Supplemental Materials

Clinical Supplemental Information:

Index Patient: The patient was a 23-year-old left-handed woman with a history of refractory epilepsy since age 14. She had two seizure types: focal dyscognitive seizures consisting of right facial numbness, followed by behavioral and speech arrest, followed either by termination with post-ictal smile, or alternatively, by progression to generalized tonic-clonic activity, right head and eye deviation, and post-ictal confusion. Her seizures otherwise lacked gelastic phenomena, post-ictal psychosis, or agitation. She was treated with multiple antiepileptic medications and continued to have seizures, so she underwent a comprehensive epilepsy surgery evaluation at an outside institution, where she was implanted with a subdural grid electrode array centered over the junction of left frontal, parietal, and superior temporal regions. Over 2 weeks during monitoring at the outside institution, one seizure was recorded with rhythmic activity localized to the posterior edge of the grid over left postcentral and supramarginal gyri, and electrical stimulation verified underlying primary motor, sensory, and language function. Rather than risk additional monitoring or neurological deficits, the grid was removed, and a responsive neurostimulator (RNS) was implanted, with two strip electrodes placed over that putative seizure focus. The RNS provided no therapeutic benefit, however, and she subsequently presented to our institution a year later for re-evaluation, including repeat intracranial EEG studies. At our institution, scalp EEG revealed poorly localized seizure onsets over the left hemisphere. Unambiguous left hemisphere language dominance was documented with standard clinical functional magnetic resonance imaging. Brain MRI was normal. PET scan revealed left temporal hypometabolism. Neuropsychological testing was non-lateralizing with a normal IQ. Our hypotheses included seizure onsets in the left posterior parietal vs. left mesial temporal region. Though intracranial monitoring had been performed at the outside institution, the left mesial temporal structures had not been implanted with electrodes, and the seizure onset zone was seen at the posterior edge of the parietal grid. Intracranial monitoring was thus repeated at our institution.

The patient had a history of mild depression which she attributed to side effects from her seizure medications. Pre-operatively, she completed Beck Depression and Anxiety Inventories (BDI-II and BAI), scoring 4 on the BDI-II ("minimal" range) and 22 on the BAI ("moderate anxiety" range). The Beck Scales discriminate among minimal, mild, moderate, and severe symptoms of depression and anxiety, where scores in the minimal and mild ranges are generally interpreted as indicating normal function. Her score indicating moderate anxiety is interpreted as evidence of a potentially clinically significant symptom burden.

Patient 2: The patient was a 40-year-old, L-handed man with a history of refractory epilepsy since age 8. He had 1 seizure type, without gelastic phenomena, post-ictal psychosis or agitation. During seizures the patient reports an unsettling feeling, flashing lights in left visual field, feeling nervous/anxious, followed by loss of awareness. He was treated with multiple antiepileptic medications and continued to have seizures, leading to a right temporal lobectomy at age 37, which ultimately did not control his seizures. At our institution, scalp EEG revealed poorly localized seizure onsets over the right hemisphere. Left language dominance was documented with Wada testing. Brain MRI was remarkable for post-operative changes related to right temporal lobectomy. PET scan revealed hypometabolism in the remaining right temporal lobe and right basal ganglia. Neuropsychological testing was non-lateralizing with a normal IQ. Surgical hypotheses included seizure onsets in the

parieto-occipital region. He underwent stereotactic EEG electrode implantation primarily sampling the right hemisphere for further seizure monitoring.

Patient 3: The patient was a 28-year-old, R-handed woman with a history of refractory epilepsy and comorbid depression since age 8. She had 1 seizure type, without gelastic phenomena, post-ictal psychosis or agitation. The patient experiences pre-ictal agitation, depression, and irritability lasting several days leading up to a seizure, which is characterized by numbness on the left side of her head, tongue, throat, and left arm, the sensation that someone is slapping her in the face or pushing her head back, fear/déjà vu, and then developing into loss of awareness. She was treated with multiple antiepileptic medications and continued to have seizures, leading to a right temporal lobectomy at age 14, followed by a resection of residual medial temporal structures three months later, which ultimately did not control her seizures. At our institution, scalp EEG revealed poorly localized seizure onsets over the right frontotemporal region. Left language dominance was documented with standard clinical functional magnetic resonance imaging. Brain MRI was remarkable for post-surgical changes of partial right temporal lobectomy. PET scan revealed right inferior posterior frontal and posterior temporal hypometabolism. Neuropsychological testing was non-lateralizing with a normal IQ. Surgical hypotheses included seizure onsets in the right insular, parietal, superior temporal gyrus, and frontopolar regions. She underwent stereotactic EEG electrode implantation primarily sampling the right hemisphere for further seizure monitoring.

Figure S1. Individual Anatomy for Patient 2

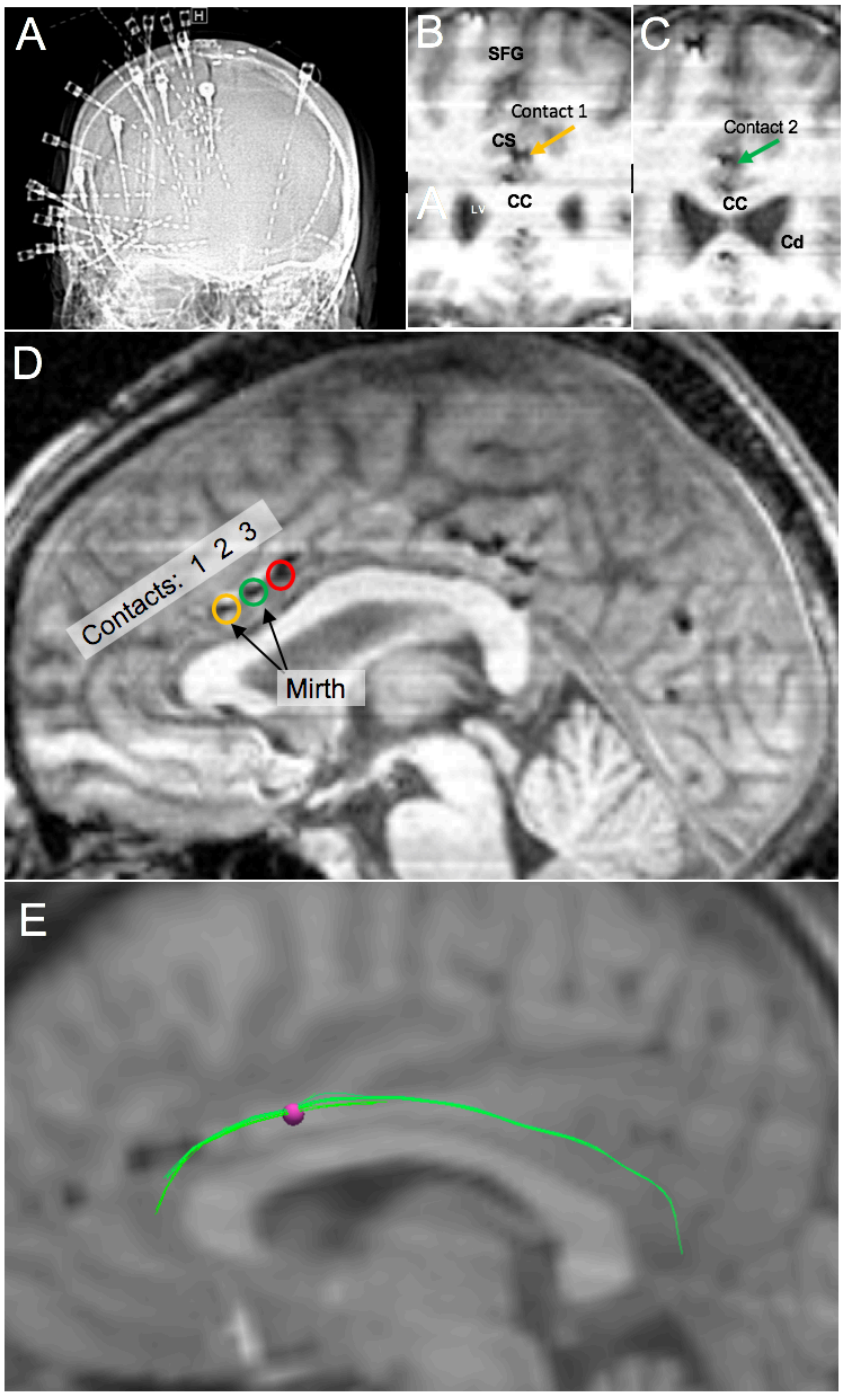


Figure S1. Location of stimulated electrodes. (A): Post-implantation skull radiograph showing relative positions of intracranial electrodes. **(B-D):** Post-implantation MRI demonstrating positions of stimulated cingulum contacts; coronal slices B and C correspond with anode (yellow) and cathode (green) of stimulation eliciting mirth. **(E):** Sagittal view of deterministic tractography seeded at the mirth-eliciting contact pair using modeled bipolar volumes of tissue activated via artificial neural nets based on 1.0mA, 130Hz, 300μs pulse width stimulation. Abbreviations: SFG = superior frontal gyrus, CS = cingulate sulcus, CG = cingulate gyrus, CC = corpus callosum, LV = lateral ventricle, Cd = caudate, Put = putamen, M1 = primary motor cortex, S1 = primary sensory cortex.

Figure S2. Individual Anatomy for Patient 3

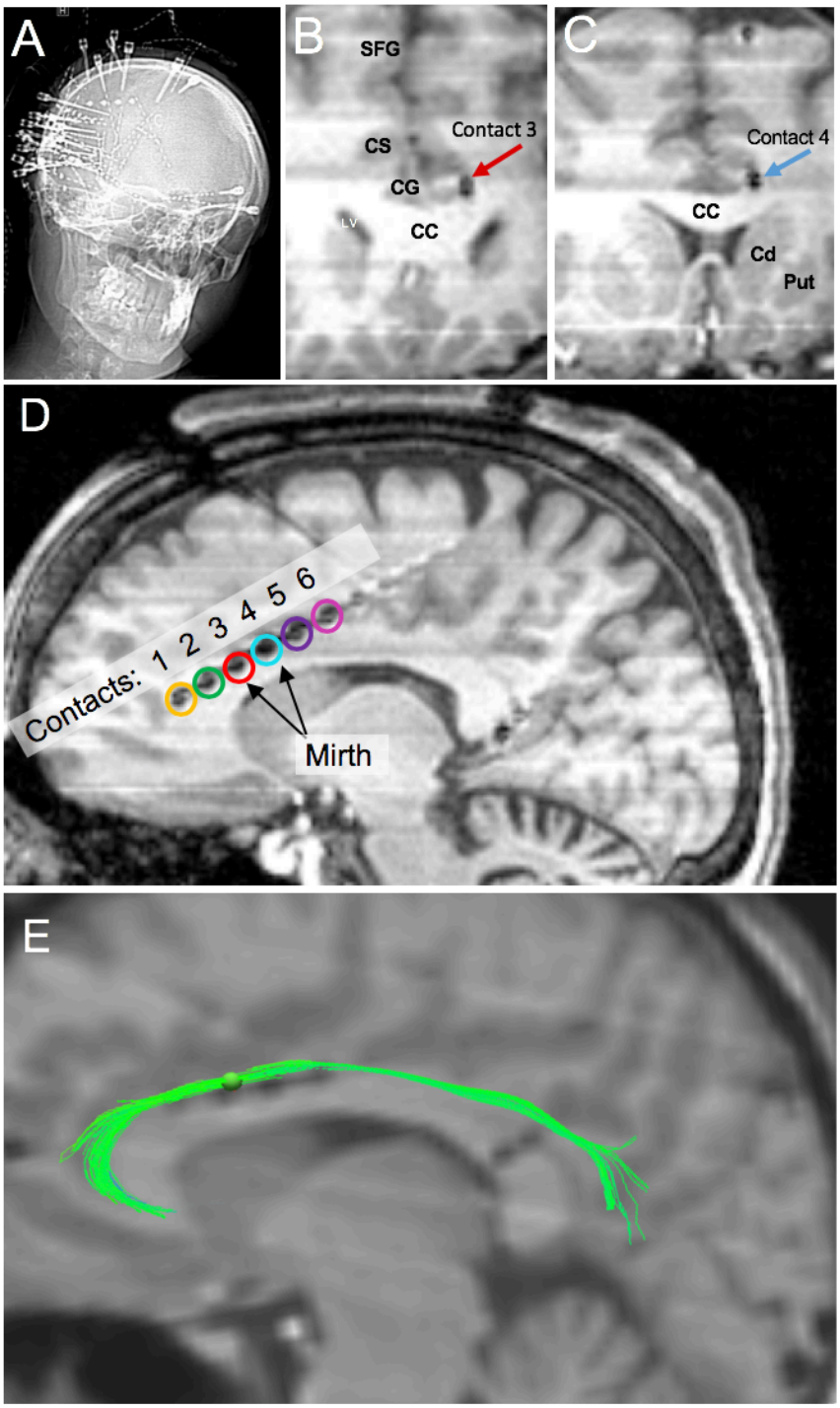


Figure S2. Location of stimulated electrodes. (A): Post-implantation skull radiograph showing relative positions of intracranial electrodes. **(B-D):** Post-implantation MRI demonstrating positions of stimulated cingulum contacts; coronal slices B and C correspond with anode (red) and cathode (blue) of stimulation eliciting mirth. Anterior cingulum stimulation utilized contacts 2-3, triggering patient auras, cingulum bundle stimulation eliciting mirth utilized contacts 3-4 (red, blue). **(E):** Sagittal view of deterministic tractography seeded at all mirth-eliciting contact pairs using modeled bipolar volumes of tissue activated via artificial neural nets based on 1.0mA, 130Hz, 300μs pulse width stimulation.

Figure S3. Cingulum stimulation promotes positive shift in interpretation of emotional faces in index patient.

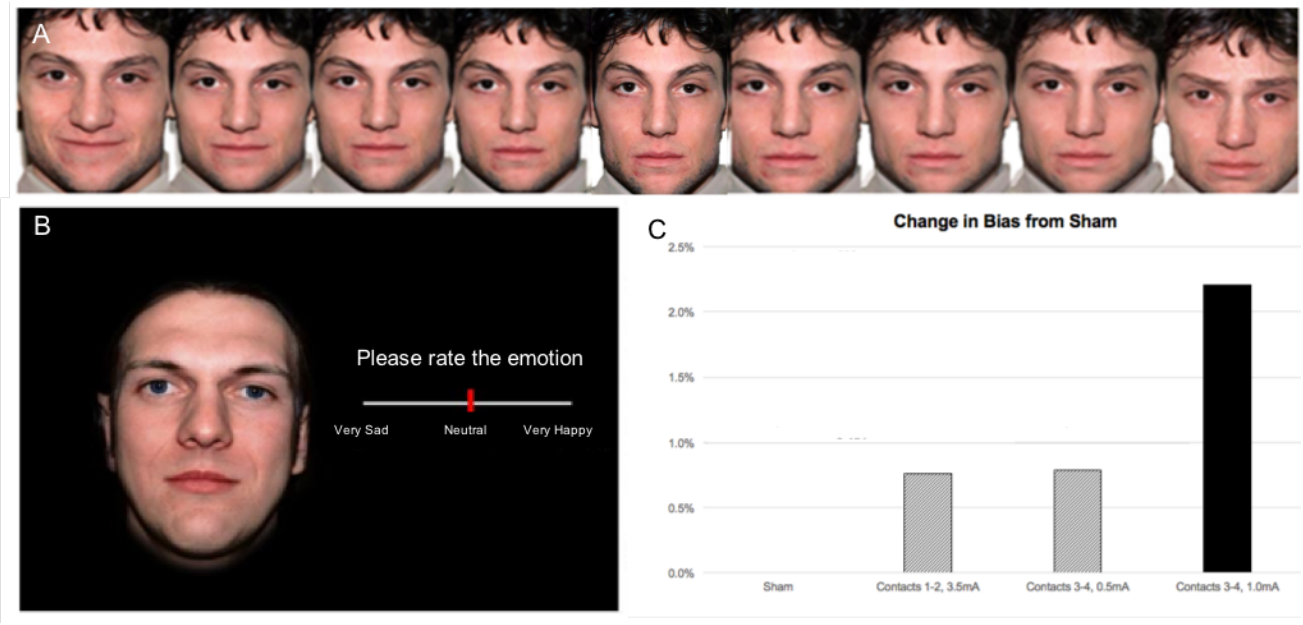
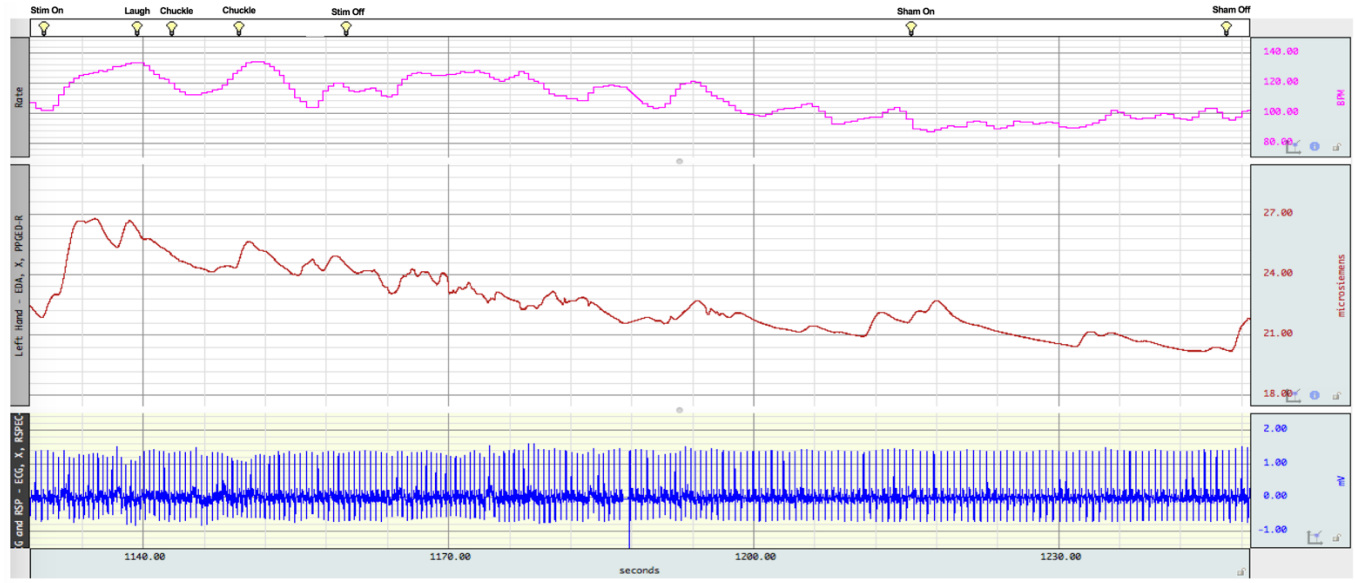
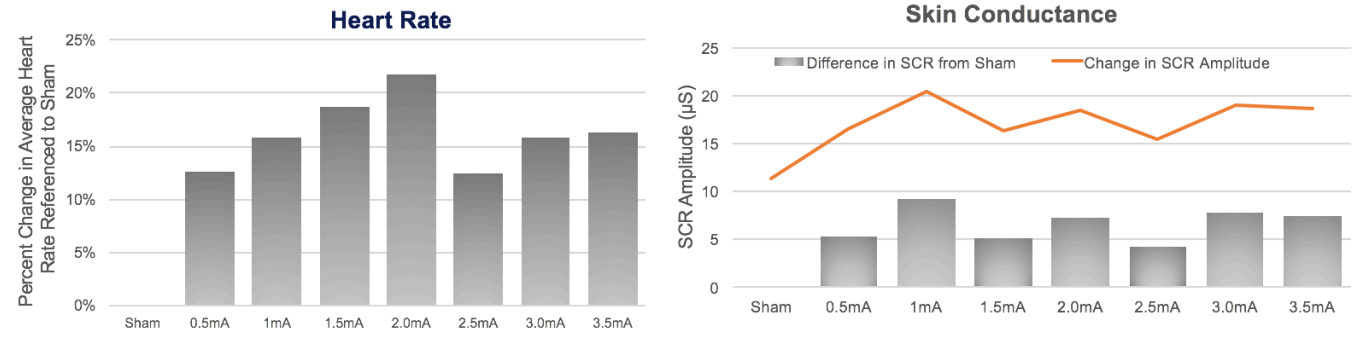


Figure S3. Cingulum stimulation promotes positive shift in interpretation of emotional faces. (A) Exemplar facial morphs presented in the affective bias task, ranging from 100% happy, to neutral, to 100% sad, including intervening morphs of 50%, 30%, and10%. Arrays of six identities (52), nine morphs of each, were presented to the participant in blocks segregated by happy and sad faces, in a semi-randomized order. **(B)** Screenshot example from 60 presented faces (trials) viewed by the subject under various stimulation conditions during the affective bias task. The patients rated the perceived emotion in each of 60 presented faces across the two blocks by placing the red slider bar along the continuous scale. **(C)** Change in average ratings on affective bias test under stimulation to contacts as defined in Figure 1, compared to sham (single-blinded false stimulation) conditions. Bars indicate percent change in intensity ratings taken across all 60 emotional facial expressions in the stimulus array, ranging from sad to neutral to happy. Dashed bars indicate stimulation below the threshold for subjective awareness. Solid bar indicates stimulation above subjective threshold. Relative to sham, cingulum stimulation (1.0 mA contacts 3-4) induced subjective happiness (and urge to smile) and a large positive shift in affective bias. Stimulation at the same location at lower dose (0.5 mA) or at a more anterior gray matter location (contacts 1-2, 3.5 mA) fell below this subjective threshold and yielded only modest shifts in bias. Results are consistent with the notion that affective bias corresponds with concurrent emotional tone.

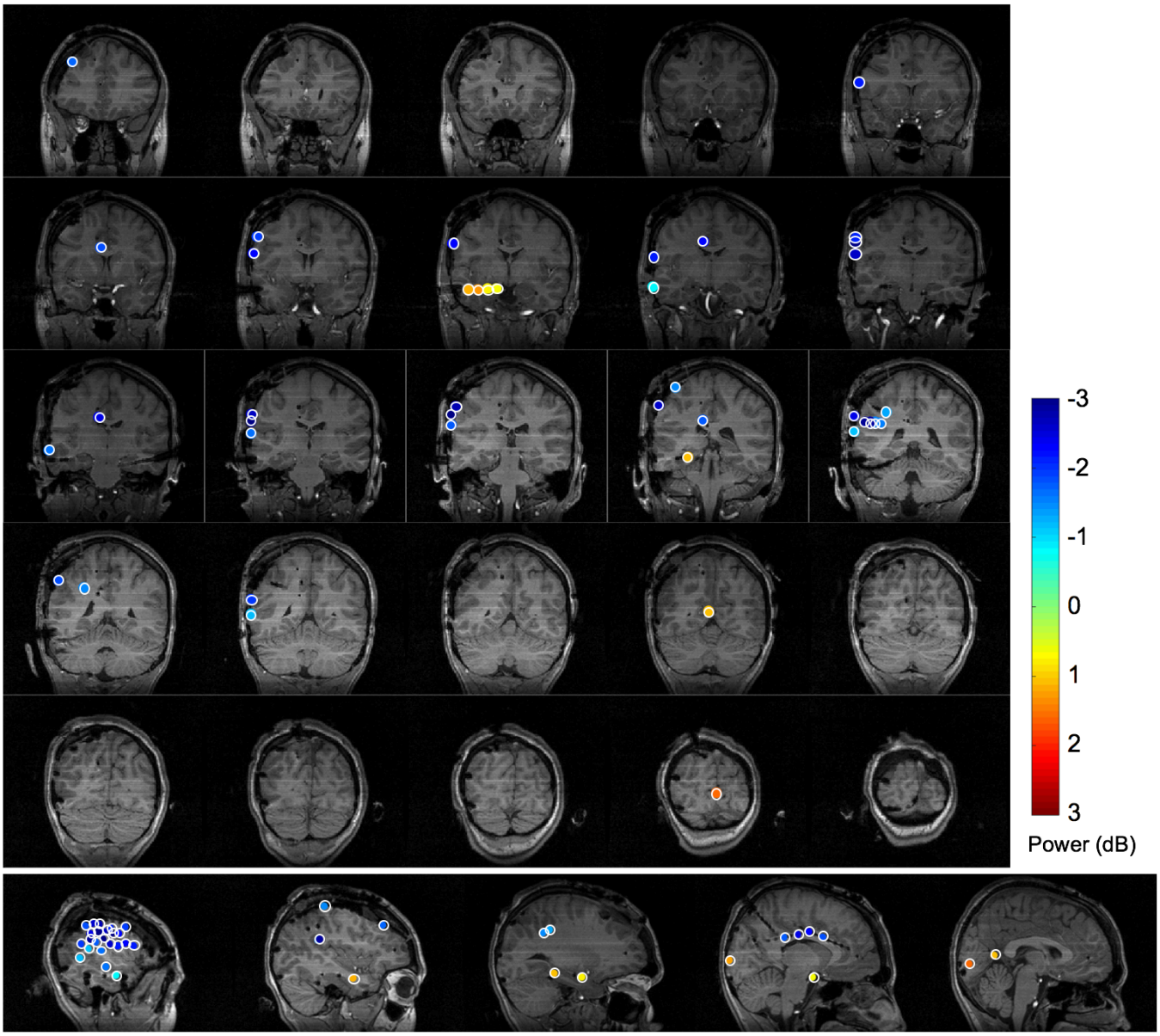
Figure S4: Autonomic measures during stimulation to dorsal cingulum bundle in index patient.





<u>Figure S4. Autonomic measures during stimulation to dorsal cingulum bundle.</u> To examine the impact of dorsal anterior cingulum bundle stimulation upon the autonomic nervous system activity, we recorded changes in skin conductance, heart rate, and respiratory rate during 30-second blocks of stimulation (130 Hz, 300µs) relative to preceding baselines in increasing steps of 0.5-3.5 mA with interleaved sham stimulations. The patient reported no emotional change under any sham condition (n = 5), and exhibited mirth at 1.0 mA, with increasing intensity and duration at successively greater current levels up to and including 3.5 mA. Future studies must endeavor to compare impacts of cingulum stimulation with those of sham stimulation (as in this case) as well as with various positive controls, to further define the specificity of the observed effects. *Upper Panel*: Exemplar trace for heart rate and skin conductance (µS) over time, starting with 2mA stimulation at 130 Hz, 300µs pulse width, then ending stimulation, initiating sham stimulation, and ending sham stimulation. *Lower Panel:* Percent change in average heart rate (left) and average maximal skin conductance response amplitude (SCR) (right) were recorded over 30-second and 15-second epochs respectively during a stepwise parameter sweep increasing stimulation current by steps of 0.5 mA. Stimulation above 1.5 mA was associated with patient report of elevated mood and occasional laughter. µS = microSiemens. The patient was silent during all conditions, with the exception of quiet laughter with stimulation above 1.5 mA.

Figure S5. LFP power mapped to electrode contacts localized in situ.



<u>Figure S5: LFP power merged with postoperative MRI with electrode contacts localized *in situ*</u>. LFP shows reduced power across the network following stimulation vs. sham. Colored dots indicate electrode locations and the corresponding power using the heat map as indicated in the legend. Only contacts with statistically significant ($p < .05$, uncorrected) changes in power are presented using colored dots; non-colorized dots indicate contact locations with non-significant changes in power. Slices have an inter-slice distance of 5mm; locations of electrodes in brain tissue are approximated to the nearest 5 mm slice presented below.

Figure S6. LFP coherence mapped to electrode contacts localized *in situ*.

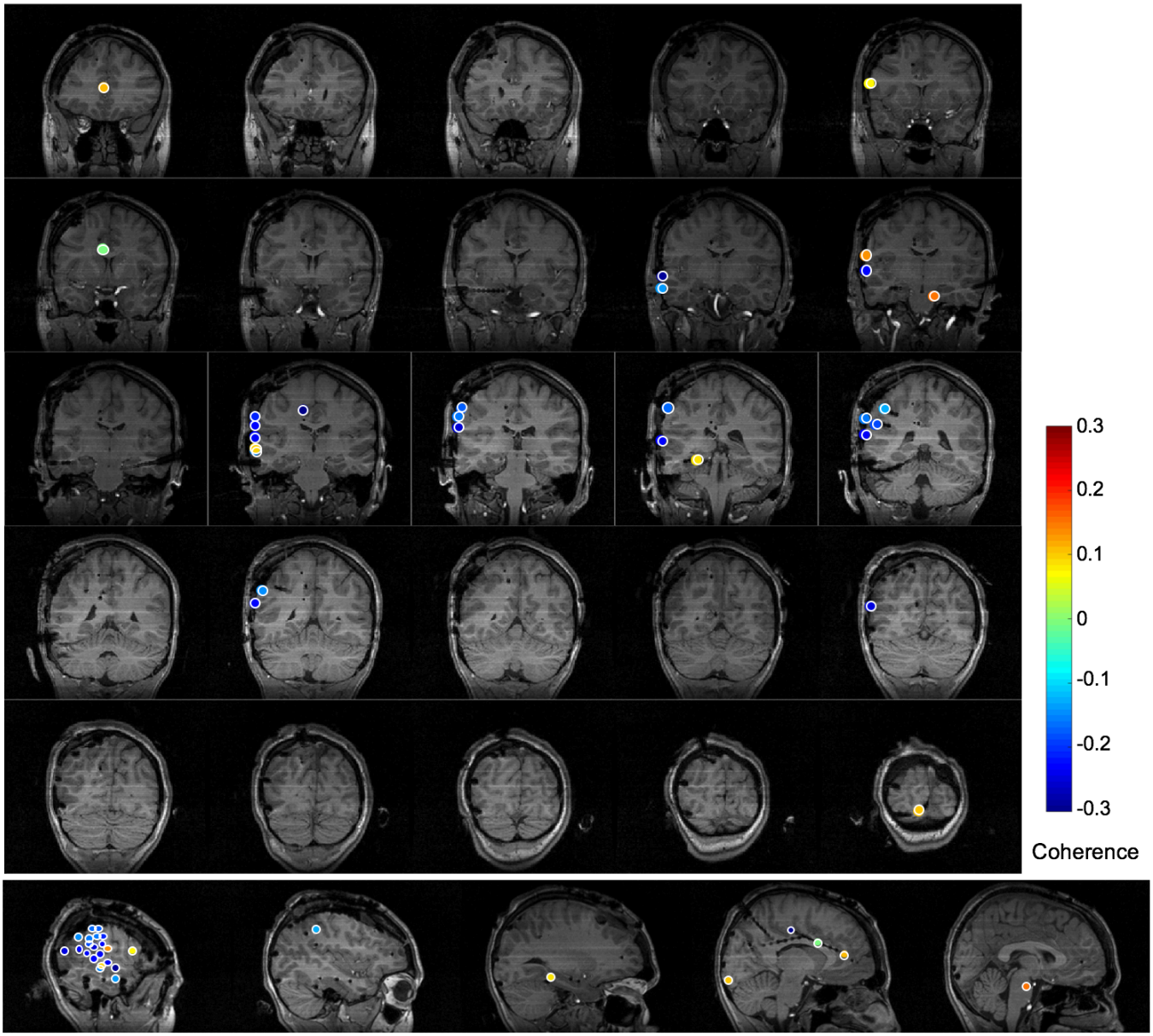


Figure S6. LFP coherence merged with postoperative MRI with electrode contacts localized *in situ*. LFP shows reduced coherence with the cingulum (Figure 1 purple) across the network following stimulation vs. sham. Colored dots indicate electrode locations and the corresponding coherence using the heat map as indicated in the legend. Only contacts with statistically significant ($p < .05$ uncorrected) changes in coherence are presented using colored dots; non-colorized dots indicate contact locations with non-significant changes in coherence. Slices have an inter-slice distance of 5mm; locations of electrodes in brain tissue are approximated to the nearest 5 mm slice presented below.

Figure S7. LFP Power by array in index patient.

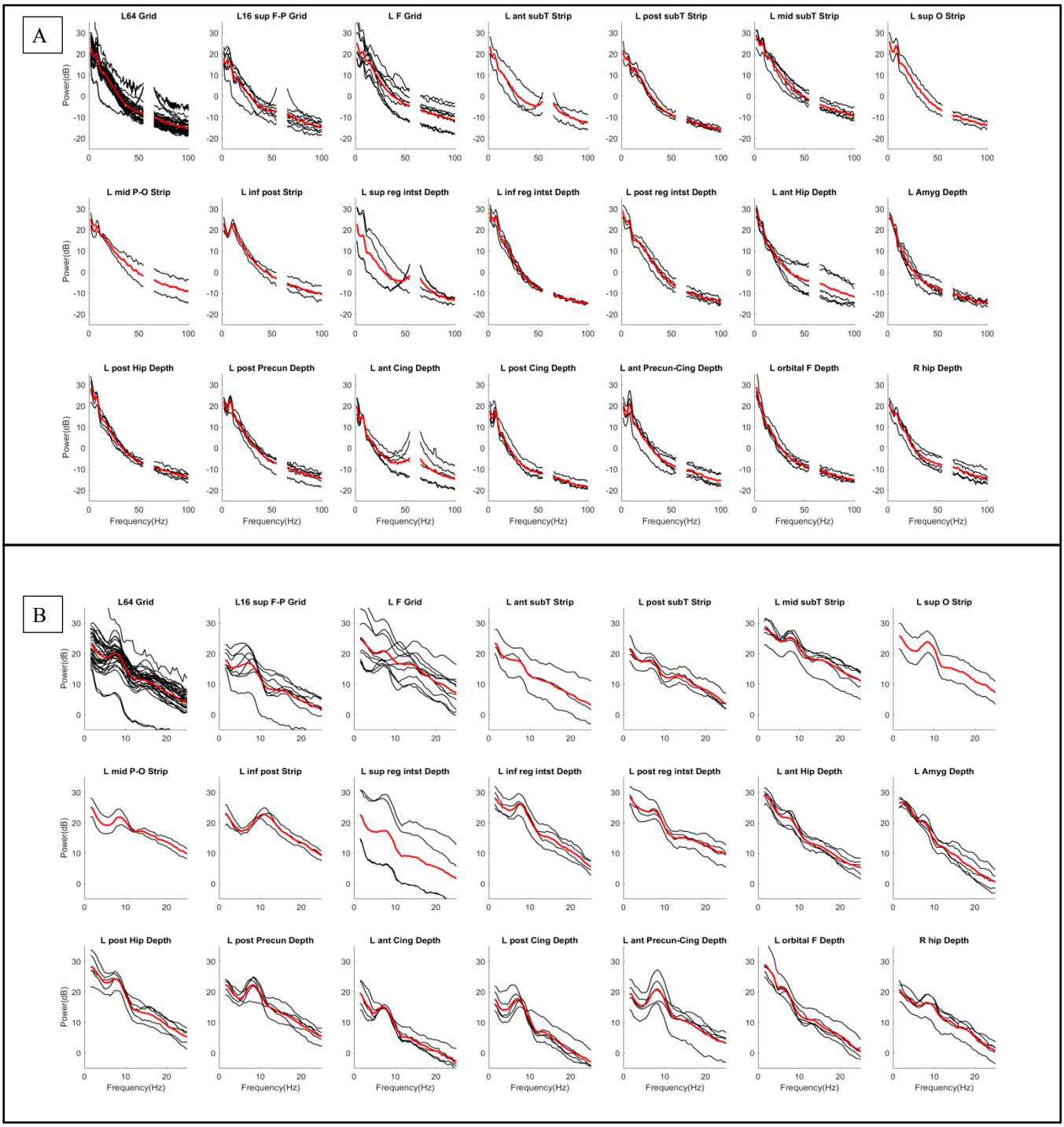


Figure S7. LFP Power by array in index patient. Panel A demonstrates power spectral density at baseline of each channel between 1 and 100Hz. Discontinuous lines reflect that we did not plot 60 Hz line noise. We have plotted all 127 channels grouped into surface grids and strips, as well as stereotactic depth electrodes, each constituted of a number of individual contacts. Each panel demonstrates a single

grid, strip, or depth electrode, where each contact in each group is plotted as a black line, overlaid with red lines indicating group means for each. Panel B provides a clearer picture of the low frequency oscillations on each channel (black) as well as in the group mean per array (red), focusing on the range between 1 and 25Hz. Abbreviations: L: left, R: right, ant: anterior, post: posterior, sup: superior, inf: inferior, F: frontal, P: parietal, T: temporal, O: occipital, Amyg: amygdala, Hip: hippocampus, Cing: cingulate, Precun: precuneus.

Figure S8: Facial motor dynamical activity analysis

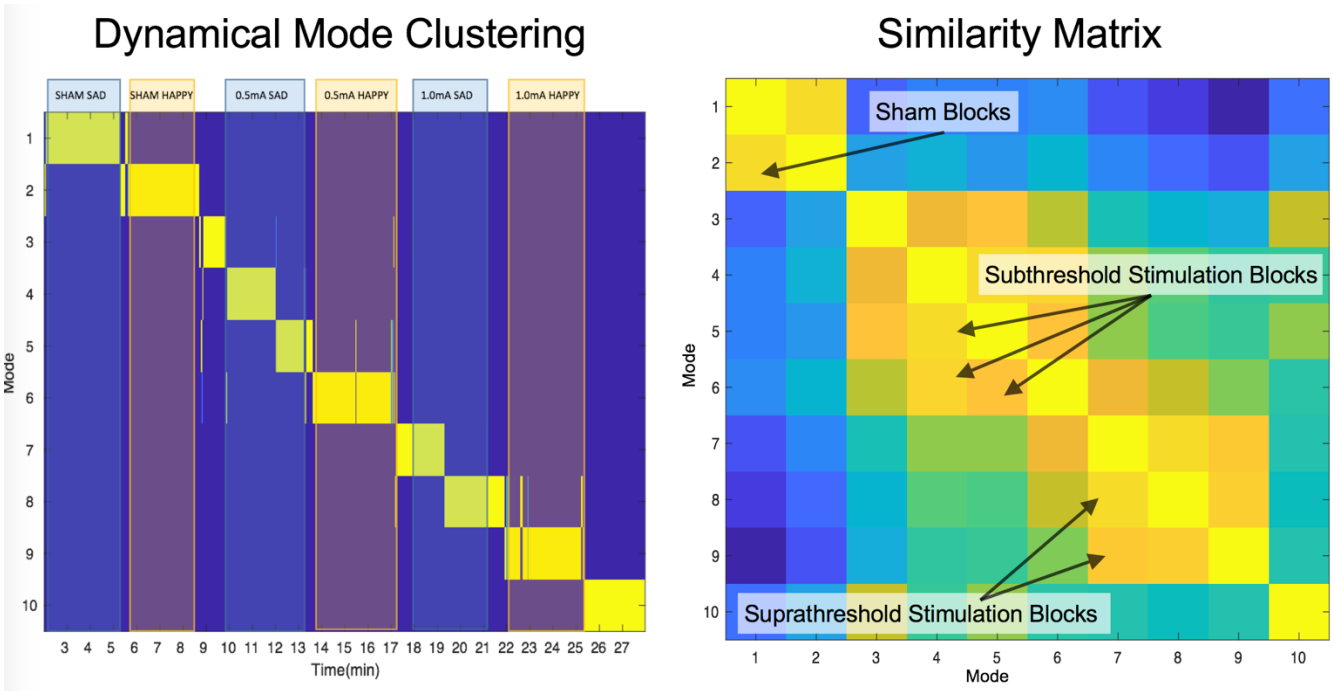


Figure S8. Facial motor dynamical activity analysis. Left Panel: Modes (pixel-wise intensity dynamical clustering) during video of patient's face during the affective bias task align with periods of time in which she was completing different blocks of the task (evaluating happy vs. sad faces) under different stimulation conditions (sham, subthreshold cingulum stimulation, suprathreshold cingulum stimulation). Right Panel: Similarity analysis compares pixel-wise intensity dynamics across time in video recorded of the patient's face during the affective bias task. Hotter colors indicate greater similarity among modes as defined in left panel. Taken together, Panels indicate greater similarity between sham blocks than stimulated blocks, different patterns of activity between sub-threshold and supra-threshold stimulation blocks. and different patterns of stimulation between blocks where the patient evaluated sad vs. happy faces during the task.

Table S1. Trial-by-trial patient self-report during cingulate gray and white matter stimulation and sham in index patient.

Left cingulate gray matter stimulation, contacts 1-2 (Figure 1 yellow and green), 50Hz, 200μs pulse width, 5 sec duration.		
Trial	**Current (mA)**	**Patient Report and Research Observations**
1	0.5mA	Denies subjective experience
2	0.5mA	Denies subjective experience
3	0.5mA	Denies subjective experience
4	1.0mA	Denies subjective experience
5	1.0mA	Denies subjective experience
6	1.0mA	Denies subjective experience
7	1.5mA	Denies subjective experience
8	1.5mA	Denies subjective experience
9	1.5mA	Denies subjective experience
10	2.0mA	Denies subjective experience
11	2.0mA	Denies subjective experience
12	2.0mA	Denies subjective experience
13	2.5mA	Denies subjective experience
14	2.5mA	Denies subjective experience
15	2.5mA	Denies subjective experience
16	3.0mA	Denies subjective experience
17	3.0mA	Denies subjective experience
18	3.0mA	Denies subjective experience, reports doing okay.
19	3.5mA	Denies subjective experience
20	3.5mA	Denies subjective experience
21	3.5mA	Patient reports no feeling from stimulation, feels “neutrally anxious”.
Left cingulate gray matter stimulation, contacts 1-2 (Figure 1 yellow and green), 130Hz, 300μs pulse width, 5 sec duration.		
Trial	**Current (mA)**	**Patient Report and Research Observations**
1	0.5mA	Denies subjective experience
2	0.5mA	Denies subjective experience
3	0.5mA	Denies subjective experience
4	1.0mA	Denies subjective experience
5	1.0mA	Denies subjective experience
6	1.0mA	Denies subjective experience
7	1.5mA	Denies subjective experience
8	1.5mA	Denies subjective experience
9	1.5mA	Denies subjective experience
10	2.0mA	Denies subjective experience
11	2.0mA	Denies subjective experience
12	2.0mA	Denies subjective experience
13	2.5mA	Denies subjective experience
14	2.5mA	Denies subjective experience
15	2.5mA	Denies subjective experience
16	3.0mA	Denies subjective experience
17	3.0mA	Denies subjective experience
18	3.0mA	Denies subjective experience

19	3.5mA	Denies subjective experience
20	3.5mA	Denies subjective experience
21	3.5mA	Denies subjective experience
Left cingulum white matter stimulation, contacts 3-4 (Figure 1 red and blue), 130Hz, 300μs pulse width, 5 sec duration.		
Trial	**Current (mA)**	**Patient Report and Research Observations**
1	0.5mA	Denies subjective experience
2	0.5mA	Denies subjective experience
3	0.5mA	Denies subjective experience
4	1.0mA	Denies subjective experience
5	1.0mA	Patient reports that she "kinda feels something", begins smiling involuntarily, reports feeling a little confused.
6	1.0mA	Patient immediately smiles, "I'm smiling because I can't help it", then reports that she felt it for the past 3 stimulations (all three times that 1.0mA stims were run).
7	1.0mA	Patient smiles and laughs, reports that she feels the same feeling as before (when the 1.0mA stims were run).
8	1.5mA	Patient smiles, reports feeling her eyebrows twitch and smiling on her right side, "feels kinda like a seizure" and feeling a little confused because something is happening to her that she doesn't understand.
9	1.5mA	Patient smiles, "I feel something", reports that it makes her feel a little restless, feels like there's a change in her mood.
10	1.5mA	Patient smiles, "No memories or anything, just a feeling of happiness", involuntary smile.
11	2.0mA	Patient smiles, "It felt the same, just more intense", in a good way.
12	2.0mA	Patient smiles, "That's awesome!"
13	2.5mA	Patient reports feeling the same (happy), feeling her eyebrows twitch more with this stimulation.
14	Sham	Denies subjective experience
15	3.0mA	Patient immediately smiles and laughs, reports feeling the same, feeling the smile more on her right side.
16	3.5mA	Patient immediately smiles and laughs, "Wow everyone should have this", more intense than the previous stimulations.
17	3.5mA	Patient immediately smiles and laughs, "I'm so happy that I wanna cry basically".
18	Sham	Run during affective bias task, patient denies subjective experience
19	Sham	Run during affective bias task, patient denies subjective experience
20	0.5mA	Run during affective bias task, patient denies subjective experience
21	0.5mA	Run during affective bias task, patient denies subjective experience
22	1.0mA	Run during affective bias task, patient smiles and laughs, reports that she felt relaxed and still felt happy.
23	1.0mA	Run during the affective bias task, patient smiles, reports that the feeling is in no way bothersome.
Left cingulum white matter stimulation, contacts 3-4 (Figure 1 red and blue), 50Hz, 200μs pulse width, 5 sec duration.		
Trial	**Current (mA)**	**Patient Report and Research Observations**
1	0.5mA	Denies subjective experience.
2	0.5mA	Denies subjective experience.
3	1.0mA	Denies subjective experience
4	1.5mA	"I can really feel that, my mind is at ease", reports feeling more relaxed.
5	Sham	Reports feeling the same, relaxed.
6	2.0mA	Patient reports feeling a high, relaxed feeling, more intense than previous stimulations.
7	2.5mA	Patient smiles on the right side of mouth, reports that on previous stimulations she could control smiling and laughing, but had less control during this one.
8	3.0mA	Patient reports feeling the sensation more on her right side.
9	Sham	Denies subjective experience
10	3.5mA	Patient reports that she can feel the same sensation but it is not the most intense one, still feels the sensation on the right side.
Left posterior cingulum white matter stimulation, contacts 5-6 (Figure 1 purple and magenta), 130Hz, 300μs pulse width, 5 sec duration.		

Trial	Current (mA)	Patient Report and Research Observations
1	0.5mA	Denies subjective experience
2	0.5mA	Denies subjective experience
3	0.5mA	Denies subjective experience
4	1.0mA	Denies subjective experience
5	1.0mA	Denies subjective experience
6	1.0mA	Denies subjective experience
7	1.5mA	Patient reports a high sensation, not confused, doesn't feel anything different in face, feels like previous stimulations.
8	1.5mA	Patient reports feeling the same high sensation, not unpleasant, feeling diminishes over time.
9	1.5mA	Patient reports the same feeling, feeling diminishes over time.
10	2.0mA	Patient reports feeling "almost paralyzed", like she was going to have a seizure, felt a little scared and anxious because she felt like she was going to have a seizure, felt back to normal before moving onto next stimulation. No seizure activity noted on intracranial EEG.
11	2.0mA	Patient reports that "it feels like too much", feeling it more on the right side which is typical of her seizures, it scared her a little.
12	1.0mA	Patient reported that she felt the same, just much less intense, more of a happy feeling.
13	0.5mA	Patient reported feeling the same happy feeling, just not as strong.
14	0.5mA	Denies subjective experience
15	Sham	Denies subjective experience
16	Sham	Denies subjective experience
17	0.5mA	Denies subjective experience
18	1.0mA	Patients reports a happy feeling but "it's not super strong", very pleasant feeling.
Transient Stimulation Experiment, left cingulum white matter stimulation, contacts 3-4 (Figure 1 red and blue), 130Hz, 300μs pulse width, 1 sec stimulation and sham duration, 10 sec inter-stimulus interval for electrophysiology recording.		
Trial	**Current (mA)**	**Patient Report and Researcher Observations**
1	3.5mA	Patient immediately smiles, only lasts for a couple seconds
2	3.5mA	Patient immediately smiles, only lasts for couple seconds
3	3.5mA	Patient immediately smiles, only lasts for a couple seconds
4	Sham	No reported reaction, no change in facial expression
5	Sham	No reported reaction, no change in facial expression
6	3.5mA	Patient immediately smiles, only lasts for a couple seconds
7	3.5mA	Patient immediately smiles, only lasts for a couple seconds
8	Sham	No reported reaction, no change in facial expression
9	3.5mA	Patient immediately smiles, only lasts for a couple seconds
10	Sham	No reported reaction, no change in facial expression
11	3.5mA	Patient immediately smiles, only lasts for a couple seconds
12	3.5mA	Patient immediately smiles, only slightly, lasts for a couple of seconds
13	3.5mA	Patient immediately smiles, only for a couple seconds
14	Sham	No reported reaction, no change in facial expression
15	3.5mA	Patient immediately smiles, only slightly, lasts for a couple seconds
16	3.5mA	Patient immediately smiles, only lasts for a couple seconds
17	Sham	No reported reaction, no change in facial expression
18	3.5mA	Patient immediately smiles, only slightly, lasts for a couple of seconds
19	3.5mA	Patient immediately smiles, only slightly, lasts for a couple of seconds
20	Sham	No reported reaction, no change in facial expression
21	3.5mA	Patient immediately smiles, only slightly, lasts for a couple of seconds
22	3.5mA	Patient immediately smiles, only lasts for a couple of seconds
23	Sham	No reported reaction, no change in facial expression
24	3.5mA	Patient immediately smiles, only lasts for a couple of seconds
25	Sham	No reported reaction, no change in facial expression
26	3.5mA	Patient immediately smiles, only slightly, lasts for a couple of seconds
27	3.5mA	Patient immediately smiles, only slightly, lasts for a couple of seconds

28	3.5mA	Patient immediately smiles, only lasts for a couple of seconds
29	3.5mA	Patient immediately smiles, only lasts for a couple seconds
30	Sham	No reported reaction, no change in facial expression

Researchers ask patient to have normal conversation, without trying to hold back laughter. Stimulation is delivered continuously to the left cingulum white matter, contacts 3-4(Figure 1 red and blue), 130Hz, 300μs pulse width, 2.0mA.

Researcher Prompt	**Time ON**	**Patient Response**
"What are you feeling?"	0:05	"I can't stop laughing, like I don't know what to say"
"Does it feel like someone is tickling you?"	0:55	"No, it just feels like I'm laughing and I'm happy and that's what it feels like"
"Does it feel like its wearing off?" "What does that mean?"	1:17	"Yeah, I think it wears off a little more over time, and then I start to feel it in my brain" "I feel more like a weird, high-ish kinda feeling"
"Weird-good? Weird-bad? Or just weird-weird?"	1:36	"It's weird-weird. I probably couldn't handle it for a long time, because this is kinda how it feels when I have a seizure"
"Is it the sense that you're not in control?" "But not like the exact feeling when you have a seizure?" Just like the sense that you are out of control of your body?"	1:55	"Yes, exactly. Like I'm not in control" "Right"
"Would you describe it as euphoria?"	2:33	"Yeah, kinda"
"Does this feel like sitting and watching a funny movie or being at a comedy club, or does this feel like something else?"	2:47	This is something else. It started out feeling like watching a funny movie, and then it turned into a weird feeling"
"Do you feel like your threshold to laugh is lower?"	4:31	"It's lower, but it's still kinda there" "…its more smile now"
"And how about that feeling in your face?"	5:17	"I still feel like this this side (right corner of mouth) is a little tight and like I don't have control over it, but other than that I can talk normally. I feel like I could function (smiles and laughs)"
"Do you think you frown right now?" "Can you try to furrow your brow?"	5:37	-Patient attempts to frown, but is unsuccessful because she can't turn mouth into a frown. Patient continues to smile and laugh -Patient attempts to furrow her brow and is able to do it for a very short period of time before she begins to laugh and smile again
"Can you think of something sad?" "Can you think of something disgusting?"	6:11	"I'm trying to think of my dog dying but it's not working" (laughs and smiles) "Yeah I can think of memories, but they're not coming up as sad memories"
Asked to describe a sad memory, and patient begins to talk about her grandfather's funeral	7:44	"…I almost feel like, right now, my threshold to cry is… [really low]" "Yeah. Like I feel like I could burst into tears right now. I don't know why"
"…can you think of a time that was really disgusting, where you saw something really gross?" "Do you feel sick to your stomach now like you did when you were watching it?"	9:03	"I was watching Grey's Anatomy last night, and they were in the burn victim's unit, and for some reason that made me really, really sick. Like it makes me want to vomit. And I remember that as a disgusting memory, but not in a mean way just in a way that would make me kinda sick…(inaudible)" "No, actually I don't at all" "I don't feel sick. I just feel this constant happiness"

"Does it come in waves?"	10:25	"Yes it comes in waves"
"How about a memory from longer ago? Like a memory from middle school or something, a happy memory from then?"	11:38	"One time I won the science fair. That was really, really, happy" [Patient smiles and laughs]
"How about your smile? Can you frown?"	12:19	"That does feel a little silly, but I can definitely feel it going away. I feel more in control of over my voice and my emotions"
"Do you still feel that happy feeling?"	13:38	"I feel happy, but like a normal happy"
"How about level of anxiety vs relaxed vs happy?"	13:47	"I'm really relaxed. I'm not anxious or anything"

Legend: Patient self-report was aggregated by an independent rater who reviewed the videos of all patient testing, transcribed all responses, synthesized summary tables and summary statements.

Table S2. Trial-by-trial patient self-report during cingulum bundle stimulation and sham in Patient 2.

Right cingulum bundle stimulation, contacts 1-2 (Figure S1 yellow and green), 130Hz, 300μs pulse width, 5 sec duration. Baseline ratings were taken for the patient at the beginning of testing using a visual analog scale for each of happiness (0 = very sad, 10 = very happy), relaxation (0 = very anxious, 10 = very relaxed), and pain (0 = no pain, 10 = excruciating pain). The patient's ratings were: Happiness = 4, Relax = 0, Pain = 4.

Trial	Current (mA)	Patient Report and Research Observations
1	0.5	No patient report
2	0.5	No patient report
3	1.0	No patient report
4	1.0	No patient report
5	1.5	No patient report
6	1.5	No patient report
7	2.0	No patient report
8	2.0	No patient report
9	2.5	Patient reported a change in facial expression from the muscles on the left side of his face.
10	2.5	No patient report, but the corner of the mouth on the left side is a pulling slightly.
11	3.0	No patient report
12	3.0	Patient reports some feeling in his left face (points to cheek and lip area). Pt: "It wasn't a noticeable jolt. It just kind of started to change a little bit…without me doing it…I had to straighten my face back down a little bit."
13	3.0	The left corner of the patient's mouth immediately pulls up. Patient could not report if the feeling was the same.
14	3.0	Patient immediately smiles. Pt: "It's strange, only it's both sides…it started just on one side (the left) …It was more left than anything else". Patient reports feeling a change in mood, feels happier now. Pt: "It definitely went up- more positive…I was about to start laughing"
15	Sham	No patient report
16	3.5	Patient immediately smiles and laughs slightly.
17	3.5	Patient immediately has a big smile and begins to laugh. Pt: "Elicit a tickling smiling response"
18	3.5	Patient immediately smiles and laughs a little. Pt: "It's just humorous I guess" Patient still feeling the pull on the muscles on both sides of his faces Pt: "It's all the sensory stuff in my face that I am cognitively aware of"

19	Sham	No patient report
20	3.5	Patient immediately smiles, however, does not report feeling the same as other stimulations at the same parameters.
Right cingulum bundle stimulation, contacts 2-3 (Figure S1 green and red), 130Hz, 300μs pulse width, 5 sec duration.		
Trial	**Current (mA)**	**Patient Report and Research Observations**
1	0.5	No patient report
2	0.5	No patient report
3	1.0	No patient report
4	1.0	No patient report
5	1.5	No patient report
6	1.5	No patient report
7	2.0	Patient reports no feeling. Patient looks around and smiles slightly.
8	2.0	Patient immediately has a small smile. Patient reports feeling "a little bit" of something
9	2.5	Patient immediately smiles and laughs a little bit. Reports that during brain mapping in the past, he would feel the stimulation before feeling the response, however, now he feels the response before the stimulation- "it's strange" Researcher asks if he feels the muscles move first then he feels a change or are they tied together- "all together."
10	2.5	Patient immediately smiles and chuckles. Felt the urge to move (adjust) whole body. Moving because he feels more "energetic". This makes it easier to move.
11	3.0	Patient immediately smiles and laughs very slightly. He also adjusts his posture and moves his whole body as soon as the stimulation is turned on.
12	3.0	Patient immediately smiles and laughs more. Pt: "…it makes me want to move…the wiggles"
Right middle temporal gyrus stimulation (as positive control), contacts 8-9, 130Hz, 300μs pulse width, 5 sec duration.		
Trial	**Current (mA)**	**Patient Report and Research Observations**
1	0.5	Denies subjective experience
2	0.5	Denies subjective experience
3	1.0	Denies subjective experience
4	1.0	Denies subjective experience
5	1.5	Denies subjective experience
6	1.5	Denies subjective experience
7	2.0	Denies subjective experience
8	2.0	Denies subjective experience
9	2.5	Denies subjective experience
10	2.5	Denies subjective experience
11	3.0	Denies subjective experience
12	3.0	Denies subjective experience
13	3.5	Denies subjective experience
14	3.5	Denies subjective experience
Right cingulum bundle stimulation, contacts 1-2 (Figure 1 yellow and green), 130Hz, 300μs pulse width, 1 sec duration per 30 second interval.		
Trial	**Current (mA)**	**Patient Report and Research Observations**
1	3.5	Patient smiled and moved both hands
2	3.5	Patient smiled and moved both hands immediately
3	Sham	No patient reaction
4	3.5	Patient smiled and moved both hands before adjusting posture.
5	3.5	Patient immediately smiled and moved left hand.
6	Sham	No patient reaction
7	3.5	Patient immediately smiles, and lifts left hand (like movement in condition #5).
8	Sham	No patient reaction
9	3.5	Patient immediately smiles and moves left hand and leg.
10	3.5	Patient immediately smiles and moves slightly.

11	Sham	No patient reaction
12	3.5	Patient immediately smiles and seems to adjust something on side table.
13	3.5	Patient immediately smiles and moves head side to side.
14	3.5	Patient immediately smiles (lasts for about 3 seconds).
15	Sham	No patient reaction
1	3.5	Patient smiled and moved both hands
2	3.5	Patient smiled and moved both hands immediately
3	Sham	No patient reaction
4	3.5	Patient smiled and moved both hands before adjusting posture.
5	3.5	Patient immediately smiled and moved left hand.
6	Sham	No patient reaction
7	3.5	Patient immediately smiles, and lifts left hand (like movement in condition #5).
8	Sham	No patient reaction
AFTER EXPERIMENT: KRB: "What did you feel while we were doing that?" Pt: "I felt the urge to laugh…whenever I did feel that I felt the urge to move around…I wasn't aware of that until you started to ask me about that. Even if it wasn't like full body movement, I would have to move my hands or move my arms"		

Table S3. Trial-by-trial patient self-report during cingulum bundle stimulation and sham in Patient 3.

Right cingulum bundle stimulation, contacts 2-3 (Figure S2 green and red), 130Hz, 300μs pulse width, 5 sec duration: Baseline ratings were taken for the patient at the beginning of testing using a visual analog scale for each of happiness (0 = very sad, 10 = very happy), relaxation (0 = very anxious, 10 = very relaxed), and pain (0 = no pain, 10 = excruciating pain). The patient's baseline ratings were: Happiness = 8, Relax = 4, Pain = 4.		
Trial	**Voltage (V)**	**Patient Response or Researcher Observation**
1	0	No patient report
2	1	No patient report and no change in ratings
3	0	No patient report and no change in ratings
4	2	No patient report and no change in ratings. Patient laughed about relaxation joke from earlier. Ratings change: • Pain:3-4 • Happiness:8 • Relax: 4
5	3	Pt: "Kind of like a déjà vu…" Did not feel like usual aura. Pt: "Like out of body…I wouldn't want to experience it…it messed with my eyes. It almost felt like my eyes were bulging" Agreed that it was unpleasant and unfamiliar feeling. Ratings change: • Pain: 2 • Happiness: 8 • Relax: 4
6	0	No patient report and no change in ratings
7	4	Pt: "More like my regular aura…". Only felt the change while the stim was on and it went away once the stim was turned off. Patient described regular aura feeling which included numbness in the tongue for a split second, and a jolt push feeling on the left side of the face (quotes are listed above in transcript)

8	4	Pt: "Almost like the second part after the aura when it's going into the seizure…like when I'm able to say that I'm having a seizure" No change in baseline ratings. Researchers decide to move contacts because they do not want to trigger a seizure.
Right cingulum bundle stimulation, contacts 3-4 (Figure S2 red and blue), 130Hz, 300us pulse width, 5 sec duration. The patient's baseline ratings were: Happiness = 7, Relax = 8, Pain = 4.		
Trial	**Voltage (V)**	**Patient Report and Research Observations**
1	1	Stabbing headache feeling above eyes but felt superficial. Other head pain 1/10, pain with stabbing 3/10 Pt: "Right above my eyes. It started right above my eyes…then it stopped when it was shut off" Change in baseline ratings: • Pain- 2 (decreased) • Happy- 8 • Relax- 6
Repeat 1	1	Felt a similar headache feeling. Other head pain is still a 1/10 Pt: "More achy and pressure...more on the left"
2	0	No patient report and no change in ratings. Other head pain increased to 5/10 (not associated with stim)
3	2	Pt: "Everything felt really far away…with my vision" Tunnel vision but did not lose peripheral vision. Went away when the stim was turned off. Not like usual seizure or aura. Head pain is still at 5/10
4	3	Patient smiled and laughed slightly. Not an unpleasant feeling. Still have the tunnel vision but didn't bother patient Change in baseline ratings: • Pain- 2 • Happy- 9 • Relax- 10
Repeat 4	3	Patient immediately smiles. Couldn't control smiling and felt like she couldn't stop smiling even if she wanted to. Not an unpleasant feeling. No change in baseline ratings.
5	0	No patient report and no change in ratings
6	4	Patient smiled, started on left side. More relaxed and happy when smiling. Tunnel vision is gone. Pt: "Out of this world…" Pt: "It didn't feel real…it was weird" This stim was more intense than condition 4.
7	0	No patient report. Head pain is back at 5/10. Change in baseline ratings: • Overall pain- 3 (slight increase)
8	5	Patient immediately smiles and laughs. Feels it more the left side. Doesn't feel like she is making herself smile. Pt: "The clock made me laugh. The six on the clock to be exact" Change in baseline ratings: • Pain- 1 • Happy (while stim on)- 9 • Relax (while stim on)- 10 • Relax (with stim off)- 7 Pt: "I don't feel out of this world or out of body" (with the stim off) Pt: "Like I'm sitting next to myself almost…outside of my body. Before it was looking down out of this world but this more outside my body"
Repeat 8	5	Patient immediately smiles. More used to out of body feeling from before Pt: "Like I got the urge to laugh and I couldn't stop myself" Change in baseline ratings:

		• Pain- 4 (increased) • Happy- 9 • Relax- 10
9	6	Patient immediately smiles. Pt: "Like I needed to laugh but I'm mad at the same time (laughs strongly) …it was a little more embarrassment" (Felt slightly more embarrassed than mad) Feeling doesn't go away during stim (it doesn't mellow out) Pt: "I ended up holding my breath" (not on purpose)
Right cingulum bundle stimulation, contacts 3-4 (Figure S2 red and blue), 130Hz, 300μs pulse width, 3 minute duration. Baseline ratings: Pain= 2, Happy = 9, Relax = 10**.**		
Trial	**Voltage (V)**	**Patient Report and Research Observations**
1	3	Patient immediately smiles and laughs, effect faded quickly. The feeling after stim also faded quickly. Completely goes away after a couple seconds. When patient did feel something: Pt: "Everything was just funny". Patient reports headache from left lateral occipital area when stimulation was turned off.
2	4	Feeling fades very quickly. Laughed slightly more than first continuous stim at 3V. No change in ratings. Had pain when she laughed that was present before. Annoyed that laugh makes it hurt. Asked to talk about sad memory- While describing situation, patient is smiling and sounds happy. Doesn't feel sad when thinking about it. Talked about sad memory of old pet and its feels less bothersome to talk about it during stim. Doesn't bother her as much as usual. Patient can frown for a few seconds before laughing after. Tried again and could hold frown a little longer. Feels a little more energetic. Has a feeling that she could go get something done (get up and do it). Also feels more optimistic because she is feeling the aura for an occipital seizure (generally), doesn't feel it in the moment though. Patient states that given the clinical environment in the EMU, she feels more tired and less focused than usual. Pt: "I couldn't sit down and write a paper or anything like that" but doesn't feel distracted.
3	0 (unblinded)	When the stim is turned off: Pt: "My headache got worse. It was at like a two and now it's at a six…in the same spot but it got worse" Patient liked that the stim took away her headache. Patient didn't like the out of body and out of this world feeling which she reported to occur only transiently at the very beginning of stimulation.

Table S4: Individual neuropsychological testing in Patient 2 prior to surgery and during 2 hours of continuous cingulum bundle stimulation.

Measure	Baseline Score (Raw)	Stimulated Score (Raw)
WAIS-IV Digit Span	29	28
WAIS-IV Symbol Search	24	
WAIS-IV Coding		62
DKEFS Design Fluency – Filled Dots	14	15
DKEFS Design Fluency – Empty Dots	9	10
DKEFS Design Fluency – Switching	9	7
Rey AVLT Learning	46	53
Rey AVLT Immediate	9	7

Rey AVLT Delay	10	6
Rey AVLT Discrimination	14	15
Rey AVLT 3 Trial	25	29
DKEFS Color/Word – Color Naming	35.75	
DKEFS Color/Word – Word Reading	32.12	
Grooved Pegs – Dominant		T = 47
Grooved Pegs – Non-dominant		T = 43

Caption for movie files:

Movies S1-S3 demonstrate the immediacy and replicability of the subjective phenomenon, patient descriptions of facial motor effects and emotional memory effects during chronic stimulation. The patient describes feeling happy and relaxed during awake resection of seizure focus, demonstrates a cued smile. Transient stimulations to dorsal cingulum bundle evoke stereotyped smiling response, sham stimulations do not.

STROBE Statement – Observational study

	Reported on page no.	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2-3	Explain the scientific background and rationale for the investigation being reported
Objectives	2-3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	3	Present key elements of study design early in the paper
Setting	3-4, 24-25	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	3-4, S1	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	6-14	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6-14	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	6-14	Describe any efforts to address potential sources of bias
Study size	3-4, S1	Explain how the study size was arrived at
Quantitative variables	6-14	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	28-29	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	3-4, S1	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	3-4, S1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	6-14	Report numbers of outcome events or summary measures over time
Main results	6-14	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear

		which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18-21	Summarise key results with reference to study objectives
Limitations	22	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	18-22	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	23-24	Discuss the generalisability (external validity) of the study results
Other information		
Funding	31	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based