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Forebrain emotional asymmetry: a neuroanatomical basis?

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There is considerable psychophysiological evidence to indicate that the left and right halves of the human forebrain differentially associate with particular emotions and affective traits. A neurobiological model is needed. Here I propose that forebrain emotional asymmetry is anatomically based on an asymmetrical representation of homeostatic activity that originates from asymmetries in the peripheral autonomic nervous system. This proposal builds on recent evidence indicating that lateralized, higher-order re-representations of homeostatic sensory activity provide a foundation for subjective human feelings. It can subsume differing views of emotion and the forebrain because it suggests that emotions are organized according to the fundamental principle of autonomic opponency for the management of physical and mental energy.

Introduction

An established model of emotion associates the right hemisphere with emotional arousal. Yet, several recent reviews of a large literature relating affect and emotion to EEG activity, cortisol secretion, immune function, and brain lesions have concluded that this model should be updated with one in which positive/negative valence, approach/withdrawal behavior, and/or affiliative/personal relevance are associated with left/right hemispheric forebrain activity, respectively [1–5], albeit with possible underlying circuits predominantly used for particular emotions. Nevertheless, multi-faceted analyses of human behavior during even relatively simple emotions such as anger appear to confound these associations [6], suggesting that a biologically based model is needed that can guide psychological categorization [2].

Recent neurobiological studies using anatomical, neurological, and functional imaging methods indicate that subjectively experienced feelings and emotions might be based on higher-order re-representations of homeostatic afferent (sensory) activity in the human forebrain [7–9], and it is particularly noteworthy that such evidence indicates a strong pattern of lateralization. Further, there is a comparable pattern of lateralization evident for the cortical control of cardiac activity [10], and this can be directly related to left/right asymmetry in the opposing parasympathetic and sympathetic components of the peripheral autonomic nervous system [11]. The confluence of these strikingly parallel asymmetries suggests a homeostatic neuroanatomical model of emotional asymmetry, in which the left forebrain is associated predominantly with parasympathetic activity, and thus with nourishment, safety, positive affect, approach (appetitive) behavior, and group-oriented (affiliative) emotions, while the right forebrain is associated predominantly with sympathetic activity, and thus with arousal, danger, negative affect, withdrawal (aversive) behavior, and individual-oriented (survival) emotions. In the model I am proposing, management of physical and mental (meaning neural) energy is the salient organizational motif, such that energy enrichment is associated with the left forebrain and energy expenditure is associated with the right forebrain, consistent with the respective roles of the parasympathetic and sympathetic efferent systems. The autonomic principle of coordinated opponent interactions between the two hemispheres could provide a fundamental management process.

This homeostatic neuroanatomical model builds directly upon a historical progression of thought relating emotion to autonomic activity (by authors such as William James, Paul MacLean, Walle Nauta, Stephen Porges, Julian Thayer, Antonio Damasio, and Ray Dolan). The concept of energy management provides a novel basis for understanding psychophysiological attributes of emotion (as opposed to appraisal) and the relationship between emotional regulation and health. The model is elucidated in the following text by summarizing evidence for lateralization in each realm, and then testable predictions and areas needing further exploration are noted.

Fundamental characteristics of the autonomic nervous system and homeostasis

The two components of the autonomic nervous system, the parasympathetic and sympathetic efferents, usually act in a reciprocal, opposing fashion on target tissues [11–13]. For example, parasympathetic activity enhances intestinal peristaltic movement (promoting nourishment during quiescence), whereas sympathetic activity inhibits such activity (when physical exertion and catabolic mobilization is required). Parasympathetic activity generally slows the heart, whereas sympathetic activity accelerates it (with different temporal patterns), and so on. Opponent processing is a fundamental functional principle for autonomic control (as it is throughout the nervous system).

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The parasympathetic and sympathetic nerves contain both efferent and afferent fibers. Together with small-diameter somatic afferent fibers that innervate all tissues of the body, these nerve fibers subserve homeostasis [8], which is the ongoing dynamic, heirarchically organized neurobiological process that maintains an optimal balance in the physiological condition of the body. Homeostasis in mammals comprises many integrated functions and includes autonomic, neuroendocrine and behavioral mechanisms. Thermoregulation is a good example of a homeostatic function, because it is subserved by integrated changes in hormonal, metabolic, cardiovascular, respiratory, water and salt balances, and because we feel an obvious affect (pleasantness, unpleasantness) in response to changes in temperature, which is the perceptual correlate of homeostatic behavioral motivation. The salient purpose of thermoregulation, and indeed of homeostasis, is optimal energy management in support of life.

Asymmetry in peripheral autonomic efferents and homeostatic afferents

The neural asymmetries in homeostasis begin in the periphery. The peripheral nerves of the autonomic nervous system are the only major nerves of the body that are asymmetric. The main parasympathetic nerves (e.g. the vagus) and the main sympathetic nerves (e.g. the splanchnic) on the left and right sides differentially innervate organs in the thoracic and abdominal cavities. For example, the hepatic nerve (which innervates the liver and is crucially involved in numerous homeostatic functions, including osmoregulation, glucose regulation, fever and sickness behavior) originates entirely from the anterior sub-diaphragmatic branch of the left vagus nerve [14]. The efferent autonomic innervation of the heart is strongly asymmetric (see Box 1). Afferent activity from the heart in the left and right vagus nerves is also physiologically asymmetric [15]. Notably, the recurrent laryngeal nerves (responsible for vocalization) that originate from the two vagus nerves are asymmetric [16], and the branchiomeric muscles that are responsible for the facial expression of emotion (which are innervated by motor fibers allied with the parasympathetic system and have cardiovascular roles [12,17]) show visible left/right differences [18].

Thus, peripheral autonomic efferents and homeostatic afferents are anatomically and functionally asymmetric. This must have deep impact on central homeostatic processing, but unfortunately, these structural asymmetries have received little attention (e.g. the central effects of activity from the left and right vagus nerves have not been compared). With the advent of functional imaging in human subjects, however, asymmetries in the central representations of homeostatic afferent activity have been revealed.

Box 1. Asymmetric autonomic innervation of the heart

Generally speaking, the right vagus predominantly controls atrial function whereas the left vagus predominantly controls ventricular function, yet the details of cardiac innervation display even stronger asymmetry [11]. Thus, heart rate (chronotropy) is controlled by sympathetic and parasympathetic innervation of the sinoatrial (SA) node, and both are asymmetric; sympathetic SA input derives mostly from the stellate cardiac nerve on the right side, and parasympathetic SA input derives mostly from the right vagus. By contrast, conduction time in atrioventricular (AV) fibers (dromotropy), which is increased by parasympathetic and decreased by sympathetic activity, is controlled mainly by inputs from the left side, again in both systems. Finally, myocardial contractility (inotropy) is enhanced mainly by sympathetic activity from the left side. Thus, autonomic control of heart rate is predominantly a right-sided function, whereas ventricular regulation and pulse pressure are predominantly controlled by the left side.

Asymmetry in the central representation of homeostatic afferents

The hypothesis that the peripheral autonomic asymmetries are maintained centrally is directly supported by anatomical evidence that the terminations of afferent fibers from the hepatic nerve occur almost entirely in the left brainstem [14]. However, in the forebrain of non-primates there is little evidence of lateralized homeostatic afferent processing and considerable evidence of modality convergence [19,20]. By contrast, in humans there is now strong evidence for homeostatic afferent pathways that show modality specificity and functional lateralization.

The homeostatic afferents from parasympathetic nerves terminate in the nucleus of the solitary tract of the brainstem, and homeostatic afferents from sympathetic and somatic nerves terminate in lamina I of the spinal dorsal horn (Figure 1). Direct ascending projections from these sites activate insular cortex by way of the basal (parasympathetic) and posterior (sympathetic) parts of the ventromedial nucleus of the thalamus [8]. These modality-specific, topographically organized projection pathways are phylogenetically distinct to primates and are enormously well-developed only in humans. These pathways become clearly lateralized as they progressively activate higher-order homeostatic afferent re-representations in more anterior portions of the human insula (see Box 2). Thus, the left anterior insula (AI) is activated predominantly by homeostatic afferents associated with parasympathetic functions (e.g. taste), and the right AI is activated predominantly by homeostatic afferents associated with sympathetic functions (e.g. pain).

Asymmetry in the cortical control of autonomic activity

Stimulation of insular cortex elicits strikingly asymmetric effects on cardiac activity that parallel the afferent asymmetries [10]. Left insula produces parasympathetic effects (bradycardia and blood pressure depression), whereas right insula produces sympathetic effects (tachycardia and pressor response). Accordingly, barbiturate inactivation of the left hemisphere (Wada test) or damage to the left insula releases increased sympathetic tone, whereas damage to the right insula can cause cardiac arhythmia and arrest [3,11]. Strong support for the conclusion that sympathetic cardiac activity is controlled by the right hemisphere and parasympathetic activity by the left hemisphere is provided by analyses of high-frequency heart rate variability (HRV), which is associated

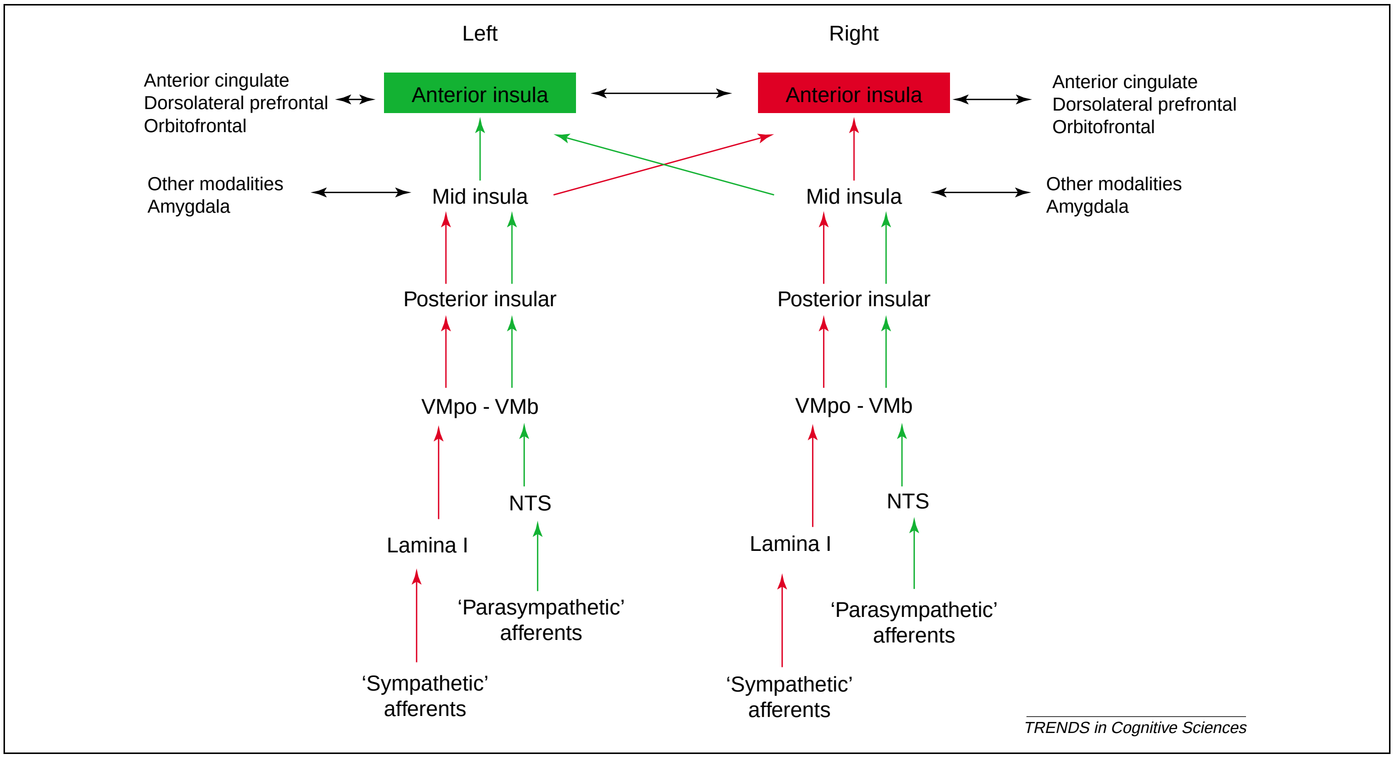

Figure 1. A schematic diagram indicating the ascending pathways of the homeostatic afferents that parallel the sympathetic and parasympathetic halves of the autonomic nervous system and how they become asymmetrically lateralized in the left and right forebrain of humans.

with vagal (parasympathetic) tone, during film presentations to the left and right visual hemi-fields [28].

Based on numerous lines of evidence, the right hemisphere is firmly associated with arousal and sympathoadrenal stress responses [11,29]. Nevertheless, few studies of efferent autonomic activation have differentiated the left or right sides in forebrain regions other than the insula. This may be in part because of methodological limitations (it is difficult to resolve laterality in activation blobs near the midline in imaging studies), in part because autonomic measures have infrequently been taken, and in part because the left and right sides have rarely been explicitly compared. However, in two studies HRV was directly correlated with activity in the anterior cingulate cortex (ACC) and/or AI on the left side, consistent with a parasympathetic role [30,31].

Notably, recent data have repositioned Broca's area, the classical region for speech articulation, in the left AI; by contrast, the right AI has been associated with the temporal control of vocalization during singing [32,33], consistent with the presence of a rhythmic representation of emotional state across time [34]. Asymmetry in motor control of both cardiac and vocal functions has been reported in non-human mammals, too, despite a lack of forebrain homeostatic afferent asymmetry [10,29,35]; nevertheless, molecular genetic evidence substantiates pronounced developmental asymmetries in human brains that are not present in rodent brains [36].

Human cortical autonomic and homeostatic asymmetry

This brief overview reveals that the cortical representations of both autonomic efferent and homeostatic afferent processing are asymmetric and coincident in the human forebrain, particularly in the insula. The left side is associated with parasympathetic function and the right side is associated with sympathetic function. In the homeostatic model I am proposing, this asymmetry in energy management relates directly to affect and emotion.

Neurobiology of the forebrain asymmetry of emotion

Although some authors have focused on the role of the amygdala, the ventral striatum and the periaqueductal gray in emotion, analyses of functional imaging studies of emotion in humans indicate that conjoint activity in the AI

Box 2. Asymmetric homeostatic afferent activation of the anterior insula

Left vagus nerve stimulation (VNS) in epileptic and depressed patients activates primarily the left anterior insula (AI) [21]. Cardiorespiratory manipulations using Valsalva maneuvers, isometric contractions and dynamic exercise activate primarily left AI [22,23]. Gustation (a special visceral modality subserved by glossopharyngeal and vagal afferents) also becomes lateralized in the left AI, consistent with a crucial role in energy acquisition [24,25]. The strong activation of left AI elicited by tasting food after a prolonged fast certainly supports an association with nourishment [26].

Conversely, various modalities conveyed by homeostatic afferents associated with sympathetic efferents produce activity in the contralateral posterior insular cortex that becomes lateralized in the right AI. Thus, innocuous thermal sensations (warm, cool), hot and cold pain, muscle and visceral pain, and sensual touch and sexual arousal all produce activation of the right AI [8]. Heartbeat-evoked EEG potentials and interoceptive awareness of heartbeat timing, which might be due to 'sympathetic' homeostatic afferent activity, are also associated with right AI activity [9,27]. The anatomical evidence suggests that the higher-order re-representations of homeostatic activity that become lateralized in the right and left AI are present only in humanoid primates [8].

and ACC occurs during the experience of virtually all emotions [8,37]. This is consistent with the idea that our emotions consist of both a feeling (engendered in AI, or limbic sensory cortex) and a motivation (engendered in ACC, or limbic motor cortex). In particular, subjective ratings of feelings from the body – such as coolness, pain, and sensual touch – are directly correlated with lateralized re-representations of homeostatic afferent activity in right AI (and ventrolateral prefrontal cortex); notably, these include both pleasant and unpleasant feelings. The right AI is also selectively activated during feelings of either disgust or trust, as well as during anger, fear, heartbeat-related anxiety, and also imitative and empathic feelings of either positive or negative valence [8,38,39]. These observations led to the view that the right AI and ACC provide a lateralized neurobiological substrate for subjective awareness of emotion based on higher-order re-representations of homeostatic afferent processing, consistent with the James–Lange theory of emotion and Damasio's 'somatic marker' hypothesis of consciousness [8]. That model also allowed for feelings about motivations and for motivational modulation of feelings (e.g. placebo analgesia) on the basis of interactions between right AI and ACC.

However, that view is confounded by newer evidence indicating that the AI and ACC are more strongly active on the left side during feelings of romantic love and maternal attachment [40,41]. The present proposal stems from the recognition that such feelings of affiliation differ in that they can be regarded as 'parasympathetic' (or, enrichment) emotions [12], whereas, by contrast, all of the emotional feelings associated with right-sided activity in the previous studies were elicited by experimental challenge and so can be viewed more generally as aroused or 'sympathetic' emotions. Thus, guided by the data reviewed above and by the concept that homeostasis is optimal energy management, the homeostatic neurobiological model proposed here enlarges the former right-sided view by associating 'parasympathetic' left forebrain activity with physical and mental energy enrichment and 'sympathetic' right forebrain activity with physical and mental energy expenditure. Further imaging evidence for this proposal is provided by a recent study of empathic pain, in which the AI and ACC were activated on both the right and left sides while watching pain being inflicted on a loved one [39], in stark contrast to the selective activation of right AI and ACC that is elicited during subjective feelings of pain; this supports the association of right AI in aroused ('sympathetic') feelings and left AI in affiliative ('parasympathetic') feelings. A confounding role of gender is possible, because most of the subjects in these imaging studies of romantic love, maternal affiliation, and empathic pain were females; nevertheless, the AI is similarly activated bilaterally during compassion meditation in trained Tibetan males and Western novices of either gender [42]. The homeostatic neurobiological model proposed here is also consistent with correlations of left forebrain (and vagal) activity with social engagement [43,44], and with correlations of right hemisphere activity with risk-taking [45], depression [see 46] and personal relevance [47], based on the homeostatic associations with energy enrichment or expenditure.

Implications of the homeostatic neurobiological model of emotion

This model instantiates neurobiologically the psychological proposal that a hypothetical 'calm and connection system' opposes the arousal/stress system [48,49]. It can incorporate not only the bivalent concept of emotion, in which positive and negative affects are different psychological dimensions, but also the core affect concept, in which energization is a key dimension [7,50]. The present model suggests that emotional feelings and behaviors might be neurobiologically differentiated by their roles in the enrichment or the expenditure of physical and mental energy. Most notably, the model provides a structural basis for suggesting that the opponent interactions between left and right AI and ACC are of great importance. Positive and negative affect also appear to interact in an opponent fashion; for example, it is well documented that social engagement (and oxytocin) can suppress arousal, stress, depression, and cortisol release, whereas conversely, the latter factors can reduce mood, sociability, and immune function [50,51]. Positive affect can suppress pain, whereas negative mood can exacerbate it [52]. The observation that symptoms of depression correlate directly with enhanced pain-evoked activation of right AI is consistent with this proposal [46]. A key finding is that, in clinically depressed patients, stimulation of the left vagus nerve, which activates the left insula and often elicits subjective mood enhancement, produces de-activation in the right AI ([53]; M. Devous, personal communication). Thus, according to this model, it is the relative balance of activity within symmetrical modules in the left and right AI and ACC that is of crucial significance for neurophysiologically coordinated emotional complexity, or mental health. For example, whereas the right AI is active during sexual arousal, the left AI might be more active during orgasm [54,55]; in this model, the interactions between left and right AI would reflect the delicate coordination of parasympathetic and sympathetic efferent activity during these behaviors and represent the concurrent energy expenditure (arousal) and energy enrichment (affiliation) that can occur during sex with a loved one.

This homeostatic model provides a new framework for psychological and neurobiological analyses of affective feelings, emotional behavior, and mood disorders, and it suggests several potentially fruitful research questions (see Box 3). Naturally, there are also conflicting reports that reveal murky areas needing further analysis (see [61]). Confounding examples include, in particular, the primal ability of music to provide psychological enrichment and social bonding in humans, which only recently has been associated with the left instead of the right AI [62], and the opposite sidedness of odor hedonic valence [60], which seems to contrast also with the sidedness of taste valence. Opposite asymmetric activation in the amygdala has also been reported, although this might reflect specialized primordial circuitry and gender [59].

Box 3. Questions for future research

- How can 'positive' (energy enrichment) emotions be induced (or perhaps enabled) that activate the left AI? This seems very important, because modalities that activate 'parasympathetic' energy enrichment could directly augment mental and physical health. (For example, we are currently testing whether slow breathing produces increased activity in the left AI and ACC.)
- How is the activation of various portions of the human central autonomic network (including ACC, hypothalamus, amygdala, ventral striatum, periaqueductal gray) related to sympathovagal balance, or autonomic opponency? (Studies are needed that test for evidence of functional asymmetry by direct comparison of activation sites on the left and right sides.)
- Similarly, how are psychophysiological attributes of emotional feelings, behavior and affective disorders related to the homeostatic opponent processes of energy management, that is, to measures of parasympathetic/sympathetic balance in autonomic output? (For example, studies of HRV or heart beat awareness in relation to emotional regulation could address this question; e.g. see [56,57].) Such analyses could lead to a new categorization of emotion and affect based on homeostatic opponency in energy management.
- How does affect based on homeostatic needs, such as the pleasantness or unpleasantness of a non-painful thermal stimulus, relate to the activation of left and right forebrain regions? (Hedonic valence might differ from affective valence in terms of energy management; see [58].)
- Are there interrelationships between homeostatic afferent asymmetry and handedness or gender (e.g. see [24,59,60])?
- Are forebrain emotional asymmetries independent from parietal or temporal asymmetries in non-affective functions (e.g. spatial attention, face recognition)?
- How do lesions of insular cortex affect human emotions and behavior? (There are reports of ageusia, analgesia, anhydrosis, threat asymbolia, mental retardation, anergia, amusia and anosognosia.)

The homeostatic basis of emotion

The idea that emotional health and physical health are intimately associated by sharing a common foundation based on homeostatic control has a long history and a surfeit of insightful applications (e.g. www.heartmath.com). The present proposal highlights emerging evidence in support of a direct neuroanatomical relationship in the human forebrain between emotion and homeostasis that mirrors the asymmetric opponent management of energy acquisition and utilization by the autonomic nervous system. This structural neural association of human affect and emotion with physical and mental energy management provides an encompassing perspective that can subsume various psychophysiological viewpoints – and perhaps resolve their differences – by relating them to a fundamental homeostatic opponent process that maintains the health of the individual and of the species.

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