 1.2-mm thick slices, TR = 6.604 ms, TE = 2.796 ms, flip angle 15°, FOV 24 cm, 256 × 256 matrix). FACES and LANGUAGE sessions each consisted of 175 volumes.

2.5. Statistical analysis

2.5.1. Analysis of demographic and behavioral data

Continuous variables in Table 1 were compared by means of independent samples t-test. For comparison of discrete variables, the Chi Square test was used. In all cases, tests applied were two tailed and significance was assumed at $\alpha < 0.05$. All statistical analysis was performed with the SPSS version 13.0 software (SPSS Inc.).

Table 1
Demographic characteristics.

	Right- handed ($n = 20$)	Nonright-handed ($n = 18$)	P
Edinburgh Handedness Scale	14.7 ± 4.0	40.1 ± 5.9	0.001
Women, n (%)	11 (55)	12 (66.7)	0.463
Age (years)	25.9 ± 5.5	29.2 ± 9.7	0.212
Education (years)	17.3 ± 3.0	15.8 ± 3.5	0.159
Smoker, n (%)	4 (20)	3 (16.7)	0.791
EQ5D	83.5 ± 5.8	78.1 ± 10.0	0.063
HAM-D	2.0 ± 2.3	4.1 ± 4.2	0.054
HAM-A	2.8 (3.3)	5.0 (5.9)	0.182

Shown are mean ± SD or number (%) of each variable, p value for independent samples t test (numeric variables) or chi-square test (categoric variables). HAM-D: Hamilton Depression Scale; HAM-A: Hamilton Anxiety Scale. EQ5D: European Quality of Life Scale.

2.6. fMRI analysis

2.6.1. Image processing

Image processing was carried out using SPM 5 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks Inc., Sherborn, MA, USA). Slice-timing correction was applied to each volume. The imaging time series was realigned to the first volume and spatially normalized to the stereotactic space of Talairach and Tournoux (1988) using Montreal Neurological Institute reference brain [22]. The normalized volumes of $2 \times 2 \times 2\,mm^3$ were spatially smoothed by an isotropic Gaussian kernel of 8 mm at full width half-maximum [23].

2.6.2. Image statistical analysis

Individual analysis was computed using the general linear model including the experimental conditions (happiness and sadness induction) and the baseline condition. The design matrix also included correction for head movements as regressors of no interest. The effects were modeled using a canonical hemodynamic response function convolved with a boxcar to create regressors of interest. Linear contrasts: HAPPINESS > REST and SADNESS > REST were evaluated for each subject. The same analysis was performed for the language task evaluating the linear contrast: LANGUAGE > REST.

The individual contrast images of affective induction task were subjected to a random effect analysis to see the effect of each condition (happiness and sadness) for both groups (right and nonright-handed). For this operation we used a statistical threshold $p < 0.05$ FWE corrected.

2.6.3. ROI selection

Based on previous works [24,25] we selected three pairs of areas left/right amygdala, left/right subgenual cingulate, and left/right anterior insula. The ROIs of amygdala and insula were defined using the Automated Anatomical Labeling (AAL) normalized atlas [26] data base. For the subgenual cingulate's ROIs (BA25) we built spheres of 7 mm of radius centered at (−7, 30, −4) and (7, 30, −4) using the MarsBar toolbox.

2.7. Laterality index

2.7.1. Language laterality index

A hemispherical language laterality index (LLI) was calculated for each subject, following hemispherical language lateralization fMRI criteria [27–29]. The number of suprathreshold active voxels in a specific region were weighted with the normalized mean intensity. The number of activated voxels above threshold $p = 0.001$ and their normalized mean intensity in each hemisphere was calculated. Laterality index was calculated by the formula $(VR \times IR - VL \times IL)/(VR \times IR + VL \times IL)$, where VL and VR stand for the number of voxels activated above the selected threshold in the left and right hemisphere, respectively, and IR and IL stand for the normalized mean intensity of the voxels above threshold in the left and right hemisphere, respectively. A positive value of the LLI refers to right hemispheric dominance and a negative value refers to left hemispheric dominance. LLI = 1 indicated exclusively right and LLI = −1 exclusively left hemispheric activation. One sample t test against the null hypothesis of no lateralization (LLI = 0) was used in order to evaluate language lateralization in each group.

2.7.2. Emotion laterality index

Emotion laterality index (ELI) was calculated within the above defined ROIs. In this case we obtained the percentage signal change of the beta values within each ROI. The laterality index was calculated by the formula (MBR-MBL), where MB stands for the mean beta value and R and L stand for right and left of each pairs of ROIs. A positive value of the ELI refers to more right side activity and a negative value refers to more left side activity.

2.8. Statistical analysis of fMRI results

Correlations of continuous variables were performed by means of Pearson's correlation test. For comparison of right handed and non-right handed individuals' activation of selected bilateral ROIs in each emotional condition, two tailed independent samples t-test was applied.

3. Results

Table 1 shows the characteristics of the sample of right- and nonright-handed subjects. Two nonright-handed individuals were excluded due to excessive head motion in the scanner. All participants were Spanish-speaking native Argentines of Caucasian ethnicity. Measures of anxiety and depression, as well as quality of life, were similar in both groups, although nonright-handed subjects displayed a nonsignificant tendency to greater anxiety symptoms and worse quality of life (Table 1). As expected, the two samples differed strongly in their Edinburgh Handedness Inventory score (Table 1).

LLI was below zero in right-handed individuals (mean −0.24, SD: 0.30, $p < 0.005$), confirming left hemisphere dominance for language in this group. In nonright-handed subjects there was a non significant trend in the same direction (mean −0.16, SD: 0.32, $p = 0.052$), suggesting variable language lateralization in this group.

Table 2 shows valence and arousal ratings assigned by participants to emotional status evoked by sad and happy faces. Values of valence and arousal did not differ among groups in either condition (Table 2). As expected, valence ratings differed significantly between happy and sad faces in both groups ($p < 0.005$ for right-handed, and $p < 0.001$ for nonright-handed), suggesting an adequate level of affective responses to both sad and happy faces. Both subject groups were similar in regards to how much time they spent looking at each face in each set of emotional stimulus while attempting to develop the picture's affect (Table 2).

Table 2
Emotion induction parameters in the fMRI session.

	Right- handed ($n = 20$)	Nonright-handed ($n = 18$)	p
Time to induce emotion			
Sad faces	8.0 ± 5.8	7.4 ± 5.7	0.192
Happy faces	4.8 ± 3.4	5.4 ± 4.1	0.489
SAM (valence)			
Sadness	4.6 ± 1.8	3.9 ± 1.0	0.169
Happiness	6.5 ± 1.1	6.8 ± 1.2	0.434
SAM (arousal)			
Sadness	3.4 ± 2.1	3.4 ± 1.6	0.883
Happiness	3.3 ± 2.5	3.6 ± 2.6	0.767

Shown are mean ± SD, p value for independent samples t test. SAM: Self-assessment Manikin (debriefing after fMRI session).

Fig. 1 depicts areas of brain activation during induced sadness in right- (A) and nonright-handed (B) individuals. Right-handed persons display specific activation in right anterior insula and frontal operculum, as well as midline diencephalic activation which locates in the hypothalamus (Fig. 1A). Nonright-handed persons as a group revealed bilateral activation in the same allocortical regions, especially anterior insula (Fig. 1B). Changes associated to happiness did not evoke consistent activation in circumscribed areas in either group at the $p < 0.05$ corrected threshold (not shown).

Fig. 2 shows the individual relationships between lateralization of brain activity induced by a category fluency task and lateralization of response in the amygdalae (top panels), subgenual cinguli (middle panels), or insulae (bottom panels) induced by either sadness (left panels) or happiness (right panels), in right- (dark circles) and nonright-handed (blank circles) participants. We observed an inverse relationship between language lateralization and lateralization of the brain response induced by sadness at the level of the amygdalae (Fig. 2, top left panel) and subgenual cinguli (Fig. 2, middle left panel), which attained significance in right- and nonright-handed participants respectively. This relationship was not observed in insula in either group (Fig. 2, bottom left panel). As shown in Fig. 2, middle right panel, induction of happiness is associated, in right-handed individuals, with a positive correlation between lateralization of language and lateralization of activity at the subgenual cinguli, not observed in nonright-handed participants, nor in the amygdala (Fig. 2, top right panel). The opposite relationship is seen in the anterior insula in the same group (i.e. more intense right activation during happiness when language is more left lateralized; Fig. 2, bottom panel).

Fig. 3 describes the relationship between lateralization of emotions of opposite valence at the amygdalae (top panel), subgenual cinguli (middle panel), and anterior insulae (bottom panel). In right-handed, left-dominant individuals, amygdala activation occurs with a similar lateralization pattern regardless of affective valence (top panel). At the insula in right-handed individuals, sadness and happiness evoke opposite lateralization responses, such that greater right lateralization of insula response during sadness correlates with greater left lateralization of insula response during happiness (bottom panel). We did not observe this relationship in nonright-handed persons, or in either group at the subgenual cinguli (Fig. 3, middle panel).

4. Discussion

To our knowledge the present study is the first report on the relationship between hemisphere specialization in the processing of emotion of opposite valence and hemispheric specialization in language processing, (i.e. a brain function long known to be lateralized in most individuals) in healthy persons with variable motor preference. Our results indicate that lateralization of emotion depends on the cerebral structure being studied, not confirming the "valence" and "right-hemisphere" hypotheses of emotion lateralization. Specifically, in persons with clear right limb preference (and left dominance for language), amygdala responses tend to show left lateralization regardless of emotion valence, whereas in anterior insula, a phylogenetically archaic allocortical structure, there is a right hemispheric activation dominance during sadness, with a contralateral dominance related to happiness. Among nonright-handed healthy individuals, this well-known relative lack of lateralization in motor function and language, is associated to a lack of lateralization in processing of affective responses. We found, however, evidence for an inverse relationship of cerebral dominance for language and subgenual cingulate activation during sadness in this group, which is similar to the finding relating language and activation of anterior insula during sadness in right handers, pointing to the presence of emotion lateralization in the former as well, although less clear than that of right-handed persons.

The present results indicate, therefore, that neither of the prevalent hypotheses on lateralization of emotion processing, namely the "right hemisphere" and the "valence" theories, can account for the complex brain regulation of affective responses. Instead, we found

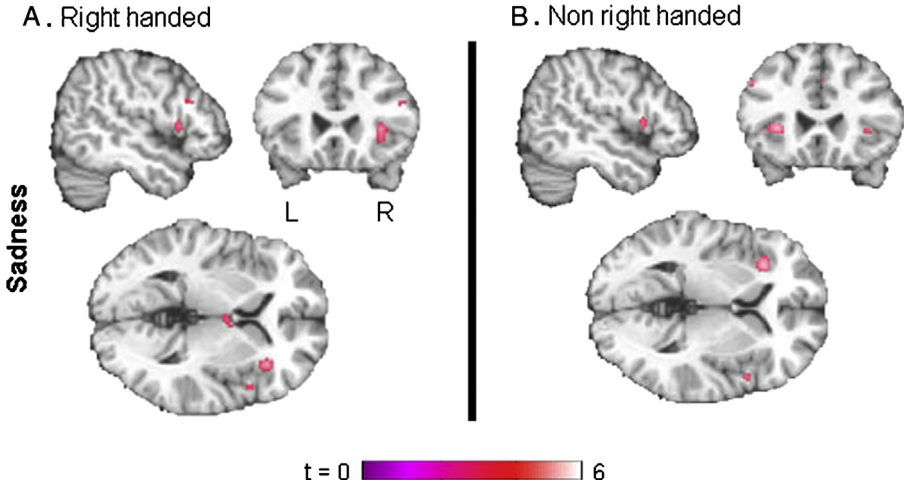

Fig. 1. Brain activation associated to the induction of sadness in right-handed (A panels) and nonright-handed (B panels) individuals. Activation occurs mainly at anterior insula, frontal operculum, and hypothalamus. In right-handed persons, cortical activation predominates in the right hemisphere, whereas in the sample of nonright-handed subjects, cortical activation tends to be bilateral. Coordinates displayed are $x = 50$, $y = 20$, $z = 8$, in the MNI system. Sagital planes correspond to the right hemisphere. Please see the text for details.

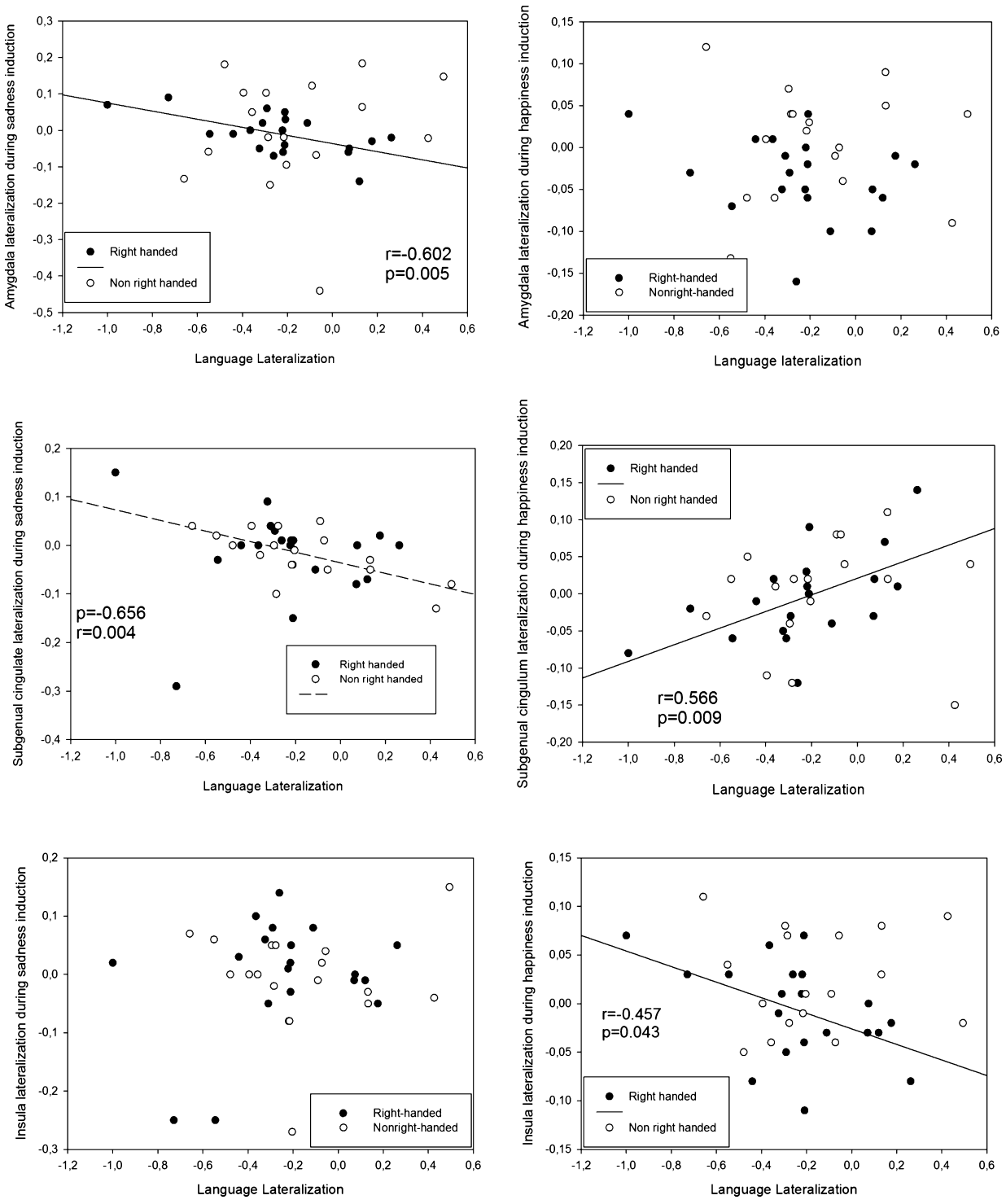

Fig. 2. Relationship of lateralization of language and lateralization of emotion at three hypothesis-driven regions of interest: amygdala, subgenual cingulate cortex, and anterior insula. Please see the text for details.

evidence that handedness reflects qualitatively diverse modes of lateralization of the adult brain. To our knowledge, this is the first observation on a relationship between cerebral dominance and lateralization of emotion processing in a sample that includes right- and nonright-handed individuals, who exhibit varying patterns of brain lateralization.

Our results are in agreement with previous observations ascribing a preeminence of the right hemisphere in the processing of negative affective responses in right handed individuals [9], but restricted to certain structures only. The results also suggest that emotion processing in the brain displays asymmetries which are in part related to cerebral dominance and handedness. Specifically, healthy persons with varying handedness and cerebral dominance display peculiarities in the relationship between language lateralization and asymmetry of emotion processing, especially in relation to cortical vs. subcortical structures such as cingular cortex and amygdala. Thus the traditional "valence" hypothesis seems applicable mainly to right-handed persons and certain cortical structures,

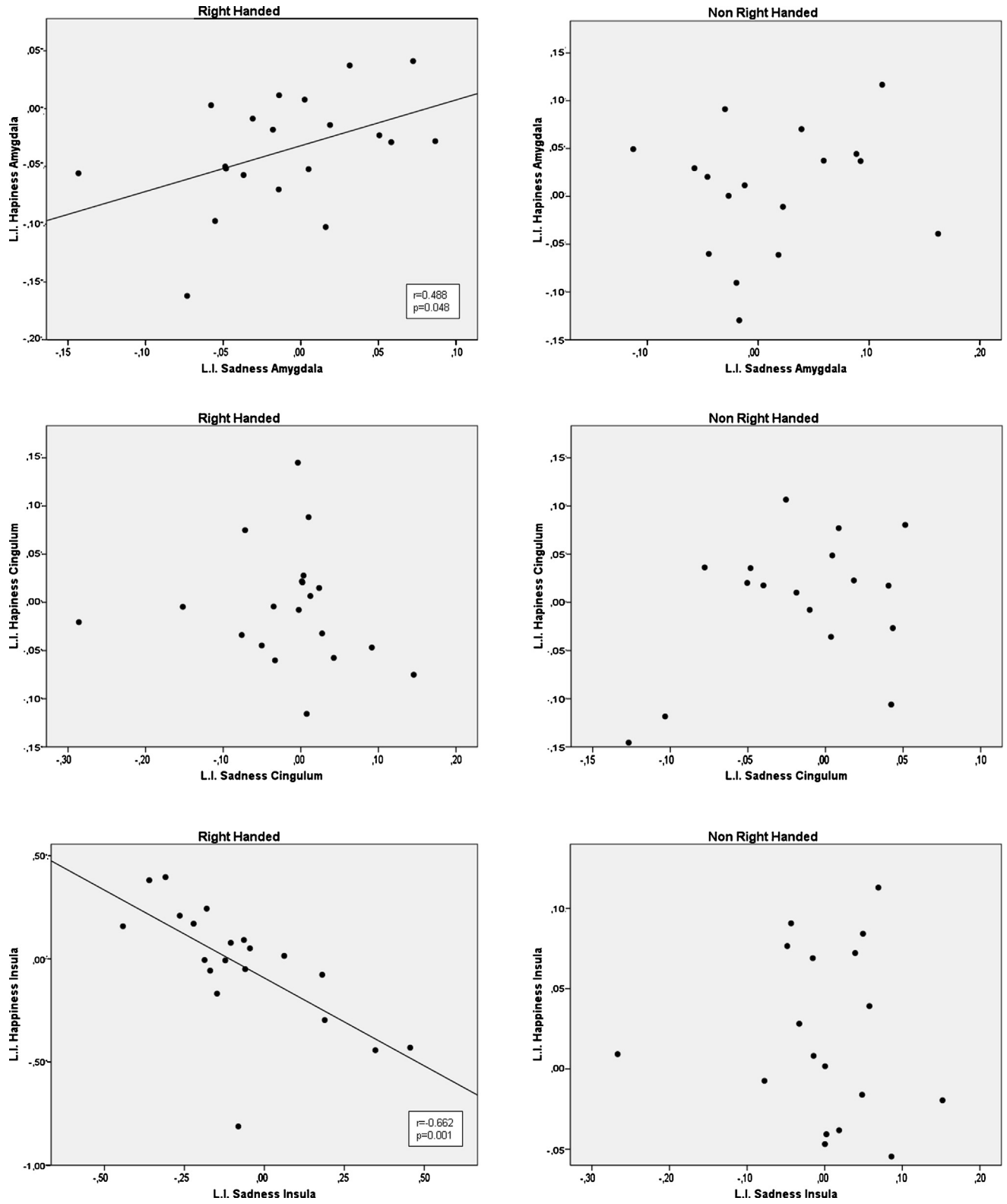

Fig. 3. Relationship of lateralization of emotions of opposite valence at the same ROIs as in Fig. 2. Please see the text for details.

especially anterior insula, which has been repeatedly associated with right > left activation during sadness [30]. As reviewed below, this might be related to the role of insula as a "map" of visceral sensory phenomena, considered the bodily correlate of emotional states. In contrast, activation is greater in the left amygdala in either sadness or happiness, probably reflecting a role of this structure in the processing of emotional arousal and salience [31]. We replicated the observation of Knecht and colleagues (2000) [32] on a direct relationship between handedness and hemispheric dominance, especially in nonright-handed persons, which suggests these are related rather than co-occurring phenomena.

Available previous evidence for a lateralization of function relevant to social behavior in non human primates suggests that the present findings on a relationship in the lateralization of diverse

functions are probably not species-specific. We are aware of at least two communications in marmoset subspecies which suggest hemispheric specialization of emotional and social parameters [33,34]. Hook-Costigan and Rogers observed a right hemispheric preference for negative emotional vocalization, and a contralateral specialization for affiliative interaction [33]. de Souza-Silva et al. reported a lateralization of monoamine content in different limbic structures, related to a series of social behavior of either positive or negative connotation [34]. On the other hand, Leroy et al. [35] have recently reported a single structural lateralized characteristic of the human brain which is not present in chimpanzees, namely the asymmetric (right greater than left) depth of the superior temporal sulcus. Interestingly, this asymmetric pattern is maintained in most tested subjects regardless their lateralization of brain function, in both normal (i.e., variable handedness, dominance for language, developmental stage) and pathological conditions (i.e., autism and aneuploidies). Only sex affects the degree of superior temporal sulcus depth asymmetry, and the authors propose this might simply represent a different brain size in males and females [35]. Alternatively, a sexual chromosome-linked gene may explain this finding, as discussed below [48].

4.1. Lateralization of affective responses related to lateralization of autonomic nervous system

A possible explanation for our findings is that emotion lateralization is simply an aspect of lateralization of motor output (including its sensory control), in this case motor autonomic output/interoception instead of motor somatic output/proprioception. In this regard, there is recent evidence favoring lateralization in the control of abnormal visceral sensation in the context of mood dysregulation. For example, Coen et al. (2009) [36] have described the patterns of brain activation during the processing of painful and non-painful visceral stimuli (esophageal distention) in different affective states. Evidence for a dominant role of the right hemisphere cortex in the bodily correlates of negative affective responses was obtained that specifically involves the right anterior cingulate (Brodmann's areas 24 and 32), right anterior insula and inferior frontal gyrus [36]. Gut sensations evoking increased heart rate, low-frequency/high-frequency (LF/HF) heart rate variability ratio and plasma epinephrine, an autonomic pattern characteristically associated with depression [37–40], are associated with increased activation of right insula, right orbitofrontal cortex, and right parahippocampal gyrus, as well as subcortical and brainstem structures [41]. Induction of negative affective responses has been associated with hyperactivity of right insula and prefrontal cortical structures in healthy volunteers as well [30]. Craig has summarized evidence explaining the lateralization of emotion processing and suggested that the right insular cortex might be the principal CNS structure responsible for sentience and self-consciousness [42,43]. He proposed that prosencephalic emotional asymmetry in turn reflects an asymmetrical representation of homeostatic activity, ultimately explained by asymmetries in the autonomic nervous system hierarchy including peripheral sympathetic and parasympathetic structures. Vagal afferents innervate the nucleus of the solitary tract, whereas sympathetic afferents terminate in lamina I of the dorsal horn of the spinal cord. From there, axons innervate the basal (parasympathetic) and posterior (sympathetic) portions of the ventromedial nucleus of the thalamus. This topographical organization is present in primates, and is extremely well-developed only in humans [42,44–46]. Ultimately, the left anterior insula is activated by afferent information related to parasympathetic functions, whereas the right anterior insula is activated by afferent information associated with sympathetic activity, e.g., pain [42]. There is, in fact, a growing body of evidence that suggests that left and right forebrain structures are associated with positive and negative emotion respectively [47]. Our results are in agreement with these observations, especially in regards to confirming the preeminent role of insula in the processing of emotion regardless of handedness (Fig. 1).

4.2. Limitations

The methodology used herein cannot categorically accept or reject the hypothesis that lateralization of emotion processing reflects hemispheric specialization in motor and sensory autonomic information. Simultaneous recording of peripheral autonomic activity would be necessary to accomplish this objective and we are currently working with such tool to discern the bodily correlate of centrally observed phenomena in relation to induction of affective responses.

The absence of lateralization of subgenual cingulate response to sad faces in relation to dominance for language in right-handed persons was an unexpected finding, given the data supporting the contribution of this structure to clinical disorders characterized by depressed mood [13]. We also observed an absence of reciprocal lateralization in conditions of positive or negative emotion in this structure, regardless of handedness. In this regard, we might have been biased by our observation of clinical response to right, but not left, subgenual deep-brain stimulation in treatment-resistant depression [25]. The present results point to the care that needs to be exerted while attempting to extrapolate findings obtained in abnormal conditions, to the explanation of normal brain functioning. That said, we cannot entirely rule out that participants in this study were free of significant genetic predisposition to mood disorders, given that we relied on self-report when excluding participants with affected first-degree relatives.

Our study was not adequately powered to discern gender differences in emotion processing lateralization. The topic might be important in light of data suggesting brain lateralization depends in part of gender, including gender differences in age of onset of major psychiatric disorders such as schizophrenia [48]. Mechanisms for the development of laterality are probably species-specific. Emerging evidence suggests that human brain lateralization is indeed specific in its characteristics to species of the *Homo* genus [49,50], and it has been proposed that language dominance and handedness are part of a general lateralization phenomenon of the human brain, possibly mediated by the presence of a sexual chromosomes-linked gene, PCDH11X/Y, which maps onto a Xq21.3/Yp11.2 human-specific region of homology [48]. Future studies should address the gender specificity of findings described herein.

In sum, to our knowledge this is the first study to investigate hemispheric differences in emotion regulation comparing healthy individuals with varying handedness. We have found evidence on differential contributions of either hemisphere to the processing of sadness and happiness regardless of manual dexterity and side of dominance for language, although the phenomenon is more clearly observed in right-handed individuals.

Conflict of Interests

Charles B. Nemeroff, M.D., Ph.D. Declaration of Financial/Propriety Interest 2011–2014. *Research/Grants*: National Institutes of Health (NIH). *Consulting*: Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Allergan, Mitsubishi Tanabe Pharma Development America, Taisho Pharmaceutical Inc., Lundbeck, Prismic Pharmaceutical. *Stockholder*: CeNeRxBioPharma, PharmaNeuroBoost, Revaax Pharma, Xhale, Celgene, Seattle Ge-netics, Abbvie. *Scientific Advisory Boards*: American Foundation for Suicide Prevention (AFSP), CeNeRxBioPharma (2012), National Alliance for Research on Schizophrenia and Depression (NARSAD), Xhale,

PharmaNeuroBoost (2012), Anxiety Disorders Association of America (ADAA), Skyland Trail. *Board of Directors*: AFSP, NovaDel (2011), Skyland Trail, Gratitude America, ADAA. *Income sources or equity of $10,000 or more:*PharmaNeuroBoost, CeNeRxBioPharma, NovaDel Pharma, ReevaxPharma, American Psychiatric Publishing, Xhale. *Patents*: Method and devices for transdermal delivery of lithium (US 6,375,990B1). Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2). *Speakers Bureau*: None. *Honoraria*: Various. *Royalties*: Various. *Expert Witness*: Various.

All of the other authors declare no potential conflict of interests.

Role of the authors

EYC, MFV, JAC, CBN, and SMG participated in the design of the study including choice of regions of interest and functional magnetic resonance imaging paradigms to test the hypotheses. EYC, MFV, LJD, MNC, MGG, MOV, and MSLG evaluated the participants and performed the experiments. EYC, MFV, LJD, MNC, CR, and SMG did the image analyses and run statistical tests. EYC, MFV, and SMG wrote the first version of the manuscript. All authors edited and approved the final manuscript.

Acknowledgements

LJD and MNC are doctoral research fellows from CONICET. University of Buenos Aires, School of Psychology (UBACYT 2012-2014 to SMG and MFV), and CONICET (PIP 2012–2015 to SMG and MFV). SDG. We thank Professor Timothy Crow for his comments on an earlier version of this manuscript.

References

[1] Chiandetti C, Galliussi J, Andrew RJ, Vallortigara G. Early-light embryonic stimulation suggests a second route, via gene activation, to cerebral lateralization in vertebrates. Sci Rep 2013;3:2701.
[2] Fitch WT, Braccini SN. Primate laterality and the biology and evolution of human handedness: a review and synthesis. Ann NY Acad Sci 2013;1288:70–85.
[3] Geschwind N. The organization of language and the brain. Science 1970;170:940–4.
[4] Broca P. Remarques sur le siége de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). Bulletin de la Société Anatomique 1861;6:330–57.
[5] Wernicke K. Der aphasische Symptomencomplex: Eine psychologische. Studie auf anatomischer Basis. Breslau M Crohn und Weigert;1874.
[6] Nottebohm F, Stokes TM, Leonard CM. Central control of song in the canary, *Serinus canarius*. J Comp Neurol 1976;165:457–86.
[7] Wichman A, Rogers LJ, Freire R. Visual lateralization and development of spatial and social spacing behaviour of chicks (Gallus gallus domesticus). Behav Processes 2009;81:14–9.
[8] Schwartz GE, Davidson RJ, Maer F. Right hemisphere lateralization for emotion in the human brain: interactions with cognition. Science 1975;190:286–8.
[9] Demaree HA, Everhart DE, Youngstrom EA, Harrison DW. Brain lateralization of emotional processing: historical roots and a future incorporating dominance. Behav Cogn Neurosci Rev 2005;4:3–20.
[10] Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain 1995;118(Pt 1):279–306.
[11] Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry 2001;6:13–34.
[12] Holmes AJ, Lee PH, Hollinshead MO, Bakst L, Roffman JL, Smoller JW, et al. Individual differences in amygdala-medial prefrontal anatomy link negative affect, impaired social functioning, and polygenic depression risk. J Neurosci 2012;32:18087–100.
[13] Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997;9:471–81.
[14] Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology 2010;35:192–216.
[15] Murrough JW, Huang Y, Hu J, Henry S, Williams W, Gallezot JD, et al. Reduced amygdala serotonin transporter binding in post traumatic stress disorder. Biol Psychiatry 2011;70:1033–8.
[16] Shackman AJ, Fox AS, Oler JA, Shelton SE, Davidson RJ, Kalin NH. Neural mechanisms underlying heterogeneity in the presentation of anxious temperament. Proc Natl Acad Sci USA 2013;110:6145–50.
[17] Crow TJ, Chance SA, Priddle TH, Radua J, James AC. Laterality interacts with sex across the schizophrenia/bipolarity continuum: an interpretation of meta-analyses of structural MRI. Psychiatry Res 2013;210:1232–44.
[18] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[19] Hamilton M. Standardised assessment and recording of depressive symptoms. Psychiatr Neurol Neurochir 1969;72:201–5.
[20] Schneider F, Gur RC, Gur RE, Muenz LR. Standardized mood induction with happy and sad facial expressions. Psychiatry Res 1994;51:19–31.
[21] Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 1994;25:49–59.
[22] Ashburner J, Friston KJ. Nonlinear spatial normalization using basis functions. Hum Brain Mapp 1999;7:254–66.
[23] Friston KJ, Josephs O, Zarahn E, Holmes AP, Rouquette S, Poline J. To smooth or not to smooth? Bias and efficiency in fMRI time-series analysis. Neuroimage 2000;12:196–208.
[24] Habel U, Kircher T, Schneider F. Functional imaging of emotional disorders and experiences in schizophrenia patients. Radiologe 2005;45:161–8.
[25] Guinjoan SM, Mayberg HS, Costanzo EY, Fahrer RD, Tenca E, Antico J, et al. Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation. J Neuropsychiatry Clin Neurosci 2010;22:265–77.
[26] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–89.
[27] Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, et al. Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology 1996;46:978–84.
[28] Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T. Human brain language areas identified by functional magnetic resonance imaging. J Neurosci 1997;17:353–62.
[29] Lehericy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, et al. Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. Neurology 2000;54:1625–33.
[30] Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 1999;156:675–82.
[31] Schneider F, Grodd W, Weiss U, Klose U, Mayer KR, Nagele T, et al. Functional MRI reveals left amygdala activation during emotion. Psychiatry Res 1997;76:75–82.
[32] Knecht S, Drager B, Deppe M, Bobe L, Lohmann H, Floel A, et al. Handedness and hemispheric language dominance in healthy humans. Brain 2000;123(Pt 12):2512–8.
[33] de Souza Silva MA, Topic B, Lamounier-Zepter V, Huston JP, Tomaz C, Barros M. Evidence for hemispheric specialization in the marmoset (*Callithrix penicillata*) based on lateralization of behavioral/neurochemical correlations. Brain Res Bull 2007;74:416–28.
[34] Hook-Costigan MA, Rogers LJ. Lateralized use of the mouth in production of vocalizations by marmosets. Neuropsychologia 1998;36:1265–73.
[35] Leroy F, Cai Q, Bogart SL, Dubois J, Coulon O, Monzalvo K, et al. New human-specific brain landmark: the depth asymmetry of superior temporal sulcus. Proc Natl Acad Sci USA 2015;112:1208–13.
[36] Coen SJ, Yaguez L, Aziz Q, Mitterschiffthaler MT, Brammer M, Williams SC, et al. Negative mood affects brain processing of visceral sensation. Gastroenterology 2009;137:253–61, 261 e251-252.
[37] Guinjoan SM, Bernabo JL, Cardinali DP. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. J Neurol Neurosurg Psychiatry 1995;59:299–302.
[38] Guinjoan SM, de Guevara MS, Correa C, Schauffele SI, Nicola-Siri L, Fahrer RD, et al. Cardiac parasympathetic dysfunction related to depression in older adults with acute coronary syndromes. J Psychosom Res 2004;56:83–8.
[39] Guinjoan SM, Castro MN, Vigo DE, Weidema H, Berbara C, Fahrer RD, et al. Depressive symptoms are related to decreased low-frequency heart rate variability in older adults with decompensated heart failure. Neuropsychobiology 2007;55:219–24.
[40] Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. Psychosom Med 2005;67(Suppl 1):S29–33.
[41] Suzuki H, Watanabe S, Hamaguchi T, Mine H, Terui T, Kanazawa M, et al. Brain activation associated with changes in heart rate, heart rate variability, and plasma catecholamines during rectal distention. Psychosom Med 2009;71:619–26.
[42] Craig AD. Forebrain emotional asymmetry: a neuroanatomical basis. Trends Cogn Sci 2005;9:566–71.
[43] Craig AD. How do you feel–now? The anterior insula and human awareness. Nat Rev Neurosci 2009;10:59–70.
[44] Rogers RC, Hermann GE. Central connections of the hepatic branch of the vagus nerve: a horseradish peroxidase histochemical study. J Auton Nerv Syst 1983;7:165–74.
[45] Hanamori T, Kunitake T, Kato K, Kannan H. Responses of neurons in the insular cortex to gustatory, visceral, and nociceptive stimuli in rats. J Neurophysiol 1998;79:2535–45.

[46] Shi CJ, Cassell MD. Cortical, thalamic, and amygdaloid connections of the anterior and posterior insular cortices. J Comp Neurol 1998;399:440–68.
[47] Davidson RJ. What does the prefrontal cortex do in affect: perspectives on frontal EEG asymmetry research. Biol Psychol 2004;67:219–33.
[48] Priddle TH, Crow TJ. The protocadherin 11X/Y (PCDH11X/Y) gene pair as determinant of cerebral asymmetry in modern Homo sapiens. Ann NY Acad Sci 2013;1288:36–47.
[49] Wager TD, Phan KL, Liberzon I, Taylor SF. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. Neuroimage 2003;19:513–31.
[50] Annett M. Handedness and Brain Asymmetry The Right Shift Theory. New York: Psychology Press; 2002.