



Intensity of affective experience is modulated by magnitude of intracranial electrical stimulation in human orbitofrontal, cingulate and insular cortices

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Abstract

The subjective and behavioral effects of intracranial electrical stimulation (iES) have been studied for decades, but there is a knowledge gap regarding the relationship between the magnitude of electric current and the type, intensity and valence of evoked subjective experiences. We report on rare iES data from 18 neurosurgical patients with implanted intracranial electrodes in the orbitofrontal cortex (OFC), the insula (INS) and the anterior portion of cingulate cortex (ACC). ACC stimulation elicited somatic and visceral sensations, whereas OFC stimulation predominantly elicited olfactory and gustatory responses, and INS stimulation elicited a mix of effects involving somatic and visceral sensations, olfaction and gustation. Further, we found striking evidence that the magnitude of electric current delivered intracranially correlated positively with the perceived intensity of subjective experience and the evoked emotional state, a relationship observed across all three regions. Finally, we observed that the majority of reported experiences were negatively valenced and unpleasant, especially those elicited by ACC stimulation. The present study provides novel case studies from the human brain confirming that these structures contribute causally to the creation of affective states and demonstrates a direct relationship between the magnitude of electrical stimulation of these structures and the qualia of elicited subjective experience.

Summary

This study provides critical knowledge about the effect of electrical charge magnitude on the intensity of human subjective experiences and emotional states. We shed light on the fundamental relationship between the electrical (physical) state of cortical tissue and the modality and intensity of human (subjective) experience. As electroceutical interventions are increasingly employed to treat neurological and psychiatric disorders, these findings highlight the importance of electrical stimulation magnitude for eliciting specific changes in human subjective experience.

Key words: intracranial electrical stimulation; emotion; subjective experience; qualia; consciousness; neuromodulation; intracranial EEG; deep brain stimulation; affective neuroscience

Received: 26 October 2018; Revised: 11 February 2019; Accepted: 18 February 2019

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Introduction

Emotion is an integral aspect of human experience, exerting a powerful influence over perception (Bar *et al.*, 2006; Phelps *et al.*, 2006), cognition (Fredrickson & Branigan, 2005; Harmon-Jones *et al.*, 2012) and behavior (Mauss *et al.*, 2005; Baumeister *et al.*, 2007). Affect is typically characterized by arousal, or the intensity of the experience, and valence, or how pleasant or unpleasant a stimulus is (Russell, 1980; Watson *et al.*, 1988). Beyond the clear importance of subcortical structures such as the amygdala, nucleus accumbens and various brainstem nuclei, affective neuroscience has implicated a diverse range of cortical regions in affective processing, especially the anterior portion of the cingulate cortex (ACC), the orbitofrontal cortex (OFC) and the insula (INS; Adolphs *et al.*, 2000; Eisenberger and Lieberman, 2004; Eisenberger *et al.*, 2006; Lewis *et al.*, 2006; Colibazzi *et al.*, 2010; Lamm and Singer, 2010; Lieberman and Eisenberger, 2015; Lindquist *et al.*, 2015; Dixon *et al.*, 2017; Gallo *et al.*, 2018). Functional neuroimaging has shown that these cortical structures are recruited during the appraisal (Lamm *et al.*, 2007; Dixon *et al.*, 2017), construction (Lindquist *et al.*, 2012) and regulation (Ochsner and Gross, 2005; Golkar *et al.*, 2012; Buhle *et al.*, 2014; Achterberg *et al.*, 2016) of affective experience, in both healthy people (Damasio, 2003; Panksepp, 2003; Izard, 2009) and those with clinical mood disorders (Bremner *et al.*, 2002; Davidson *et al.*, 2002).

The overwhelming majority of treatments for mood disorders in recent decades have used pharmacological interventions to modulate activity in these cortical regions. For instance, antidepressants and anxiolytics have been shown to decrease activity in the ACC and INS, which are hyperactive in patients with anxiety disorders (Mayberg *et al.*, 1997; Barbas *et al.*, 2003; Etkin and Wager, 2007; Paulus and Stein, 2006; Simmons *et al.*, 2009). Building on the discovery that intracranial electrical stimulation (IES) of the brain in neurosurgical patients alters both neural activity as well as subjective experience (Feindel and Penfield, 1954; Mullan and Penfield, 1959), clinicians are now seeking to go beyond purely pharmacological interventions by directly modulating affective experience in severe neuropsychiatric conditions using a variety of implanted and transcranial stimulation methods—hence the term electroceuticals (Famm *et al.*, 2013). As the use of deep brain stimulation (DBS) and related intracranial interventions is becoming increasingly common in the treatment of neuropsychiatric conditions, however (Roy *et al.*, 2018), initially promising clinical findings (Mayberg *et al.*, 2005) have often failed to replicate (Morishita *et al.*, 2014), prompting recognition that a more thorough and rigorous exploration of stimulation targets and parameters is necessary (Mayberg *et al.*, 2016; Fins *et al.*, 2017). Yet, overall, very little is known about the subjective emotional effects of electrical stimulation to most cortical regions. The few scattered case studies published to date suggest that the ACC, OFC and INS yield distinctive affective responses following electrical stimulation: stimulation of the ACC has been reported to elicit changes in autonomic reactivity (Pool and Ransohoff, 1949; Mangina and Beuzeron-Mangina, 1996; Mulak *et al.*, 2008; Parvizi *et al.*, 2013) as well as emotional experiences of anxiety and fear (Mulak *et al.*, 2008); stimulation of the OFC has elicited epigastric sensations (Mulak *et al.*, 2008) and emotionally valenced smells and tastes (Fox *et al.*, 2018); and INS stimulation has evoked anxiety and fear (Feindel and Penfield, 1954; Mullan and Penfield, 1959), pleasant affective experiences (Ostrowsky *et al.*, 2000), cardiovascular changes (Oppenheimer *et al.*, 1992), nausea (Feindel and Penfield, 1954) and sensations involving olfaction and gustation (Ostrowsky *et al.*, 2000).

As Guillory and Bujarski (2014) concluded in a recent review, extant findings from these case studies corroborate correlational neuroimaging data and confirm that the ACC, OFC and INS play a crucial role in affective experience, but a better understanding is clearly needed of both the specific parameters ideal for the neuromodulation of affect (e.g. optimal frequency, magnitude and duration) as well as the wider effects of focal stimulation on distributed brain networks (Alhourani *et al.*, 2015). Moreover, the question of the ideal neuroanatomical location of stimulation for eliciting a specific effect on emotional state remains virtually unexplored. As a first step toward addressing these outstanding questions, here we present rare data from a sizable cohort of 18 neurosurgical patients with intracranial electrodes implanted in the ACC, OFC and INS. Using archival reports from routine functional mapping sessions conducted at the bedside, we investigated the effects of anatomical location and intensity of intracranial electrical charge on the modality and perceived intensity of affective experience.

Based on our own prior work suggesting that increased iES current magnitude yields corresponding increases in the intensity of elicited visual experiences (Winawer and Parvizi, 2016), we hypothesized that a similar positive relationship might exist between current magnitude and the intensity of affective experiences. We also sought to clarify whether iES of specific regions or subregions might show category-specific specialization.

Materials and methods

Patient characteristics

Data were drawn from a pool of 129 patients admitted to the Stanford Hospital for invasive monitoring of medically refractory epilepsy. We only included cases where (i) focality of seizures was confirmed with initial intracranial electroencephalography (EEG) findings, (ii) functional mapping had been applied to at least one of our three cortical regions of interest (ROIs), (iii) stimulation parameters had also been systematically varied and (iv) post-operative computerized tomography (CT) and pre-operative magnetic resonance imaging (MRI) scans were available for the precise reconstruction of electrode locations. Ultimately, our sample consisted of 18 patients (8 female) with 140 electrodes of interest implanted in the ACC, OFC and INS where stimulation parameters (i.e. amplitude and/or frequency) were systematically varied (Figure 1). The research was approved by the Stanford University Institutional Review Board.

Regions of interest

We chose to explore effects of iES in three cortical regions unambiguously involved in human affect: ACC, OFC and INS (Figure 2A). As the present study was retrospective, it was not designed to explore the effects of iES across the entire extent of the ROIs or comprehensively throughout the entire brain. Rather, the sites available in each region were chosen as preliminary samples to study the relationship between anatomy, electrical charge and affective experience.

Notably, the amygdala is near epileptic tissue, or itself pathological, in the overwhelming majority of our patients. We therefore did not include effects of amygdala stimulation in our current report. In the 18 patients included in the present study,

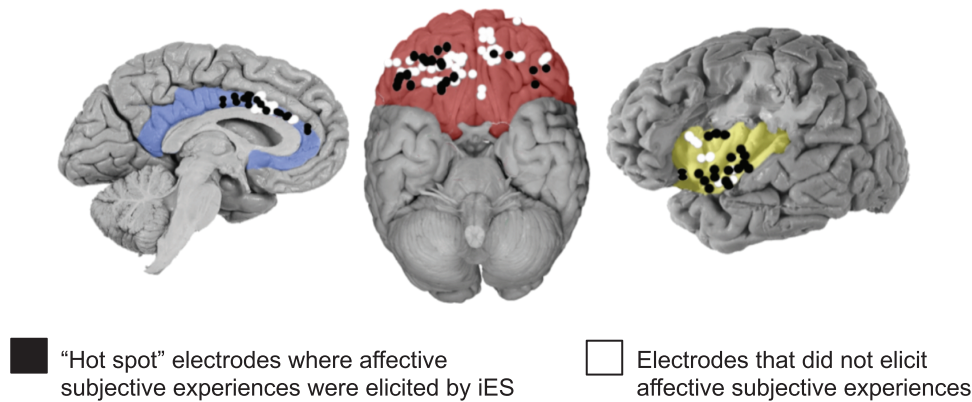


Fig. 1. Elicitation of affective subjective experiences with iES. The anterior cingulate gyrus (ACC; in blue), OFC (in red), and insular cortex (INS; in yellow) were chosen as the ROIs because of their known involvement in affective processing. Notably, all cingulate electrodes were in the anterior half of the cingulate gyrus (ACC). Across all patients, 140 electrodes in the ACC, OFC and INS were stimulated at varying stimulation parameters (i.e. amplitude and/or frequency). In 46% of these electrodes, affective subjective experiences were elicited by iES. We plotted the anatomical location of all electrodes in standardized anatomical space. The location of each electrode may not be precisely in the shown locations. It is worth noting that, though there are more hot spot electrodes in the right compared to the left OFC, there were no hemispheric differences in the relative frequencies of hot spot electrodes in OFC. In addition, there were no hemispheric differences in the relative frequencies of hot spot electrodes in ACC or in INS. Thus, for ACC and INS, we projected all electrodes onto the left hemisphere.

ACC, OFC and INS structures were free of clinical seizures or electrographic ictal activity.

Procedures

Electrode placement and localization. Patients were implanted with subdural grid/strip electrode arrays ($n = 5$), depth electrodes ($n = 11$) or a mix of both ($n = 2$). Placement of all electrodes (AdTech Medical Instruments, Racine, WI) was determined strictly according to clinical criteria. To precisely establish electrode locations for each patient, electrodes were localized in the subject’s own native anatomical space using a post-operative CT scan and a pre-operative T1-weighted MRI scan. To pool results for visualization purposes, electrodes in subject-specific space were normalized to Montreal Neurological Institute (MNI) space and displayed on a standard brain template using the FreeSurfer Software Suite (Reuter et al., 2012). For certain electrodes in ACC and INS, which did not appear in the correct ROI after normalization to MNI space, we manually corrected electrode locations to accurately reflect actual electrode placement in subject-specific anatomy.

Intracranial electrical stimulation. Cortical mapping was undertaken as part of a routine clinical mapping procedure at the Stanford University Medical Center. The rationale for this practice is to determine the precise location of epileptic tissue in the patient’s brain. Initial pulses were delivered with low intensity to test if the stimulated tissue evokes any of the patient’s typical seizure auras.

Across patients, we identified 65 electrodes where subjective affective experiences were elicited by iES (‘hot spot’ electrodes) during routine functional mapping sessions (Figures 1 and 2A). Notably, stimulation of right OFC elicited more affective experiences than left OFC stimulation, due to the fact that 65% of OFC electrodes were located in the right hemisphere (Figure 1). Indeed, there were no hemispheric differences in the relative frequencies of hot spot electrodes in OFC [$\chi^2(1) = 0.02, P = 0.89$]. Moreover, the majority of ACC (58%) and INS (53%) hot spot electrodes were located in the left hemisphere. Given that there were no hemispheric difference in the relative frequencies of hot spot electrodes in ACC [$\chi^2(1) = 1.10, P = 0.29$] or in INS [$\chi^2(1) = 0.48, P = 0.49$], we projected all electrodes in these ROIs to the left hemisphere.

(1) = 0.48, $P = 0.49$], we projected all electrodes in these ROIs to the left hemisphere.

Stimulations were always applied with charge-balanced pulses and within the safe limits of charge density (Table 1). Bipolar iES was delivered at these 65 unique electrode sites using an alternating square wave current applied across two adjacent electrodes with a pulse width of 200–300 μ s. Further details of stimulation methods and parameters are described extensively in our prior research (Parvizi et al., 2013; Foster and Parvizi, 2017).

We remind the reader that, due to the clinical nature of bedside electrical stimulation procedures, the present study was a retrospective archival report of clinical data obtained during routine bedside brain mapping procedures performed in 18 patients where stimulation parameters (current magnitude or frequency) were systematically varied within each patient (for clinical reasons) while probing subjects’ verbal reports. Given its retrospective nature, the present study does not describe an experimental investigation that methodically titrated parameters of iES and sham stimulation across patients who shared identical coverage. Nonetheless, we highlight the effect of anatomical specificity in millimeter space on subjective experience, while also addressing the relationship between the electrical dose and the intensity of subjective experience.

Evaluating subjective effects of stimulation. We considered the effect of stimulation to be valid only if (i) the tissue stimulated was not determined to be epileptic, (ii) stimulation at a given site did not result in seizures or after discharges and (iii) sham stimulations did not lead to similar effects. Following iES or sham stimulation, patients were asked standardized questions probing if any experiences were evoked (e.g. ‘Did you notice anything?’ or ‘Any change?’). As needed, follow-up questions were asked to further clarify the character of reported effects (e.g. ‘Is it something you would like more or less of?’ or ‘Is it something you would prefer to approach or avoid?’). Specific iES parameters and elicited subjective experiences (or lack thereof) were logged for each stimulation. Raters (J.Y. and D.E.B.) viewed and coded digitized iES reports and video-EEG recordings to confirm results.

Reported affective experiences were classified within the following data-driven categories: (i) sensations involv-

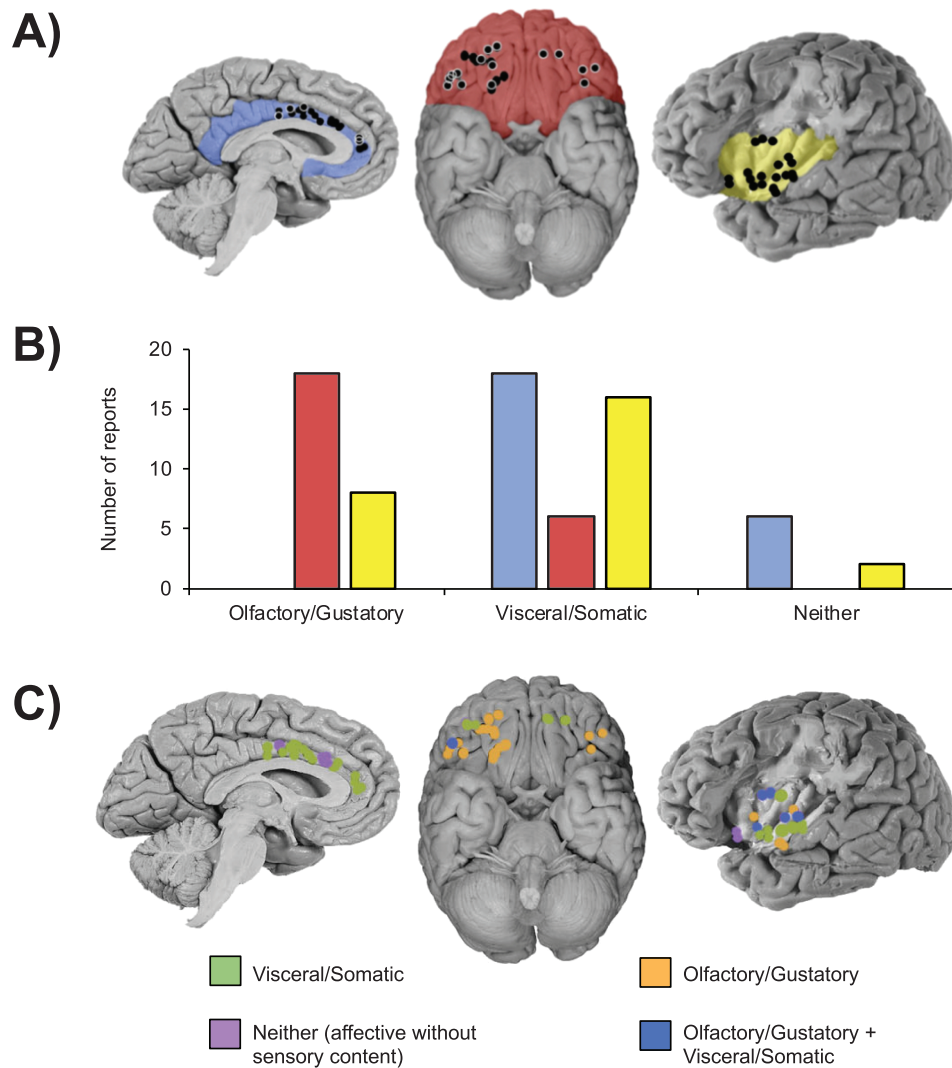


Fig. 2. Regionally specific effects of iES. (A) We plotted the anatomical location of our 65 'hot spot' electrodes on standardized anatomical space to summarize the anatomical location of changes in subjective affective experience (white outline indicates a subdural electrode). Each electrode exhibited a change in intensity when stimulation magnitude was modulated. Given that there were no hemispheric differences for ACC or for INS, we projected all electrodes in these ROIs onto the left hemisphere. (B) Different profiles of affective experience were elicited by stimulation to each anatomical ROI. (C) Different modalities of affective experiences were elicited by stimulation to specific regions within each ROI.

ing smell, taste or both; (ii) visceral sensations (e.g. sensations in the gut or upper chest; feelings of changes in heart rate); and (iii) neither olfactory/gustatory nor visceral/somatic sensations, but rather, affective experiences devoid of any particular sensory content. Notably, all subjective experiences, including olfactory, gustatory and visceral sensations, were considered affective. Some of these sensations occurred with additional experiential qualities (e.g. anxiety that involved chest sensations related to breathing), whereas

some experiences were completely devoid of any sensory content (e.g. anxiety without any reported visceral sensations). Prior research has uncovered close links between olfaction/gustation and affective processing (Zald and Pardo, 1997; Rolls, 2000; Royet et al., 2003; Gottfried and Zald, 2005; Jabbi et al., 2007), and visceral/somatic sensations are commonly considered a defining component of emotion, especially with respect to the physiological elements of affect (Izard, 2010; Mulligan and Scherer, 2012). Indeed, some research suggests

Table 1. Descriptive statistics on iES parameters of interest

ROI	Amplitude range	Amplitude mean (s.d.)	Frequency range	Frequency mean (s.d.)
ACC	1–8 mA	4.65 (2.10) mA	50–50 Hz	50.00 (0.00) Hz
OFC	1–10 mA	4.73 (2.82) mA	2–50 Hz	40.27 (18.46) Hz
INS	2–10 mA	5.16 (2.47) mA	10–50 Hz	48.16 (9.26) Hz

Table 2. Demographic information about patient characteristics for electrodes in anterior cingulate, orbitofrontal, and insular cortices

Subject ID	Age (years)	Sex	Dominant hand	Electrode type	Stimulated electrodes of interest	Stimulated ROI	General effects
1	57	F	Right	Subdural	12	OFC	Olfactory
2	38	M	Right	Subdural	3	ACC	Visceral/somatic
3	50	M	Left	Depth	11	ACC and INS	Visceral/somatic
4	47	M	Right	Depth	13	ACC and OFC	Gustatory; visceral/somatic
5	41	M	Right	Depth	9	ACC and INS	Affective without sensory content
6	48	F	Right	Subdural	5	OFC	Olfactory; visceral/somatic
7	60	M	Right	Depth	10	OFC	Olfactory and gustatory
8	65	F	Right	Subdural	7	OFC	Olfactory and gustatory; visceral/somatic
9	35	M	Right	Both	1	OFC	Olfactory; visceral/somatic
10	45	M	Left	Subdural	7	ACC and OFC	Olfactory; visceral/somatic
11	25	F	Right	Depth	3	ACC	Visceral/somatic
12	36	F	Right	Both	6	OFC	Olfactory
13	30	M	Right	Depth	23	ACC, OFC and INS	Olfactory; visceral/somatic; affective without sensory content
14	25	F	Right	Depth	1	ACC	Visceral/somatic
15	47	F	Right	Depth	5	INS	Olfactory and gustatory; visceral/somatic
16	31	M	Right	Depth	11	INS	Gustatory; visceral/somatic
17	19	F	Right	Depth	4	ACC and INS	Visceral/somatic
18	23	M	Right	Depth	9	ACC and INS	Olfactory; visceral/somatic; affective without sensory content

that somatic sensations play an integral, causal role in emotion (Wilson-Mendenhall et al., 2013; Critchley and Garfinkel, 2017), though the present study was not designed to investigate the temporal dynamics of emotion generation. To characterize an effect as an olfactory, gustatory, visceral or bodily sensation, we relied upon verbal reports from patients describing each effect (see Table 2 for a general summary of reported effects for each patient). Alterations in subjective experience following manipulation of stimulation parameters were classified as changes in (i) intensity, (ii) valence or (iii) any other quality aside from intensity or valence.

In addition to classifying effects based on modality and how subjective experience was modulated, we classified the valence of effects within four categories: (i) negatively valenced or unpleasant experiences; (ii) positively valenced or pleasant experiences; (iii) mixed valence experiences that involved both negative and positive qualities; or (iv) unclear, which typically indicated a lack of information from the patient's verbal report.

Controlling for potential confounds. To account for the confounding effects of any ictal phenomena, we ensured that none of the patients had an epileptic focus within, or required resection of, stimulated ROIs. Second, we ensured that data from any electrodes determined to be in the epileptic zone were excluded from all analyses. Finally, some patients had electrode grids placed over the ventral surface of the OFC; any smell-related effects

elicited by stimulation of electrodes along the midline of the ventral surface were excluded from all analyses as potentially confounded by stimulation of the olfactory nerve (for further details, see Fox et al., 2018).

To control for potential demand characteristics, occasional sham stimulations were randomly administered. During these sham stimulations, the clinician behaved exactly as during veridical stimulation, continuing to adjust settings on the stimulator and press the same buttons while asking the same standardized questions about any changes in subjective experience—the only difference being that no electrical current was actually delivered. Because some patients had few electrodes in the ROIs and received correspondingly few administrations of iES, sham stimulations were only delivered in 11 patients, rather than every patient in the sample. In general, given the retrospective nature of our data, we acknowledge that there is a possibility of sample bias, for instance with respect to anatomical sampling. However, no bias in subjective reports is to be expected, as all patients were asked the same set of standardized questions after each iES or sham stimulation.

Statistical analyses. Chi-squared tests of independence were used to test for differences in frequency among specific modalities of experience for each ROI, as well as differences

Table 3. Effects elicited by modulating the parameters of stimulation

Subject ID	Electrode pairing (label indicates ROI, with REF as reference electrode not in ROI)	Modulated stimulation parameters	Affective subjective report
1	OFC 1, OFC 2	1–3 mA	'Sickening sweet' smell that became stronger
2	ACC 1, ACC 2	4–2 mA	'Sexually excited', euphoric sensation that became nothing
2	ACC 2, ACC 3	4–6 mA	'Erotic' feeling that became stronger ('whoa!')
2	ACC 3, REF	4–6 mA	Erection sensation that became a 'good' feeling
2	ACC 3, REF	6–8 mA	Good feeling that became a sensation of someone moving him from within
3	INS 1, INS 2	6–8 mA	Nothing became a nauseous feeling ('almost had a dry heave')
3	ACC 1, ACC 2	4–6 mA	Nothing became an upper respiratory sensation and foreboding feeling (like 'driving into a storm')
3	ACC 2, ACC 3	4–5 mA	Nothing became sexual arousal
4	ACC 1, ACC 2	3–5 mA	Irritable feeling that became 'hot flash' in chest, face and neck with a feeling of impatience
4	ACC 1, ACC 2	5–4 mA	Hot flash that became a feeling of needing to fight ('I am worried that something bad is going to happen to me physically')
4	OFC 1, OFC 2	10–1 mA	Dull 'metallic, saline' taste became nothing
4	OFC 1, OFC 2	1–3 mA	Nothing became dull saline taste
4	OFC 3, OFC 4	5–7 mA	Slight anger that became a very upset feeling with crying behavior
4	OFC 3, OFC 4	7–5 mA	Anger that became 'a little bit negative and angry'
4	OFC 3, OFC 4	5–7 mA	Nothing became anger ('mad about something')
5	INS 1, INS 2	8–4 mA	Scared feeling became a scared feeling that gradually ramped up (similar to aura, but not as intense)
5	INS 1, INS 2	2–4 mA	Nothing became 'scared feeling'
5	ACC 1, ACC 2	2–4 mA	Nothing became 'general welling up, anticipation' feeling that was negative
5	ACC 1, ACC 2	4–2 mA	Negative feeling became nothing
6	OFC 1, OFC 2	4–6 mA	Nothing became numbness in the left arm
6	OFC 1, OFC 2	8–10 mA	Nothing became dizziness
7	OFC 1, OFC 2	6–4 mA	'Candy' taste that became a milder 'sniff of fruit'
8	OFC 1, OFC 3	2–4 mA	Slight smell that became a 'broader' and 'familiar' smell and taste that 'had a soapy coating to it'
8	OFC 1, OFC 3	50–5 Hz	Smell and taste that became just a smell that was 'not as intense'
8	OFC 1, OFC 3	5–2 Hz	Smell and taste that became a 'mild' smell
8	REF, OFC 3	2–50 Hz	Brief smell that became a sharp taste
8	REF, OFC 3	5–10 Hz	Brief smell became an immediate smell paired with 'rough' sensation in the mouth
8	REF, OFC 3	4–8 mA	Familiar, broad 'chemical' taste that became an unpleasant organic taste
8	REF, OFC 3	20–2 Hz	Unpleasant taste that became nothing
8	REF, OFC 3	2–5 Hz	Nothing became a brief smell
8	OFC 2, REF	8–4 mA	Strong unpleasant smell that became nothing
8	REF, OFC 4	6–4 mA	Mild, 'soapy' smell that became nothing
8	REF, OFC 5	4–6 mA	'Faint, organic' smell that became 'chili pepper' taste that was neither pleasant nor unpleasant
9	OFC 1, REF	4–8 mA	Smell and cold sensation in the nose ('as if I was in a colder temperature') that became stronger and 'more sensitive'
10	ACC 1, ACC 2	5–1 mA	Sudden pain and fear paired with crying that became nothing
10	ACC 1, ACC 2	1–2 mA	Nothing that became pain and fear
10	OFC 1, OFC 3	50 Hz, 1 s to 2 Hz, 5 s	Bad smell (15%) became less (10%) bad
10	OFC 1, OFC 3	2–5 Hz	'Very little smell' that was 10% distasteful became 'bad (20% distasteful)'
10	OFC 1, OFC 3	5–10 Hz	Bad smell that was 20% distasteful became 'distasteful (40%)'
10	OFC 1, OFC 3	10–20 Hz	'Distasteful (40%)' smell became 'very distasteful (60%)'
10	OFC 1, OFC 2	10 Hz, 5 s to 20 Hz, 1 s	Neither bad nor good smell with an intensity of 30% went to bad smell at 50%
11	ACC 1, ACC 2	4–6 mA	'Roller coaster' sensation that became a 'scary' feeling that reaches from the right leg to the face
11	ACC 1, ACC 2	2–4 mA	Nothing became a 'roller coaster feeling'
11	ACC 2, ACC 3	4–6 mA	'Tingling sensation' that became 'moving up' sensation paired with fear, sadness and crying
12	OFC 1, OFC 2	5–2 Hz	'Slight smell' that became negative

Continued.

Table 3. (Continued)

Subject ID	Electrode pairing (label indicates ROI, with REF as reference electrode not in ROI)	Modulated stimulation parameters	Affective subjective report
12	OFC 1, OFC 2	2 mA, 50 Hz to 6 mA, 5 Hz	'Sharp', negative smell that became a 'slight smell'
13	ACC 1, ACC 2	6–8 mA	Anxiety that became fear
13	INS 1, INS 2	6–8 mA	Anxiety that 'stopped breath' that became stronger
13	INS 1, INS 2	8–6 mA	Strong anxiety that became bodily sensation
13	INS 2, OFC 1	6–8 mA	Smell in the mouth that became diffused in the nasal areas ('opens up my nasal area')
13	INS 2, OFC 1	8–10 mA	Broad smell that became nothing
14	REF, ACC 1	2–4 mA	Stiffness in bones that became fear and 'shaky' sensation
15	INS 1, INS 2	4 to 6 mA	'Weird' smell that became a 'bad chocolate' taste
15	INS 1, INS 2	6 to 4 mA	Bad chocolate taste that became smell and taste
15	INS 1, INS 2	10 mA, 10 Hz to 4 mA, 20 Hz	Nothing became 'heart rate increase'
15	INS 1, INS 2	4 to 6 mA	Heart rate increase became a fluttering sensation in the chest
15	INS 1, INS 2	6 mA, 20 Hz to 4 mA, 50 Hz	Chest fluttering sensation that became a 'bad smell'
16	INS 1, INS 2	6–4 mA	Smell and 'shaky' sensation that became a 'good' taste
16	INS 1, INS 2	4–2 mA	Good taste that became nothing
16	INS 1, INS 2	2–3 mA	Nothing became taste in the throat and the nose
16	INS 3, INS 4	6–3 mA	Mild taste that became a warm sensation in the throat
16	INS 3 INS 4	2–6 mA	Nothing became mild taste ('flavor')
17	ACC 1, ACC 2	5–2 mA	Fear and sensation of shock in the heart, out of my mouth and down my arms that became less intense
17	INS 1, INS 2	3.5–2.5 mA	Burning throat sensation and a nervous feeling that became less intense
18	RAIN 5, RAIN 6	2–4 mA	Slight pleasant smell of 'rain' that became stronger
18	RAIN 4, RAIN 5	4–6 mA	Nothing became a sensation of increased heart rate 'like when you finish running'
18	RACI 2, RACI 3	4 to 6 mA	Nothing became a 'lightheaded' sensation
18	RACI 2, RACI 3	6 to 8 mA	'Lightheaded' sensation that became stronger
18	RMCI 1, RMCI 2	4 to 6 mA	Nothing became an anxious feeling 'like something bad is going to happen'
18	RMCI 1, RMCI 2	6–8 mA	Anxious feeling that became fear 'but hopeful in a weird way'
18	RMIN 3, RMIN 4	4–6 mA	Nothing became a sensation of 'falling backwards'

in frequency among valence-specific effects of electrical stimulation to each ROI. All statistical analyses were conducted in the R programming environment [Version 3.4.4; (R Core Team, 2018)].

Results

Region-specific modalities of elicited affective experiences

We found that the type of affective experience elicited by iES was dependent on the region stimulated (Figure 2B and C). ACC stimulations elicited responses that were largely related to the autonomic nervous system and the body. Specifically, ACC stimulation involved significantly more visceral/somatic sensations (75%) compared to other modalities of experience [$\chi^2(2) = 12.13$, $P = 0.002$; $\phi = 0.50$] and never resulted in smell or taste responses. In contrast, the majority of subjective experiences evoked by OFC stimulation (75%) involved olfactory and gustatory content and only a minority of elicited responses (25%) involved visceral/somatic sensations. The frequencies for each experiential modality elicited by OFC stimulation were significantly different [$\chi^2(2) = 12.13$, $P = 0.002$], and the size of the effect was large (ϕ

$= 0.50$). Finally, a large proportion (62%) of responses elicited by INS stimulation involved visceral/somatic sensations, whereas only a minority of responses (31%) involved olfactory/gustatory sensations. These differences in modality frequencies were significant [$\chi^2(2) = 6.37$, $P = 0.041$; $\phi = 0.35$].

In each subregion, the anatomical specificity of the evoked responses was specific within a 5–10 mm window around the stimulated electrode, as previously reported for ACC stimulations (Parvizi et al., 2013). For instance, after moving the site of stimulation by 5–10 mm, the effect of stimulation either disappeared or changed to another domain (Table 3 and Supplementary Table 1).

Extending beyond sensations, four patients reported affective experiences devoid of sensory content (i.e. neither olfactory/gustatory nor visceral/somatic sensations). These subjective reports reflected what is known as the purely 'experiential' or 'feeling' component of emotional states (Izard, 2009). Subject 5 reported a 'scared feeling' akin to fear with 4 mA of left INS stimulation, whereas both subjects 13 (left ACC) and 18 (right ACC) reported experiences of anxiety and fear upon ACC stimulation at various magnitudes (Table 3). In addition to reports of negative emotion, subject 2 reported an 'aroused' and 'sexually excited' feeling at 4 mA of stimulation to one left ACC electrode pairing.

Indeed, two male subjects reported feelings of sexual euphoria upon stimulation of the ACC (Table 3). As described above, subject 2 reported a purely experiential effect of stimulation with 4 mA of current to a left ACC electrode pairing and this affective experience was qualitatively different than the one elicited by stimulation to a neighboring, more ACC site, which evoked the sensation of having an erection (albeit without any concomitant motor effects). Strikingly, subject 3 also reported a 'very sexually aroused' feeling with 5 mA of right ACC stimulation; stimulation at this site also elicited visceral/somatic sensations.

Visual inspection of electrode coverage in the INS suggests that, across subjects, we had three clusters of electrodes within this region. We more closely examined the stimulations within each of these clusters to determine if each cluster was implicated in specific modalities of subjective experience. First, upon stimulation of the two most anterior INS electrodes in our sample (purple circles, Figure 2C), fear was reported. Second, in our three most superior INS electrodes (Figure 2C), effects related mostly to taste and smell (blue circles), as well as heart rate (green circle), were reported, implicating this region in both sensory and also non-sensory experiences. Third, in the largest cluster of electrodes, which extended from middle to posterior INS along its ventral aspect (Figure 2C), we observed smell and taste sensations across two patients as well as reports of anxiety from two patients and of nausea from one patient.

Changes in perceived intensity with changes in stimulation magnitude

Our main results are presented in the form of a comprehensive table including all the electrode pairs whose stimulation led to reportable changes in the sensory, visceral or purely affective domain (Table 3). Upon closer examination of the subjective reports, we found a striking pattern. Among the 65 electrode sites where affective experiences were elicited by DES and where stimulation magnitude was also systematically varied (Figure 2A), changes in stimulation magnitude always elicited changes in perceived intensity: stimulation magnitude and perceived intensity exhibited a positive correlation in all cases—i.e. increases in stimulation magnitude were associated with increased intensity of subjective experience and decreased stimulation magnitude corresponded with decreases in perceived intensity. In addition to the detailed findings for each subject presented in Table 3 and Supplementary Table 1, a few examples are especially noteworthy. For instance, Subject 17 reported fear and the sensation of a 'shock in my heart, out of my mouth, and down my arms' at 50 Hz/5 mA stimulation of left ACC that became less intense when stimulation amplitude was reduced to 50 Hz/2 mA. With stimulation to the right OFC, subject 4 reported a slight feeling of anger at 50 Hz/5 mA of stimulation that became a very upset feeling paired with bodily changes, including crying, at 50 Hz/7 mA of stimulation. In another example, subject 13 reported anxiety that 'stopped my breath' at 50 Hz/6 mA of right INS stimulation that became more intense when stimulation amplitude was increased to 8 mA.

Importantly, though the majority of reported effects were elicited by a change in the amplitude of electrical charge, there were several instances across four subjects in which the frequency of stimulation was changed. In those cases, we observed changes in the modality and intensity of subjective experience with increased frequency (Supplementary Tables 1 and 2). In general, as both frequency and amplitude per trial were increased, perceived intensity also increased. Moreover,

there were instances when subjective experience was seemingly intensified solely by increases in frequency. For example, with stimulation to left OFC, subject 10 experienced a neutral smell with a reported intensity of 30% that became a bad smell with 50% intensity when frequency was increased from 10 to 20 Hz, despite the fact that the charge per trial actually decreased (50–20 μ C).

Valence of elicited affective experiences

Across all regions of interest, 58% of reported subjective affective experiences were negatively valenced and unpleasant, whereas 15% of experiences were positive and pleasant. These results are consistent with nearly 100 years of intracranial stimulation research, which has found that, for reasons unknown, negatively valenced experiences are elicited with far greater frequency than positively valenced experiences (Guillory and Bujarski, 2014; Selimbeyoglu and Parvizi, 2010). Additionally, 9% of elicited effects were classified as mixed affective experiences that involved both pleasant and unpleasant qualities. For example, subject 1 reported a 'sickening sweet' smell that we coded as both negative and positive in valence. Finally, we were unable to classify the remaining 17% of affective experiences based on valence; these experiences all involved smell and taste sensations that were not specifically probed on valence, and we were unable to infer the valence of the experience based on the available subjective reports.

Focusing on each region of interest, ACC stimulation elicited negative affective experiences significantly more often than positively valenced effects or mixed-valence experiences [$\chi^2(3) = 15.66, P = 0.001; \phi = 0.57$]. Notably, stimulation of more posterior regions of the ACC elicited pleasant affective experiences, whereas unpleasant affective effects were elicited with stimulation across ACC (Figure 3). Though approximately half of the affective experiences elicited by OFC stimulation (50%) and by INS stimulation (47%) were unpleasant, there were no significant differences between the frequencies of each valence category for either OFC stimulation [$\chi^2(3) = 5.28, P = 0.15$] or INS stimulation [$\chi^2(3) = 2.17, P = 0.54$].

In a small number of stimulated electrodes (9%), changes in valence occurred along with changes in perceived intensity. Subject 15 was an especially compelling case study as she reported a chocolate taste at lower intensity, which became a distasteful 'bad' chocolate taste with increased dose and duration of stimulation to the same electrode pairing (Supplementary Table 1). In one instance, subject 15 even made a disgusted expression with her face, which had been neutral in prior stimulations (Video 1). Emotional expression is considered to be a more



Video 1. With increased dose and duration of stimulation, a previously pleasant smell becomes an unpleasant taste, coupled with the emotional expression of disgust.

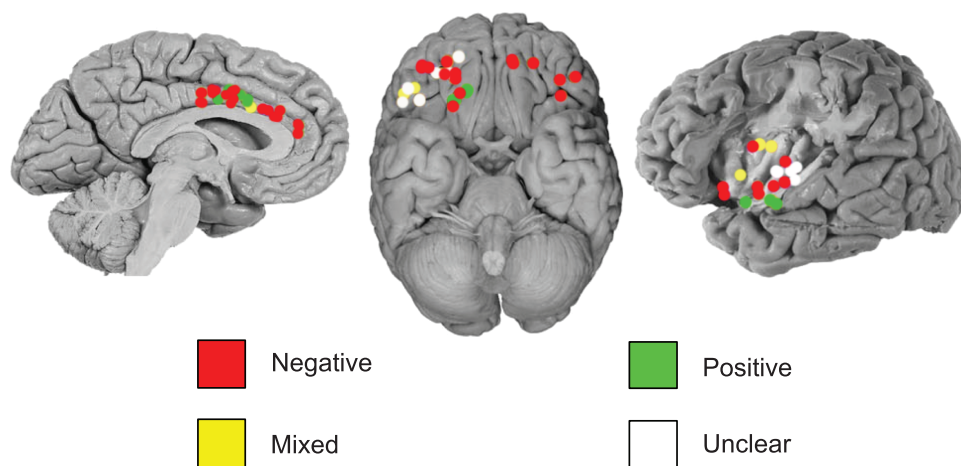


Fig. 3. Valence-specific effects of iES. We categorized each subjective experience based on valence and found that distinctly valenced affective experiences were elicited by stimulation to specific regions within each ROI.

objective component of emotion compared to the subjective component of experience.

Discussion

Prior observations of affective experience induced by the electrical stimulation of cortical structures have tended to be restricted to small samples and isolated brain regions (Pool and Ransohoff, 1949; Feindel and Penfield, 1954; Mullan and Penfield, 1959; Oppenheimer et al., 1992; Mangina and Beuzeron-Mangina, 1996; Ostrowsky et al., 2000; Mulak et al., 2008; Parvizi et al., 2013; Caruana et al., 2018; Fox et al., 2018; Inman et al., 2018). Though previous studies have specifically documented the subjective qualia of these affective experiences (Halgren et al., 1978), to our knowledge, no previous study has systematically investigated the effect of varying stimulation parameters on these experiences. Building upon these pioneering investigations, here we explored how systematically varying the anatomical location and stimulation parameters of iES throughout the human brain relates to the modality and intensity of elicited affective experiences.

Our central finding, that current magnitude correlates with subjective intensity, parallels our previous observations of a clear relationship in the primary visual cortex between the magnitude of electrical stimulation, the size of cortical area being activated and the size of perceived visual phosphenes (Winawer and Parvizi, 2016)—a finding that was recently replicated (Bosking et al., 2017). The present study extends this research to so-called ‘limbic’ structures and demonstrates a compelling relationship between stimulation magnitude and the intensity of affective experiences, not merely simple visual phenomena such as phosphenes.

Although this finding is intuitive and might appear obvious in hindsight, the extant literature has, to our knowledge, never demonstrated a relationship between the magnitude of electrical charge and the intensity of purely subjective experiences such as emotion. Some limited research has discussed the effects of increasing stimulation magnitude on other components of emotion—namely, the autonomic (Mangina and Beuzeron-Mangina, 1996; Inman et al., 2018;) and expressive components (Fried et al., 1998; Sperli et al., 2006)—but has been silent on the topic of truly subjective and experiential aspects of affective experience. Indeed, although increasing the amplitude of

amygdala stimulation has elicited corresponding increases in physiological arousal (Inman et al., 2018), greater amygdala stimulation generally had no discernible relationship with subjective emotional experience. Our study therefore represents the first demonstration of a consistent positive relationship between stimulation magnitude and the perceived intensity of affective experience.

It is important to note, however, that all of our selected ROIs represent relatively large swathes of cortex, and none of these regions is homogenous at the cytoarchitectonic or functional level (Vogt et al., 2003; Kringelbach, 2005; Craig, 2009). Although our relatively small number of electrodes precludes venturing any strong inferences about subregional specialization, some interesting trends are worth noting. For instance, different effects of stimulations across the three ROIs clearly suggest that the three separate structures are involved in distinct functions in the service of creating affective states. Moreover, there could also be subregional specialization within each of the ROIs. For instance, the two ‘pure’ (i.e. devoid of specific sensory content) affective experiences we observed in the INS were located in the far anterior insular cortex, whereas more concrete visceral/somatic effects tended to cluster in the mid/posterior regions (Figure 2C). These findings are consistent with models of insular function positing a rostrocaudal gradient with primary interoceptive cortex in posterior aspects gradually transitioning to higher-level viscerosomatic integration in the most anterior portions (Craig, 2009). Similarly, the handful of integrative, higher-level viscerosomatic experiences elicited in the OFC were at the most anterior electrodes, whereas more basic, unimodal olfactory and gustatory experiences predominated in the mid-to-posterior electrode sites (Figure 2C). Again, this trend (if robust) is consistent with a posterior-anterior functional gradient of simpler to more complex and integrative processing (Kringelbach, 2005; Fox et al., 2018). Some intriguing trends were also apparent with respect to valence: positively valenced effects tended to cluster in the posterior ACC, the right OFC and the ventral-anterior aspect of the INS (Figure 3). Although these trends are based on relatively few electrodes and their significance remains unclear, they suggest patterns of regional specialization that could be further explored and refined in larger cohorts (Guillory and Bujarski, 2014). In the OFC at least, they complement and are consistent with the findings from a meta-analysis of 65 neuroimaging studies

(Wager et al., 2003) as well as our recent report of the left-lateralization of negatively valenced effects induced by iES (Fox et al., 2018). Nonetheless, given inconsistencies in the literature on lateralization and affect, a meta-analysis spanning across method types is warranted to draw strong conclusions regarding the lateralization of valence.

Although much of the recent literature on the neural correlates of consciousness has focused on high-frequency electrical activity (Koch et al., 2016), our data suggest that subjective experiences can be elicited by stimulation of specific sites within the human brain at frequencies significantly below the gamma (>40 Hz) range. Our preliminary results are consistent with several previous investigations showing that low-frequency stimulation may perturb subjective affective experience (Halgren et al., 1978; Pugnaghi et al., 2011), but more systematic work is needed to build upon the present study.

Our finding that ACC stimulation in two of our subjects elicited pleasurable feelings of sexual arousal is consistent with prior research implicating the cingulate cortex in sexual behaviors in healthy adults (Ortigue et al., 2010; Georgiadis and Kringsbach, 2012;) and patient populations (Devinsky et al., 1995). Most past research has relied upon neuroimaging methods involving heterosexual males (Georgiadis and Kringsbach, 2012), however, and our observations of sexual euphoria elicited by ACC stimulation also came from two single male subjects; further research is therefore needed to replicate these effects in males and explore whether they extend to female participants as well.

Taken together, the present study represents an important step forward in the investigation of how modulating the amount of electrical charge may influence human affective states. Although it is apparent that such research can only be investigated in human subjects that are able to share their subjective experiences, we are mindful of several limitations of the present study's invasive intracranial approach.

The first limitation of our study is that our data are derived from patients with intractable epilepsy, which is a heterogeneous disease with variable severity, clinical appearance and pathogenic mechanisms. At one end of the spectrum, severe epilepsy syndromes are hallmarked by multifocal epileptiform discharges, abnormal baseline brain activity, severe cognitive impairment and behavioral regression. At the other end of the spectrum, focal epilepsies are seen in high-functioning adult patients who have normal intelligence and only localized abnormalities in affected brain structures. We mitigated the effect of epilepsy by recruiting patients in whom the focality of seizures was confirmed with initial intracranial EEG findings. In these cases, as we have recently reported (Parvizi and Kastner, 2018), only a minority of electrodes show epileptic activity, with over 80% of implanted electrodes showing no epileptic activity. To minimize the potentially confounding effects of epileptic abnormalities, we included only those subjects in whom the three ROIs were void of epileptic abnormality and seizures. Furthermore, to minimize the effect of postictal state in our observations, clinical electrical stimulation procedures were performed several hours outside the window of seizures. Lastly, and perhaps most importantly, the reliability of our findings can be demonstrated by showing that the observed findings are anatomically and functionally consistent across patients with different types of epilepsy and variable seizure foci.

The second limitation of our study is that we used an archival method that does not permit for a methodologically rigorous study of the relationship between different parameters of iES and standardized questionnaires probing subjective reports in each individual patient. For instance, in ideal conditions,

we would have relied upon a systematic experiment across all patients that used random sequences of iES and sham stimulations, with iES stimulations delivered at randomly varying levels of electrical charge. However, such experiments are difficult, if not impossible, to perform in patient populations because of clinical safety concerns as well as severe time constraints in the clinical setting. In our report, we relied on clinical bedside observations throughout the past 10 years, carefully selecting those cases in which the clinicians had performed clinical bedside electrical stimulation procedure with different frequencies or amplitudes in one of the three ROIs. In these clinical procedures, for safety reasons, we aimed to keep the number of stimulations at a given site to the bare minimum. Therefore, though retrospective and largely descriptive in nature, our findings represent a unique and rare dataset on electrical stimulation of human brain structures. We hope that our findings will motivate future research to further examine the relationship between current amplitude or frequency and various aspects of subjective experience.

The third limitation of our study pertains to its 'cortico-centric' approach (Parvizi, 2009). We were not able to investigate the many subcortical structures known to play crucial roles in affect. There have been isolated case reports of direct electrical stimulation to subcortical areas eliciting diverse (and often intense) affective experiences (Selimbeyoglu and Parvizi, 2010; Guillory and Bujarski, 2014; Inman et al., 2018). Our focus on cortical structures was a result of the limitations of our sample and electrode implantations and is by no means intended to minimize the role of subcortical regions in complex affective states (Parvizi, 2009). More systematic investigations of affective responses to electrical stimulation in human subcortical regions would be a welcome addition to this emerging field.

Finally, the present study was limited in that we used two different electrode types for iES, i.e. subdural grids and strips versus depth electrodes. Subdural electrodes rest upon and stimulate the cortical surface. In contrast, depth electrodes are inserted deep into grey matter structures. These different electrode types likely exhibit distinct patterns of current flow, which could potentially confound our findings. Nonetheless, our central finding of the relationship between stimulation magnitude and the intensity of subjective affective experience remained consistent across both types of electrodes (Figure 2A), suggesting that this was not the case in our sample. Further research, however, is clearly needed to better understand the biophysics of electrical stimulation in the human brain (Buzsáki et al., 2012; Parvizi and Kastner, 2018).

Limitations of our approach aside, several aspects of the present study are noteworthy: first, we relied solely on subjective qualitative reports of experience and allowed subjects to openly express their affective states without asking them to fill out questionnaires. Although this method did not allow us to quantitatively measure the precise effects of stimulation, a free-response approach allowed our subjects to openly express themselves and use their own natural words to denote changes in intensity or other aspects of their experiences. Moreover, for each electrode of interest, we evaluated how experiences changed as stimulation magnitude was modulated. With changes in intensity, subjects often specifically stated that a previously reported effect became stronger or weaker, despite being completely blinded to stimulation magnitude. In light of the open nature of self-report and the enormous range of possible subjective experience, it is remarkable how individual subjective reports across multiple subjects fell within specific domains

of affective experience, and that these domains were largely determined by anatomical location and predictably modulated by changes in iES magnitude.

Another notable feature of the present study is its focus on within-subject changes in affective experience during iES. There are critical individual differences in electrical excitability of tissue (Krause and Cohen Kadosh, 2014), interoceptive awareness (Craig, 2004; Garfinkel et al., 2015) and other factors likely to confound between-subject investigations of this kind. However, given our within-subject approach, any bias introduced by inter-subject variability should not have influenced our primary finding of the correlation between the intensity of subjective experiences elicited by iES of varying magnitude.

Our observations remind us of both the promise and perils of the ongoing efforts to tune and manipulate human emotional experience through the use of technological devices. As implanted electroceutical interventions are increasingly employed to treat neurological and psychiatric conditions (Roy et al., 2018), we hope that our findings will have useful implications for clinicians aiming to modulate emotional experience with intracranial electrical devices.

Supplementary data

Supplementary data are available at SCAN online.

Acknowledgments

The authors thank the EEG technicians at the Stanford Epilepsy Monitoring Unit (Harinder Kaur, Luida Schomacher and Thi Pham) for their invaluable assistance during the clinical functional mapping procedures; neurosurgeons Dr Jaimie Henderson and Dr Casey Halpern for their role in the implantation of intracranial electrodes; Omri Raccah for assistance with data visualization; Lin Shi for assistance with transforming coordinate data from subject-specific to standard MNI space; and Alexander O. King for assistance with creating video footage.

Funding

J.Y. was supported by the National Science Foundation (NSF; grant BCS-1756466); D.E.B. was supported by the Stanford Undergraduate Advising and Research Student Grant; K.C.R.F. was supported by a postdoctoral fellowship from the Natural Sciences and Engineering Research Council of Canada; and J.P. acknowledges support from NSF (grant BCS-1756466).

Conflict of interest. None declared.

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