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Exploring emotions using invasive methods: review of 60 years of human intracranial electrophysiology

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Over the past 60 years, human intracranial electrophysiology (HIE) has been used to characterize seizures in patients with epilepsy. Secondary to the clinical objectives, electrodes implanted intracranially have been used to investigate mechanisms of human cognition. In addition to studies of memory and language, HIE methods have been used to investigate emotions. The aim of this review is to outline the contribution of HIE (electrocorticography, single-unit recording and electrical brain stimulation) to our understanding of the neural representations of emotions. We identified 64 papers dating back to the mid-1950s which used HIE techniques to study emotional states. Evidence from HIE studies supports the existence of widely distributed networks in the neocortex, limbic/paralimbic regions and subcortical nuclei which contribute to the representation of emotional states. In addition, evidence from HIE supports hemispheric dominance for emotional valence. Furthermore, evidence from HIE supports the existence of overlapping neural areas for emotion perception, experience and expression. Lastly, HIE provides unique insights into the temporal dynamics of neural activation during perception, experience and expression of emotional states. In conclusion, we propose that HIE techniques offer important evidence which must be incorporated into our current models of emotion representation in the human brain.

Keywords: intracranial; EEG; epilepsy; emotion; social; stimulation; laughter; mirth; electrophysiology; microelectrodes

INTRODUCTION

The study of the neural representation of emotions is one of the cornerstones of cognitive neuroscience research. One encompassing definition sees emotions as helping to coordinate, adapt and reinforce sets of changes to the brain and body towards the triggering event (Adolphs *et al.*, 2010). Despite enormous progress over the past 15 years in our understanding of the neural representation of emotions in the human brain thanks to functional neuroimaging, several recent meta-analyses point out continued controversy over many central concepts (e.g. Murphy *et al.*, 2003; Phan *et al.*, 2002; Kober *et al.*, 2008; Lindquist *et al.*, 2012). For instance, despite general agreement that emotional states causes wide-spread brain activation, some investigators postulate that the data support the existence of discrete emotional processing centers in the brain while others see the data as supporting less discrete, more network-based processing. The more *locationist* view argues that a small set of discrete emotions (e.g. anger) are represented by discrete, evolutionarily conserved anatomical systems in the brain (e.g. amygdala) (Adolphs *et al.*, 1994; Bechara *et al.*, 1995; Calder *et al.*, 1996; Scott *et al.*, 1997; Adolphs *et al.*1999; Schmolck and Squire, 2001; Vytal and Hamann, 2010; Lench *et al.*, 2011). The contrary position is a *distributionist* view which argues that no single macro-anatomical structure uniquely specializes for individual emotion categories and proposes a dimensional view (i.e. positive and negative valence, high and low arousal) of emotions. In certain views, emotion categories are composed of even more basic psychological units called 'psychological primitives' (Cunningham and Zelazo, 2007; Barrett, 2011, 2012; LeDoux, 2012; Lindquist and Barrett, 2012; Lindquist *et al.*, 2012; Russell, 2012; Barrett and Satpute, 2013; Lindquist *et al.*, 2013; Hamann, 2012). While these distributionist theories either focus on some combination of the psychological and the neural levels, the ones we will focus on will primarily be of the neural level.

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While to some extent the dispute over what the evidence shows may stem from presuppositions of the investigators, it is possible that limitations in methods used to investigate human emotions are fueling this dispute. Techniques typically used in the neuroscience of emotion depend on the organisms under study. Human studies primarily use some form of neuroimaging (e.g. fMRI, EEG, MEG) and either temporary (e.g. TMS) or permanent lesion participants. One limitation could be the spatiotemporal resolution of functional neuroimaging. Perhaps the processing units of interest can be better dissociated at a level smaller and faster than conventional neuroimaging can detect? A second limitation stems from caveats of inferring causality from lesion studies. Lesion map data primarily come from stroke patients with the possibility of wide lesions that effect cortical, subcortical and white matter regions (Duffau, 2012). Even focal lesions that are localized to a single region have been shown to produce different behavioral results in different participants (Feinstein, 2013). The individual variability and lack of control leads to many third-variable confounds that hurt causal inferences.

To alleviate some of these issues, studying animal models opens up an array of different invasive techniques with the best spatiotemporal resolution possible. Research with non-human models typically uses invasive forms of electrophysiology [e.g. single neuron recordings, local field potentials (LEPs), etc.] and lesion techniques. While these studies in rodents and non-human primates have contributed to our understanding of emotion and pro-social behavior (LeDoux, 2000; Burgdorf and Panksepp, 2006), there are numerous, complex behaviors unique to humans that are not possible to study in animals yet are critical to the understanding of hypothesized neural emotion models.

Human Intracranial Electrophysiology

Human intracranial electrophysiology (HIE) techniques have been used since the 1950's for characterization of epilepsy in people who experience seizures despite optimal treatment with medications. The clinical goal of HIE is to establish which regions of the brain generate seizures and to determine if surgical removal of this tissue is possible. Following the implantation of intracranial electrodes, regions of the brain that are epileptogenic are identified. In addition, areas around

epileptogenic tissue are tested for cognitive and sensorimotor function by electric current stimulation via the implanted electrodes.

Secondary to the clinical goals, HIE techniques can be used for research by allowing measurement of localized brain activity during the performance of cognitive tasks (Engel *et al.* 2005; Adolphs. 2007). The type of brain activation seen using HIE techniques depends mainly on the type of electrode used for recording. If macroelectrode contacts (2–5 mm discs) are used, then LFPs can be recorded. If microelectrodes (20–40 μ wires) are used, then activity of single neurons is seen and referred to as single-unit activity (SUA). In addition to measurements of brain activation, electrical brain stimulation (EBS) via macroelectrode contacts can be used to determine if temporary neural suppression or activation leads to an effect on cognitive function.

Advantages of HIE Methods

HIE methods allow for the measurement of electrical activity similar to scalp EEG but with greater spatial resolution, better gamma frequency resolution (30–150 Hz activity) and higher signal-to-noise ratio (Mukamel and Fried, 2012). Compared to functional MRI, HIE techniques offer comparable spatial resolution but with microsecond temporal resolution which is on the same order of magnitude as the speed of cognitive processing. Furthermore, HIE recordings are somewhat immune to muscle and eye movement artifact (Kovach *et al.*, 2011). This allows for the study of phenomena involving motor actions which is difficult when using functional MRI, such as laughter.

An additional major advantage of HIE methods includes the ability to deliver targeted EBS which is useful for making causal inferences. Methods like EEG, fMRI and intracranial recordings can establish covariance between brain and behavior but temporal precedence and third-variable exclusion is necessary to make a causal inference. HIE stimulation techniques have the advantage of the stimulation having temporary effects (*vs* lesion) and having the ability to record from the same electrodes used for stimulation (*vs* TMS). Intraoperative stimulation procedures can also afford the opportunity to stimulate subcortical and white matter tracts (Duffau, 2010). The induction of distinct behaviors with EBS offers compelling evidence that this brain region is in some way involved in the neural representation of that emotional state.

Signal analysis techniques used in HIE are similar to techniques for scalp EEG (Makeig *et al.*, 2004). If the question is focused on looking at the neural signal during a specific event, there are time-locking methods for looking at the evoked potentials or the frequency distribution. If the question is focused on looking at the similarity of processing across brain areas, then techniques that are similar to fMRI network analysis can be used (Lachaux *et al.*, 2003).

Limitations of HIE techniques

Several significant limitations of HIE techniques exist. First, the recordings are performed in patients with epilepsy, not neurotypical subjects. While it is true that parts of their brains are impaired, it is not correct to assume that the entire brain is pathological. A historical example of how data from intracranial patients can inform healthy brain activity is Wilder Penfield's work on the somatotopic organization of primary sensory and motor cortex. Intracranial electrodes are generally implanted to cover wide areas of the brain with the goal of understanding which brain regions are pathological and which are healthy. Electrodes which record from pathological brain areas are excluded from analysis.

Second limitation of HIE research is the issue of limited spatial coverage in a single patient. In fact, as many as 10 000 intracranial recording sites would be necessary to get the same whole-brain spatial coverage as fMRI (Lachaux *et al.*, 2003). This limitation can be partially circumvented by hypothesis-driven study designs which ask questions about focal networks. For instance, a typical intracranial electrode placement for suspected temporal lobe epilepsy may cover the amygdala, hippocampus, temporal pole, temporal neocortex and occipital-temporal cortex. This implant strategy may allow for the testing of hypotheses regarding visual processing of fear-inducing stimuli. However, this implant strategy does not allow for the understanding of how the rest of the brain functions during the task.

Third limitation of HIE research involves inferences which can be drawn from EBS. EBS can either activate a brain region (e.g. causing hand movements during stimulation of the motor cortex), inhibit a brain region (e.g. causing language arrest during stimulation of Broca's area), or activate a whole sub-network distant to the site of stimulation (David *et al.*, 2010; Mandonnet *et al.*, 2010). Therefore, the experience of fear during stimulation of the amygdala may result from activation of the amygdala itself, may result from activation of a distant brain region via neural connections, or conversely may result from disinhibition of a distant brain region by inhibition of the amygdala. Furthermore, it is difficult to assess from stimulation experiments the extent of the brain volume which is influenced by the stimulation. Some of these uncertainties have been addressed by reports of good motor outcomes in surgical resections up to 1 cm of cortical distance from eloquent regions mapped by stimulation (Gregorie and Goldring, 1984). In addition, during EBS it is often noted that adjacent electrode sites are not affected by the stimulation.

The authors are interested in the use of HIE to study the neural basis of emotions because the methodology has many strengths which complement conventional neuroimaging. The goals of this review are 2-fold. First, we aim to organize the findings from half-a-century of HIE research into human emotions. Second, we aim to draw conclusions on what the evidence from HIE adds to our present understanding of the neural representation of emotions. By the end of the manuscript, we will see how the current HIE evidence gives answers to the following questions: (i) Are emotional responses localized specifically and consistently to specific brain regions or are they widely distributed? (ii) Do experience, expression and perception share any neural machinery? (iii) Is there any (absolute or relative) hemispheric lateralization during emotion?

CRITERIA FOR INCLUSION

A Pubmed and Google Scholar search was performed using the following keywords: emotions, social, face, intracranial, iEEG, EcOG, cortical stimulation, deep brain stimulation, laughter, intraoperative, sad, fear, mirth, dyad. For the purpose of finding as many articles as possible for this review, three delineating terms for different emotion phenomena needs to be defined. We will be defining emotional perception as the cognitive capability to perceive the emotion of another human being. Emotional expression will be defined as the motoric act associated with having an emotion. This is independent from the emotional experience, which is the subjective feeling associated with an emotional event. Several related topics were not included in this review. Studies investigating reward processing, learning, and decision making were omitted (for review, see Oya *et al.*, 2005; and Lega *et al.*, 2011). Second, studies aimed at investigation of DBS in treatment of mood disorders were not included (for review, see Holtzheimer and Mayberg, 2011). Lastly, studies of pain experience were not included (for review, see Selimbeyoglu and Parvizi, 2010). Only English-language articles and chapters were used.

QUALITATIVE FINDINGS

Overview of articles

Sixty-four studies which investigated emotional processing using HIE methods were identified. Year of publication ranged from 1954

to 2012. Twenty-one studies examined neural activity during perception of emotional states in others (Table 1). Twenty-seven studies examined neural activity during the experience of negatively valenced emotional states (Table 2) and 12 papers during the experience of positively valenced emotional states (Table 3). Eleven studies examined neural activity during the motoric expression of emotional states (Table 4). Some papers are listed under more than one table. The investigated brain regions include significant portions of the temporal, frontal, parietal and occipital neocortex, multiple limbic areas including the hippocampus, amygdala, insula and cingulate gyrus, and several subcortical regions including the subthalamic nucleus, substantia nigra, zona incerta and various parts of the internal capsule. To see this same data organized by brain regions, please refer to tables in the Supplementary Data.

The studies reviewed varied in many ways. There was a lack of consistent methodological standardization in the study designs, stimulus presentation, recording techniques, analysis techniques and electrode localization methods. In addition, most authors did not describe the exact type of epilepsy that the patient was suffering from or how trials or electrodes with epileptic activity were excluded from the analysis. For these reasons, quantitative meta-analysis was not possible with this data. In turn, data were organized in a semi-quantitative fashion based on reported neuroanatomy and descriptions of emotional processes.

Perception of emotional states in others

Most investigators used pictures of static faces with emotional expressions as stimuli and recorded neuronal activity in the fusiform gyrus, the amygdala and multiple regions of the temporal and frontal lobes (Table 1). Other tasks included studying emotional prosody either in a specific emotion framework or on a positive/negative gradient scale.

Experience of positively and negatively valenced emotional states

Emotional experience was studies by two distinct methods. The first method involved measuring neural activity during the presentation of emotionally provocative stimuli, such as International Affective Picture System (IAPS) pictures. These pictures were designed to evoke changes in different aspects of emotion experience in general (e.g. valence and arousal) and do not elicit a specific emotion per se. The second method involved subjective reports of emotional states induced by electrical stimulation of various brain regions (Tables 2 and 3). Stimulation findings are primarily incidental in that the emotional experience was spontaneously elicited and self-reported by the patients.

Motoric execution of emotional expression

Studies in this section include reports of elicitation of facial expression of an emotional state with the subject reporting no associated emotional experience. Regions of the brain include areas of the frontal lobe and subcortical structures (Table 4). Many of these expressions elicited were complex phenomena like laughing or crying without the appropriate emotion. The more subtle emotional expressions elicited are taken on face value from the clinician's reports but future researchers should take care that these motoric acts are specific to emotions and not under voluntary control for communicative purposes (Fridlund, 1991).

DISCUSSION

The study of emotions in the human brain using HIE techniques dates back almost 60 years to the pioneering work of Wilder Penfield. Studies reviewed can be divided into two main types. The first type includes studies which aimed to measure brain activation during viewing of emotionally provoking stimuli. The types of stimuli included presentation of faces with emotional facial expressions (e.g. Ekman

Table 1 Emotion perception

Study	Year	Type of study	Areas	Results
Krolak-Salmon *et al.*	2003	ERP, Stimulation	Anterior insula	Regions with differential potentials for disgust face perception also elicit negative valence experience during stimulation
Krolak-Salmon *et al.*	2004	ERP	Amygdala	Amygdala active in fear perception > other emotions
Tsuchiya *et al.*	2008	ERP	Fusiform, STS	Fusiform gyrus participates in emotion decoding
Pourtois *et al.*	2010a	ERP	Fusiform	Early face response and late emotion and eye direction response
Pourtois *et al.*	2010b	ERP	Amygdala	Different early and late responses in amygdala. Only late modulated by attention.
Jung *et al.*	2011	ERP	Lateral orbitofrontal	OFC active in negative emotion processing
Rømer-Thomsen *et al.*	2011	ERP	ACC	ACC showed differences between happy and sad faces ~500 ms
Ojemann *et al.*	1992	Single unit	Right lateral temporal	SUA to facial emotion perception.
Fried *et al.*	1997	Single unit	Hippocampus, amygdala	SUA to facial emotion encoding and recognition.
Fried *et al.*	1982	Stimulation	Lateral temporal	Impaired judgment of emotional facial expressions.
Péron *et al.*	2010a	Stimulation	STN	Impairment of recognition for sad and fearful facial expressions
Péron *et al.*	2010b	Stimulation	STN	Impairment in recognizing the emotional prosody in speech stimuli.
Mukamel *et al.*	2010	Single Unit	SMA, MTL	Responsive firing for emotional face perception and execution
Brück *et al.*	2011	Stimulation	STN	Enhanced processing of highly-conflicting emotional messages.
Marinkovic *et al.*	2000	ERP, Stimulation	Anterior inferior PFC	Intracranial recording and stimulation evidence found cortex sensitive for faces (including hallucinations of faces when stimulated). Area was resected and produced deficits in emotional face recognition (especially fear)
Sato *et al.*	2011	iEEG	Amygdala	Greater gamma-band activity in response to fearful compared with neutral facial expressions between 50 and 150 ms
Biseul *et al.*	2005	Stimulation	STN	Impaired recognition of fear expressions
Schroeder *et al.*	2004	Stimulation	STN	Impaired recognition of angry expressions
Dujardin *et al.*	2004	Stimulation	STN	Impaired recognition of angry and sad expressions
Drapier *et al.*	2008	Stimulation	STN	Impaired recognition of fear and sad expressions. Apathy scores had also worsened after DBS implantation.
Le Jeune *et al.*	2008	Stimulation, PET	STN, orbitofrontal	Impaired recognition of fear faces. These results positively correlate with glucose metabolism in the right orbitofrontal cortex.

Abbreviations: ACC, Anterior cingulate cortex; ERP, Event-related potentials; iEEG, Intracranial electroencephalography; MTL, Medial temporal lobe; PET, Positron emission tomography; PFC, Prefrontal cortex; SMA, Supplementary motor cortex; STN, Subthalamic nucleus; STS, Superior temporal sulcus

Table 2 Experience of negative emotional states

Study	Year	Type of study	Areas	Results
Oya *et al.*	2002	ERP	Amygdala	Response to negative emotions
Naccache *et al.*	2005	ERP	Amygdala	Response to emotional words
Kawasaki *et al.*	2001	Single Unit	vmPFC	Response to negative emotional states
Penfield	1958	Stimulation	ITL	Fear
Penfield and Perot	1963	Stimulation	STG, TPJ	Fear
Bancaud *et al.*	1994	Stimulation	STG	Fear
Meletti *et al.*	2006	Stimulation	MTL, Amygdala	Of the 79 emotional responses elicited, 67 were fearful, 9 were happy, and 3 were sad. 12% of these responses were in the amygdala and these were all fear responses.
Lanteaume *et al.*	2006	Stimulation	Amygdala	Right amygdala induced negative emotions, especially fear and sadness. Left amygdala was able to induce either pleasant (happiness) or unpleasant (fear, anxiety, sadness) emotions.
Halgren *et al.*	1978	Stimulation	Amygdala, Hippocampus	Fear, sadness, anger.
Mazzola	2009	Stimulation	Insula	Fear, anxiety
Feindel and Penfield	1954	Stimulation	Insula	Fear
Ostrowsky *et al.*	2002	Stimulation	Temporal pole	Anxiety, sadness
Gordon *et al.*	1996	Stimulation	Temporal pole	Positive and negative emotions
Mullan et. al	1959	Stimulation	MTG, STG, Insula	Fear
Van Buren	1961	Stimulation	MTL	Fear, laughter
Fish *et al.*	1993	Stimulation	Amygdala, Hippocampus	Fear
Blomstedt *et al.*	2008	Stimulation	STN	Stimulation caused acute transient depression with crying and feeling of not wanting to live.
Benedetti *et al.*	2004	Stimulation	STN, zona incerta, substantia nigra pars reticulata	Zona incerta and the dorsal pole of the subthalamic nucleus produced autonomic responses that were constant over time. In contrast, the stimulation of the ventral pole of the subthalamic nucleus and the substantia nigra pars reticulate produced autonomic and emotional responses that were inconstant over time and varied according to the condition.
Tommasi *et al.*	2008	Stimulation	STN, substantia nigra, zona incerta, fields of forel	Stimulation caused acute transient depression.
Bejjani *et. al*	1999	Stimulation	Left substantia nigra	Stimulation caused acute transient depression with crying and feeling of hopelessness.
Okun *et al.*	2004	Stimulation	STN	All leads elicited pathological crying but one lead elicited fear, one elicited anxiety, and the rest had no emotion at all.
Brázdil *et al.*	2009	ERP	Medial and lateral temporal, medial and lateral PFC, posterior parietal, precuneus and insula	Unpleasant pictures elicited more activity in temporal and frontal regions. Significant findings to emotional stimuli were found in rarely investigated regions (posterior parietal, precuneus and insula).
Krolak-Salmon *et al*	2003	ERP, Stimulation	anterior insula	Regions with differential potentials for disgust face perception also elicit negative valence experience during stimulation
Smith *et al.*	2006	Stimulation	cingulate, OFC, MTL, amygdala and insula	Negative responses were more associated with right-sided stimulation. Positive responses were found in each hemisphere (left ACC, right insula).
Vicente *et al.*	2009	Stimulation	STN	Lower levels of differentiating sad and fearful videos and less intense feelings towards negative valence videos.
Sabolek *et al.*	2009	Stimulation	STN, substantia nigra	Acute fear induced with right substantia nigra stimulation. Depressive feelings induced with caudal STN stimulation.
Burdick *et al.*	2011	Stimulation	STN, Globus pallidus interna, Vim	STN and GPi DBS were associated with higher anger scores. It was not confirmed if this was a lesion or a stimulation effect.

Abbreviations: ACC, Anterior cingulate cortex; ERP, Event-related potentials; iEEG, Intracranial electroencephalography; ITL, Inferior temporal lobe; MTG, Middle temporal gyrus; MTL, Medial temporal lobe; PET, Positron emission tomography; PFC, Prefrontal cortex; OFC, Orbitofrontal cortex; SMA, Supplementary motor cortex; STG, Superior temporal gyrus; STN, Subthalamic nucleus; TPJ, Temporoparietal junction; Vim, Ventral intermediate nucleus; vmPFC, Ventral medial prefrontal cortex

faces), presentation of emotionally provoking pictures (e.g. IAPS pictures) and audio presentations of emotionally provoking stories. In these studies, brain activity was measured using one of several methods: time-locked analysis of evoked LFPs, frequency analysis of synchronization or desynchronization, or change in the firing frequency of a neuron if recording SUA. Second type of study involved EBS of specific brain regions and measuring of either self-reports of descriptions of evoked emotional states or measuring the ability of the patient to detect emotional states in others.

Synthesis of reviewed articles

HIE techniques offer evidence in support of six conclusions with regards to the neural representation of emotions:

(1) ***Evidence from HIE methods supports a model of widely distributed representations of emotions spanning the subcortical nuclei, the limbic/paralimbic regions and the neocortex (Figure 1).*** Evidence from HIE suggests that subcortical nuclei play an important role in representation of emotional states. Stimulation of subcortical nuclei such as the STN can impair perception of sadness, fear and anger and impair recognition of emotional prosody in speech stimuli (Table 1). Stimulation of STN, zona incerta, substantia nigra pars reticulata, fields of Forel, globus pallidus interna and ventral intermediate nucleus of thalamus can induce experience of sadness and crying (Table 2) while stimulation of the nucleus accumbens, anterior limb of the internal capsule, and ventral STN has been associated with sensation of joy and mirth (Table 3). In addition, recording of LFPs and stimulation of amygdala, hippocampus, insula, orbitofrontal cortex, temporal pole and anterior cingulate cortex clearly points to limbic/paralimbic representation of emotional states (Tables 1, 2 and 3). Furthermore, HIE evidence implicates neocortical regions in representation of emotional states. Stimulation of the basal temporal lobe, superior

Table 3 Experience of positive emotional states

Study	Year	Type of study	Areas	Results
Satow *et al.*	2003	Stimulation	Left ITL	Mirth or mirth with laughter depending on intensity of stimulation
Gordon *et al.*	1996	Stimulation	Temporal pole	Positive and negative emotions
Van Buren	1961	Stimulation	MTL	Fear, laughter
Meletti *et al.*	2006	Stimulation	MTL, Amygdala	Of the 79 emotional responses elicited, 67 were fearful, 9 were happy, and 3 were sad. 12% of these responses were in the amygdala and these were all fear responses.
Lanteaume *et al.*	2006	Stimulation	Amygdala	Right amygdala induced negative emotions, especially fear and sadness. Left amygdala was able to induce either pleasant (happiness) or unpleasant (fear, anxiety, sadness) emotions.
Smith *et al.*	2006	Stimulation	ACC, OFC, MTL, amygdala, and insula	Negative responses were more associated with right-sided stimulation. Positive responses were found in each hemisphere (left ACC, right insula).
Haq *et al.*	2011	Stimulation	ALIC, Nucleus accumbens	After stimulation, patients felt mirth followed by a smile or laugh. For sites with smiling or laughing, the mood was congruent in 28 of 31 conditions. For sites with smiling or laughing, mood positively correlated with voltage.
Krack *et al.*	2001	Stimulation	STN	Laughter with mirth was elicited in two Parkinson's patients. When the stimulation was set to the therapeutic parameters, there is an improvement in akinesia symptoms
Stefan *et al.*	2004	Stimulation	Temporal, frontal, parietal	Ictal pleasantness localized mainly to temporal mesiobasal areas, but also found it localized in frontal and parietal in a minority of patients.
Greenhouse *et al.*	2011	Stimulation	Ventral STN	Ventral contact stimulation led to an increase of positive emotion.
Fernandez-Baca Vaca	2011	Stimulation	Left IFG	Mirth and laughter
Arroyo *et al.*	1993	Stimulation	ACC, parahippocampal, fusiform	Patient with gelastic seizures without mirth had onset at left ACC. Other patients elicited laughter with mirth when stimulated around the fusiform and parahippocampal gyri.

Abbreviations: ACC, Anterior cingulate cortex; ALIC, Anterior limb of the internal capsule; ITL, Inferior temporal lobe; MTL, Medial temporal lobe; OFC, Orbitofrontal cortex; STN, Subthalamic nucleus

Table 4 Isolated motoric expression of emotion

Study	Year	Type of study	Areas	Results
Davis *et al.*	2005	Single unit	Caudal ACC	Attention-demanding stroop task involving emotional content can alter the firing rate
Mukamel *et al.*	2010	Single unit	SMA, MTL	Responsive firing for emotional face perception and execution
Chassagnon *et al.*	2008	Stimulation	Cingulate motor area	In one patient, the urge to laugh without mirth was elicited
Fried *et. al*	1998	Stimulation	SMA	The duration and intensity of the laughter increased with stimulation current. Smiling was induced at lower currents. The patient consistently contributed the laughter to some outside source.
Sperli *et al.*	2006	Stimulation	Right cingulate	Stimulation induced smiling and laughing without mirth.
Schmitt *et al.*	2006	Stimulation	SMA and pre-motor area	Laughter without mirth was elicited.
Bartolomei *et al.*	2005	iEEG	ACC, orbitofrontal, amygdala, temporal pole	Negative motoric expression preceding seizures located in ACC, Orbitofrontal, and Temporal Pole. These expressions also associated with signal decorrelation between orbitofrontal and amygdala.
Arroyo *et al.*	1993	Stimulation	ACC, parahippocampal, fusiform	Patient with gelastic seizures without mirth had onset at left ACC. Other patients elicited laughter with mirth when stimulated around the fusiform and parahippocampal gyri.
Krolak-Salmon *et al.*	2006	iEEG, Stimulation	SMA	Stimulation of left pre-SMA consistently got a smile or a laugh from the patient when stimulated (needed at least 0.6 mA at 50 Hz). The patient reported the mirth followed the movement. At .8mA, crying followed the laughter. The field potentials in this area responded mainly for happy faces.
Wojtecki *et al.*	2007	Stimulation	STN	Pathological crying
Low *et al.*	2008	Stimulation	Caudal internal capsule	Pathological crying
Hiyoshi *et al.*	1989	iEEG	Lateral and mesial temporal lobe	Disgust expression with mesial temporal focus and happy expression with lateral temporal focus.

Abbreviations: ACC, Anterior cingulate cortex; iEEG, Intracranial electroencephalography; MTL, Medial temporal lobe; SMA, Supplementary motor cortex; STN, Subthalamic nucleus

temporal gyrus, middle temporal gyrus, temporal-parietal junction, inferior frontal gyrus and supplementary motor area has been shown to induce states of fear and mirth (Tables 2 and 3).

(2) ***HIE methods supports the idea that emotional state categories (such as fear) are represented in multiple brain areas (Figure 2).*** Evidence comes especially from EBS studies. For example, self-reported experience of fear has been evoked by EBS of the amygdala, insula, inferior temporal lobe, middle temporal gyrus, superior temporal gyrus, hippocampus, temporo-occipital junction and even substantia nigra (Table 1). Furthermore, experience of mirth has been evoked by EBS of left inferior temporal lobe, left inferior frontal gyrus, supplementary motor area, cingulate gyrus, parahippocampal and fusiform gyri (Table 1). Further evidence comes from ERP studies showing for instance that the hippocampus, amygdala, pre-frontal cortex, insula and precuneus activate during presentation of fearful stimuli (Brázdil et al., 2009).

(3) ***HIE methods support the existence of right hemisphere dominant networks for representation of negatively valenced emotional states (e.g. fear) and left-hemisphere dominant networks for positively valenced emotions states (e.g. mirth) (Figure 3).*** Evidence for hemispheric dominance for emotional valence comes primarily from qualitative analysis of EBS studies. Multiple investigators report the induction of negatively valenced emotional states (e.g. fear, anger, sadness) with EBS of the right hemisphere and

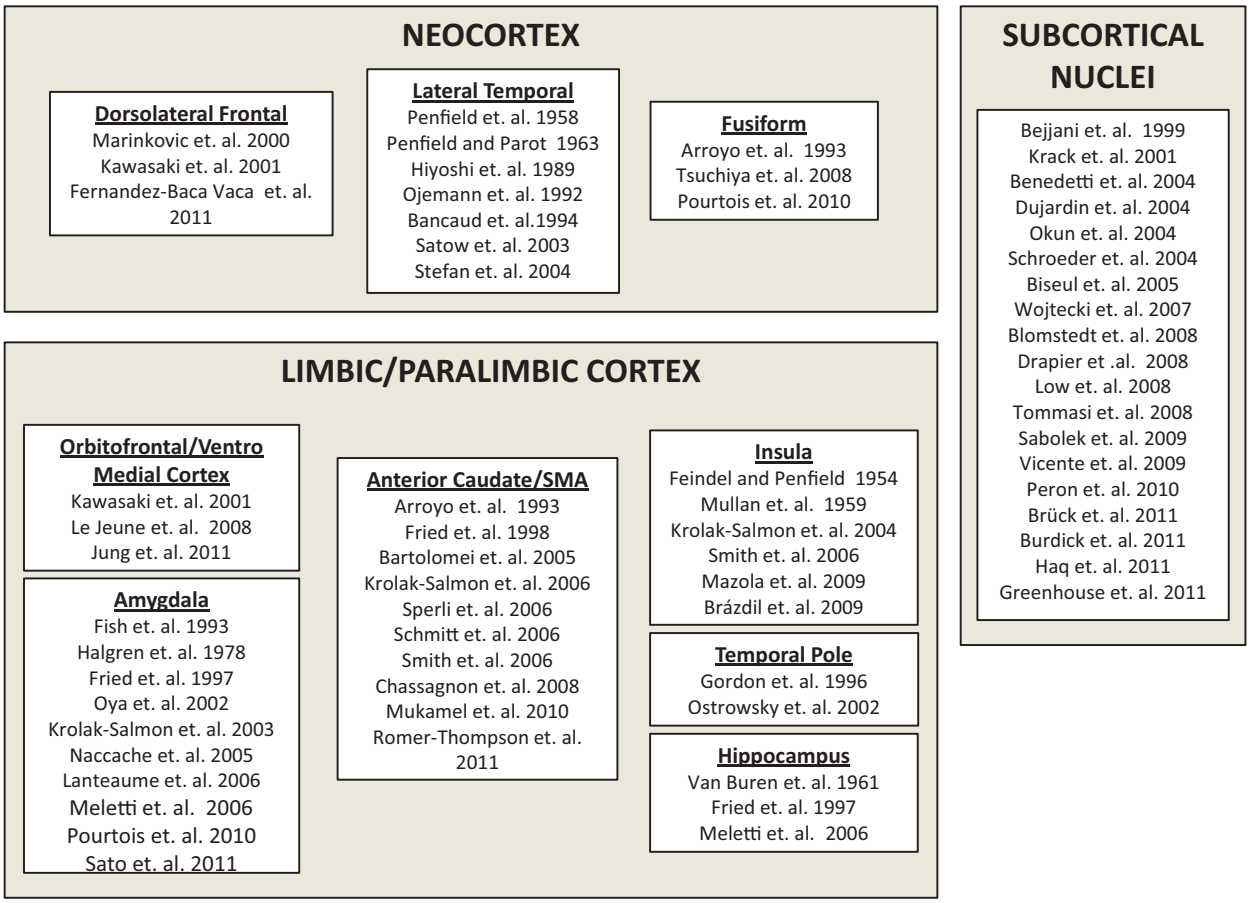

Fig. 1 HIE studies which reported neural representation of emotional states separated by region.

positively valenced emotional states (e.g. mirth) with EBS of the left hemisphere (Tables 2 and 3). However, HIE studies do not suggest absolute separation of emotional valence by hemisphere, only dominance. For example, stimulation of the left amygdala can induce either pleasant (e.g. happiness) or unpleasant (e.g. fear) emotions (Lanteaume *et al.*, 2006).

(4) ***Evidence from HIE methods supports the existence of distinct yet partially overlapping neural systems for emotion perception, emotion experience, and formation of emotional motoric acts (Figure 4)***. This conclusion is supported by EBS studies, by LFP recordings, and by SUA recordings. EBS of regions in the neocortex, limbic/paralimbic cortex or deep nuclei has been shown to induce motoric expressions of emotional states without the accompanied emotional state as reported by the patient. For example, EBS of the left SMA cortex elicited 'laughter without mirth', and stimulation of the STN induced 'crying without sadness' (Table 4). An interesting EBS study by Satow *et al.* found the experience of 'mirth only' with low EBS intensities and 'mirth accompanied by laughter' at high EBS intensities (Satow *et al.*, 2003). These findings suggest that neural regions for *emotion expression* and *emotion experience* are distinct but partially overlapping. Further support for this conclusion comes from LFP recordings and EBS studies of the amygdala. The amygdala activates during perception of negatively valenced emotional faces, during experience of negatively valenced emotional states and EBS of the amygdala can induce the experience of negatively valenced emotional states (Tables 1, 2 and 3). Lastly, this conclusion is supported by single unit recordings in the SMA and basal temporal cortex by Mukamel *et al.* which revealed that not only the same region, but also the same neuron can fire during perception and during motoric execution of emotional faces (Mukamel *et al.*, 2010). These findings are largely consistent with concepts gleamed from fMRI (Grimm *et al.*, 2006; Schiller and Delgado, 2010; Satpute *et al.*, 2013).

(5) ***HIE methods elucidate the dynamics of neural activation (Figure 5)***. The high temporal resolution of HIE methods offers a unique window into the mechanics of human cognition. A fantastic example comes from recording of LFPs during processing of facial expressions as reported by multiple investigators. In these studies, intracranial macroelectrodes are placed over occipital, lateral temporal, amygdalar and orbitofrontal regions. Following the presentation of a photograph depicting a face with emotional expression, initial activation occurs in the primary visual cortex ~100 ms following stimulus presentation. Next, activation in the fusiform face area (FFA) occurs at 120–200 ms following presentation of facial stimuli but not to non-facial stimuli (e.g. Pourtois *et al.*, 2010a). Next, the FFA and the superior temporal gyrus (STG) activate to morphing emotional faces between 200 and 500 ms (Tsuchiya *et al.*, 2008). Surprisingly, activation of the amygdala to fearful expressions occurs within 200 ms following stimulus presentation, which precedes activation in the FFA, STG and orbitofrontal cortex (Krolak-Salmon *et al.*, 2004). This suggests that the amygdala may modulate the activity of the FFA in a retrograde fashion. Last, activation of the orbitofrontal cortex occurs 500–1000 ms following presentation of fearful stimuli (Jung *et al.*, 2011). Amygdala and temporal lobe findings are consistent

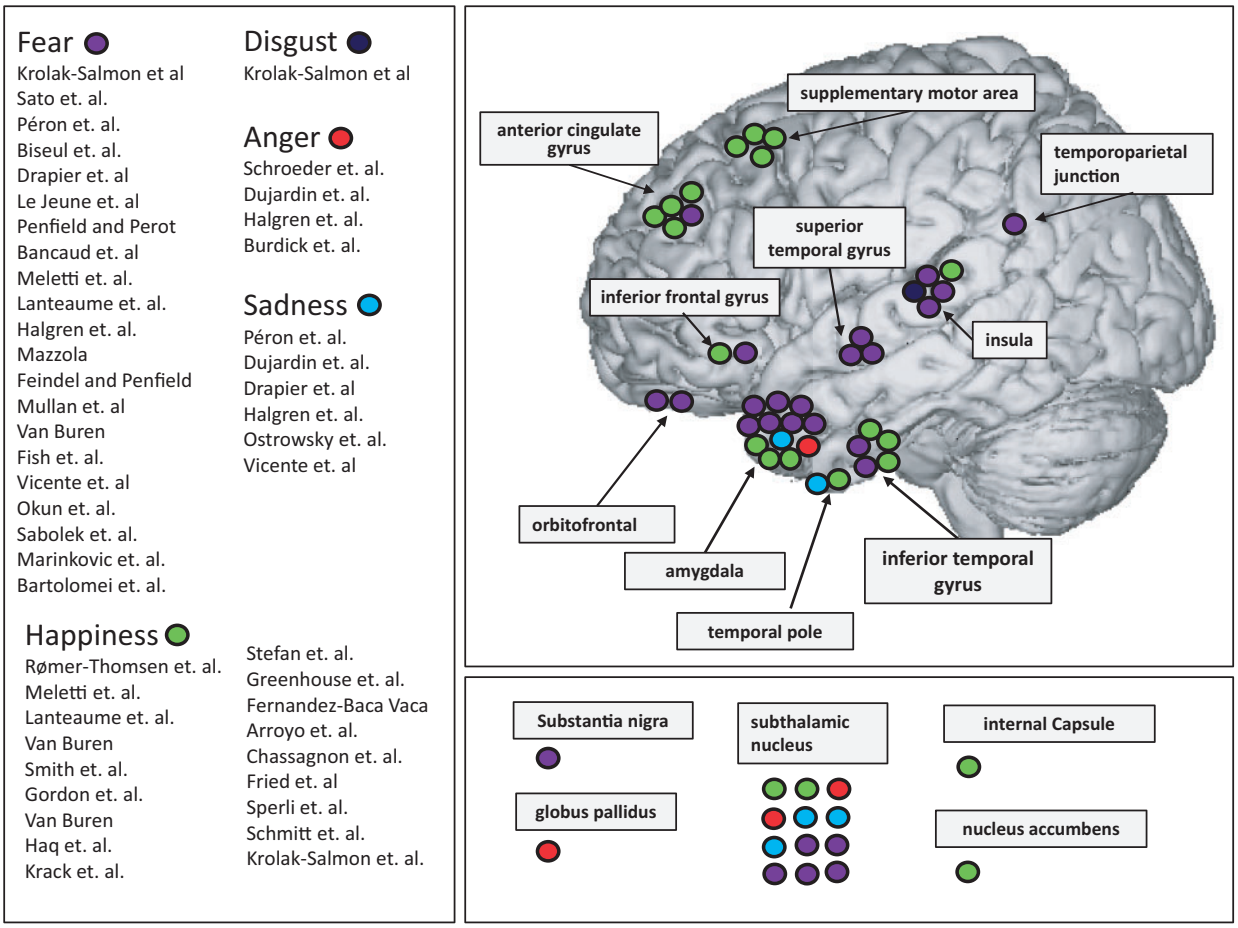

Fig. 2 HIE studies which reported neural representation of emotion separated by emotion type.

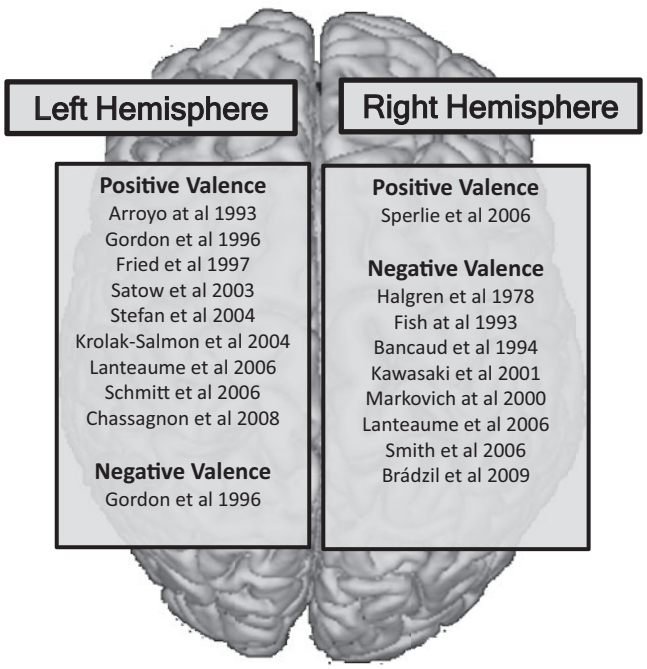

Fig. 3 Valence-based hemispheric dominance of emotions in HIE studies

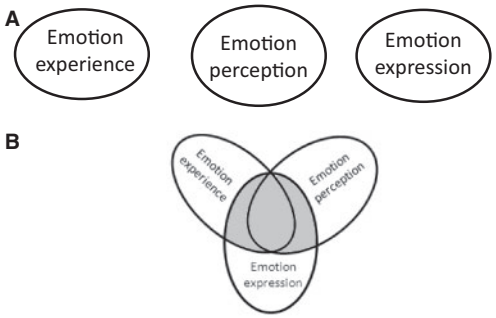

Fig. 4 Graphic conceptual depictions of two distinct models of the neural representation of emotion processing. (**A**) Emotion experience, perception and expression are distinctly represented in the brain. (**B**) Emotion experience, perception and expression share partial overlapping representation. HIE studies support this model.

with previous EEG/MEG reviews (Pessoa and Adolphs, 2010) but much faster (<200 ms) activity has been observed in frontal scalp EEG findings (Barrett and Bar, 2009). Localizing neural sources from scalp responses is problematic and it cannot be assumed that the electrical activity came from parenchyma adjacent to the cortex. Nonetheless, it is interesting that sub-100 ms activity has been observed in scalp studies and where this activity is localized would be an excellent future direction.

(6) ***HIE methods suggest that the processing function of brain regions may change with respect to the temporal latency from the***

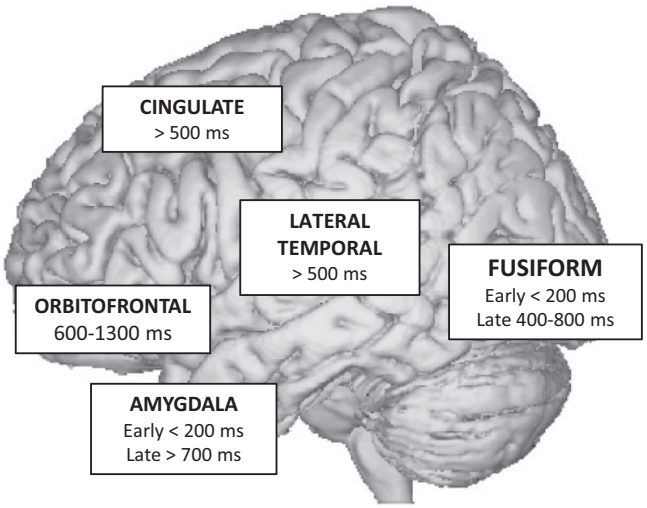

Fig. 5 HIE provides information on the temporal sequence of activation during perception of emotional faces.

stimulus onset. The FFA shows early activation to faces independent of facial emotion at ~200 ms and distinct late activation based on facial emotion and eye direction at ~500 ms (Pourtois *et al.*, 2010a). This finding provides evidence to suggest that the role of a certain brain region in cognitive processing may change depending on the latency from stimulus presentation, i.e. the FFA processes all faces early and only later processes facial emotion. The high temporal resolution of HIE suggest a slightly different model of emotion processing as compared to fMRI. HIE model suggests that FFA processes most of the information during perception of static and dynamic facial expressions, the only difference being the latency from stimulus presentation.

CONCLUSIONS AND COMPARISON TO NON-HIE EVIDENCE

Evidence from HIE methods supports several general conclusions. First, HIE offers strong evidence against the existence of super-specialized macro-anatomical structures for representation of single emotion categories (e.g. amygdala for fear) but rather offers evidence that their representation is more broadly distributed between the subcortical nuclei, the limbic/paralimbic regions, and the neocortex. Although many investigators report clear descriptions of emotional experiences during EBS of neuroanatomically confined areas (i.e. fear with amygdala), induction of same emotional experiences have been reported during EBS of many other areas (e.g. insula, parahippocampal gyrus) with significant variability between studies. Evidence from HIE for broad distribution of emotional representation is largely consistent with neuroimaging and animal studies, especially for subcortical and limbic system involvement. However, it is important to note clear and strong evidence from HIE for neocortical involvement in emotion representation in light of the controversy in this area (Barrett *et al.*, 2007; Panksepp, 2007).

Second, HIE methods offers modest evidence in support of hemispheric specialization for positive or negative emotional valence, with left hemisphere being dominant for positive and right hemisphere dominant for negative emotion valence. The neuroimaging literature has mixed results when it comes to laterality differences. Some work finds left prefrontal as primarily involved with approach mechanisms while right prefrontal as involved with avoidance mechanisms (Spielberg *et al.*, 2013). Other neuroimaging reviews do not find laterality differences (Kringelbach and Rolls, 2004) or found laterality with opposite valences assigned (Wager *et al.*, 2008).

Third, HIE methods offer strong evidence that neural representation of emotion observation, emotion experience, and emotion expression are partially dissociated and partially overlapping, findings which are largely consistent with neuroimaging and animal research. Evidence from HIE offers further support to the theory of embodied cognition which holds that the nature of the human mind is largely determined by the form of the human body (Niedenthal *et al.*, 2005; Barrett, 2006). Further research needs to be done in terms of better outlining the overlap of emotional processes in the brain and this is one topic which is uniquely situated for HIE methods to explore.

Fourth, HIE reveals that processing of emotional information has complex dynamics which may be largely imperceptible to fMRI. The temporal sequence of activation gleaned during processing of facial emotion observation can be extended to other emotional processes. In addition, HIE evidence that same brain area processes different information depending on the temporal latency from stimulus onset (i.e. temporally dependent processing) cannot be adequately investigated using fMRI. Temporal latency dependence for function has been briefly hypothesized in previous fMRI work (Lindquist *et al.*, 2012) but it is still currently untested in the imaging modality.

Future directions

HIE methods have been largely underutilized in the study of emotional phenomena in humans. For instance, the approach successfully utilized to study temporal dynamic of amygdalar activation during perception of fearful stimuli has not been utilized in the study of other emotion categories. In addition, despite being well suited to clarify long-standing dispute over the existence of basic emotions, core affect or psychological primitives HIE methods have never been used to investigate these concepts. For instance, SUA methods have the necessary spatial-temporal resolution to uncover if individual emotion categories can be further broken down into more basic component parts. Furthermore, while the HIE results do not show single localization for an emotional process, there has yet to be reported evidence of functional connectivity between involved brain regions the same way that it's been show in fMRI research. It is entirely possible to do this with HIE techniques, in fact, there is the added benefit of being able to stimulate across electrodes to causally test connectivity but it simply has not been done.

In future studies, we encourage HIE researchers to obtain exact stereotactic coordinates for electrode placement to make meta-analyses a feasible option. In addition, we encourage HIE researchers to utilize standardized scales of emotional assessment as self-reported measures are imprecise.

The main indication for HIE is to define the borders between pathological and functionally necessary brain regions. Unfortunately, the only cognitive domains typically mapped during routine clinical practice are motor and language while mapping for social and emotional phenomena has not reached clinical threshold. In our opinion, the goals of HIE should be elevated to encompass mapping cognitive functions that are specific to the patient's individual personality, occupation, hobbies and social life. With as long as HIE methods have been around, mapping for social and emotional phenomena has not reached established methods as with sensorimotor and language mapping. To make this mission a reality will take more basic research (invasive and non-invasive) that is aimed at these goals. There are many types of studies that have not been run with HIE and the technology is steadily improving to allow for more 'wireless' studies of brain activity so one could study how real life situations and contexts may influence emotional processing (which could answer long standing debates on how emotions are represented in the brain). With the combination of non-invasive and HIE methods, the only thing to limit finding out about

emotional phenomena are the questions asked and the experiments commenced.

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