



State-dependent responses to intracranial brain stimulation in a patient with depression

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Deep brain stimulation is a promising treatment for severe depression, but lack of efficacy in randomized trials raises questions regarding anatomical targeting. We implanted multi-site intracranial electrodes in a severely depressed patient and systematically assessed the acute response to focal electrical neuromodulation. We found an elaborate repertoire of distinctive emotional responses that were rapid in onset, reproducible, and context and state dependent. Results provide proof of concept for personalized, circuit-specific medicine in psychiatry.

Major depressive disorder (MDD) is a common, highly disabling disorder¹ associated with a high level of treatment resistance². Deep brain stimulation (DBS) emerged in 2003 as a highly promising addition to the therapeutic armamentarium³ for the most refractory patients². However, early tantalizing results were not consistently replicated across three randomized, controlled studies^{4–6}. Although trial design might have been a key factor in trial outcome^{7,8}, low response rates suggest that novel strategies in DBS treatment are needed⁷. One such strategy is personalization of DBS circuit targeting, which is supported by positive findings in open-label DBS studies targeting different brain regions^{3,9}. Personalization of therapy is proposed as a means to improve outcomes in medicine generally but has remained elusive in the field of psychiatry¹⁰. Direct neural recordings and intracranial stimulation are promising tools for evaluating whether it is possible to establish proof of concept for a circuit-targeted precision medicine approach, where dysfunctional neural circuits are reliably identified and targeted to change a specific set of symptoms experienced by an individual. It has been shown that engagement of brain stimulation targets based on patient-level anatomy can improve outcome in DBS for depression^{11,12}, and personalized electrocortical stimulation mapping is considered the gold standard for functional cortex localization before surgical resection in epilepsy¹³. In this study, we built on these two approaches and the early intracranial stimulation work of Bishop et al.¹⁴ by carrying out personalized electrocortical stimulation mapping that could serve as a basis for personalized DBS in depression. We implanted temporary intracranial electrodes across corticolimbic circuits for a 10-d inpatient monitoring interval to evaluate responses to an array of focal stimulations and to establish the relationships between stimulation characteristics and clinical response. Here we describe the findings from stimulus–response mapping and demonstrate new properties of brain stimulation responses that provide proof of concept for personalized medicine in psychiatry.

The patient was a 36-year-old woman with severe treatment-resistant MDD (trMDD) (Montgomery Asberg Depression Rating

Scale: 36/54) with childhood onset and a family history of suicide. She had three distinct lifetime episodes of depression with periods of better functioning in between and experienced the full constellation of depression symptoms within each episode. Her primary symptoms of the most recent 4-year episode included anhedonia, energy and cognitive deficits. This depression episode was not adequately responsive to four antidepressant medications, augmentation strategies, electroconvulsive therapy and transcranial magnetic stimulation (Supplementary Information). Owing to her level of treatment resistance, she was enrolled in a clinical trial of personalized closed-loop DBS for trMDD.

This trial included a 10-d exploratory stage, where ten stereo-electroencephalography electrodes (160 contacts) were implanted across the orbitofrontal cortex (OFC), amygdala, hippocampus, ventral capsule/ventral striatum (VC/VS) and subgenual cingulate (SGC)^{3,9,15–17} bilaterally for the purpose of personalized target selection. During this time, we assessed clinical response to a pre-selected set of stimulation parameters using a five-point Likert scale combining subjective responses with physician-rated affect, visual analog scales of depression, anxiety and energy and a six-question subscale of the 17-item Hamilton Depression Rating Scale¹⁸. An elaborate repertoire of emotions across different sites and stimulation parameters was observed with ~90 s of stimulation (summarized in Fig. 1a). For example, she reported ‘tingles of pleasure’ with 100-Hz VC/VS stimulation, ‘neutral alertness ... less cobwebs and cotton’ with 100-Hz SGC stimulation and calm pleasure ‘like ... reading a good book’ with 1-Hz OFC stimulation. Despite the patient being blinded to the stimulation site, her verbal reports were remarkably consistent with many reports in the literature^{15,19,20} and revealed new associations as well, such as the anxiolytic, sedating effects of the OFC (Fig. 1b).

Stimulation paradigms that exhibited positive responses were tested with sham-controlled stimulation with 3-min stimulation periods. We were surprised to identify three paradigms in a single patient that all reliably improved symptoms but targeted different dimensions of depression (Fig. 1c). Two of these paradigms—100-Hz stimulation of the SGC³ and the VC/VS⁹—were consistent with previous DBS studies. The third was a novel location and stimulation condition: low-frequency stimulation across a broad region of the OFC (Fig. 1d).

We next tested brain–behavioral relationships of prolonged stimulation (10 min) at these three stimulation paradigms. Notably, we observed that response to stimulation interplayed closely with the patient’s core symptoms and symptom state at the time of stimulation. First, we found that responses were reproducible as a function

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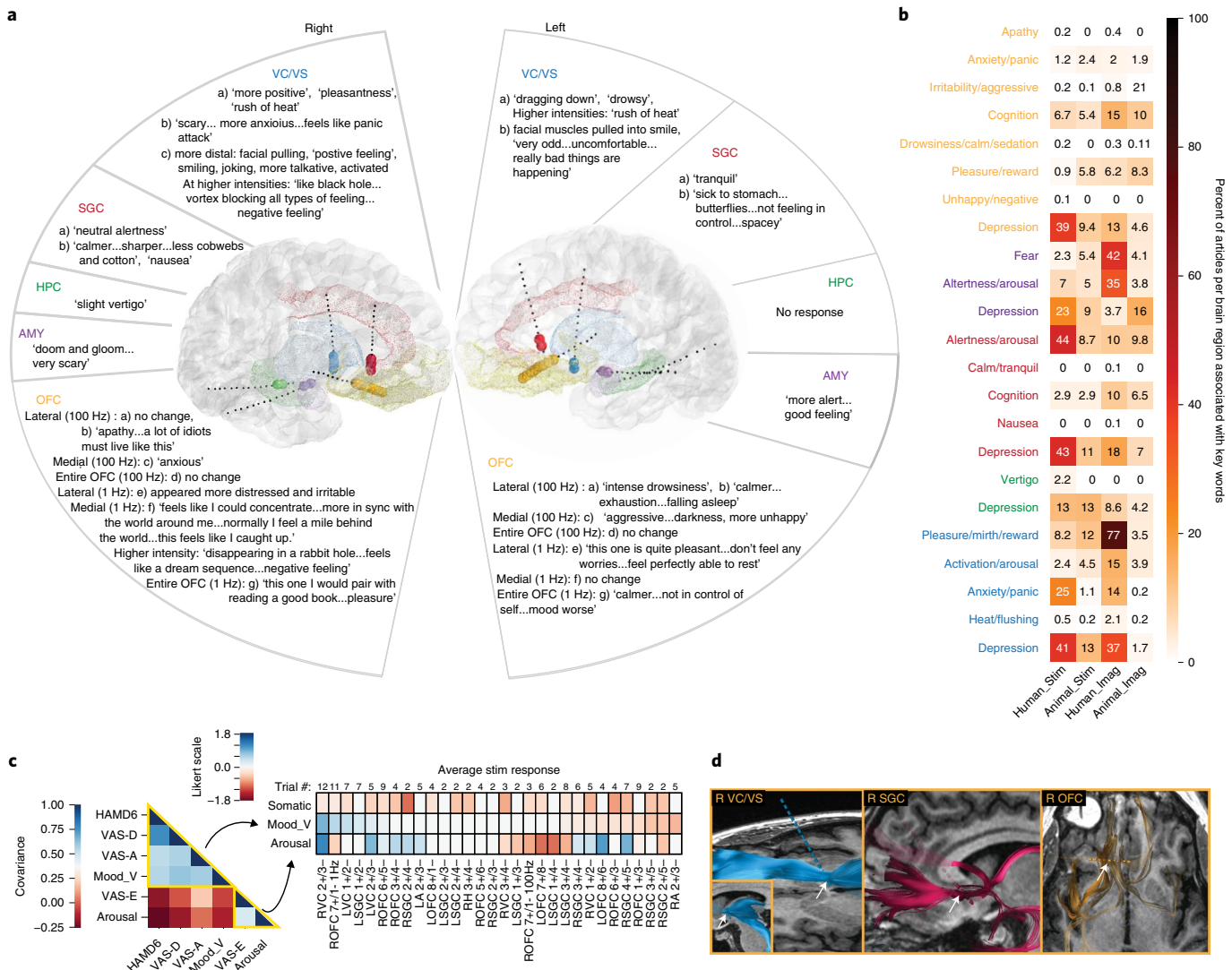


Fig. 1 | Mapping mood across the corticolimbic circuit. a, Examples of the clinical responses to -90 s of stimulation. Electrodes that demonstrated a positive or negative mood response to stimulation are enlarged for emphasis and shaded with color of respective region. **b**, Relationship of patient response to literature. **c**, Covariance matrix of relationship between depression measures (Methods) (left) and heat map of average Likert scores per stimulation condition (right). Somatic symptoms (side effects) of stimulation are also shown. **d**, Location of stereoelectroencephalography leads in the VC/VS, SGC and OFC with neighboring fiber tracts defined by diffusion tensor imaging. Left, Anterior thalamic radiations and VC-brainstem tracts (inset); middle, forceps minor, stria terminalis/cingulum bundle and uncinate fasciculus; and right, forceps minor and uncinate fasciculus. AMY, amygdala; HAMD, Hamilton Depression Rating Scale; HPC, hippocampus; VAS, Visual Analog Scale.

of context and state at time of stimulation on 100% of trials that elicited a response (Fig. 2 and Supplementary Information). For example, in the OFC, the effect was positive and calming if delivered during a high/neutral arousal state but worsened mood if delivered during a low arousal state, causing the patient to feel excessively drowsy (Fig. 2b). The opposite pattern was observed in the SGC and VC/VS—regions where stimulation increased arousal (Fig. 2c). This patient's primary symptom was anhedonia, and she perceived the most consistent benefit from stimulation in one region of the VC/VS. However, when she was in a highly aroused state, broad OFC stimulation was preferred. We next examined properties of the stimulation response that would inform whether it would be possible to deliver stimulation specifically when a particular symptom state is present. We found a clear dose response for both activation and mood valence (Fig. 2d) and found that the response to stimulation was sustained beyond the stimulation period itself, even up to 40 min (Fig. 2e).

In summary, we present a novel approach to DBS that includes a 10-d inpatient interval where multi-day, multi-site stimulation-response mapping is performed before implantation of a chronic neuromodulation device to characterize the complex interplay among symptoms, mood state and neural stimulation. These findings extend previous work that suggested that different stimulation targets within and across brain regions have different clinical effects¹² and further demonstrate the putative importance of a patient's symptom profile in interpreting the clinical response to stimulation. Furthermore, they suggest that the time a patient spends in a particular mood state could be a consideration in the selection of a DBS target. Although traditional DBS delivers stimulation continuously, 'closed-loop' DBS aims to vary stimulation parameters in response to ongoing changes in the state of neural networks⁷. The conceptual framework of a closed-loop approach is that brief intermittent stimulation delivered only when the patient is in a target state can be delivered on a long-term basis and could be a means of treating chronic

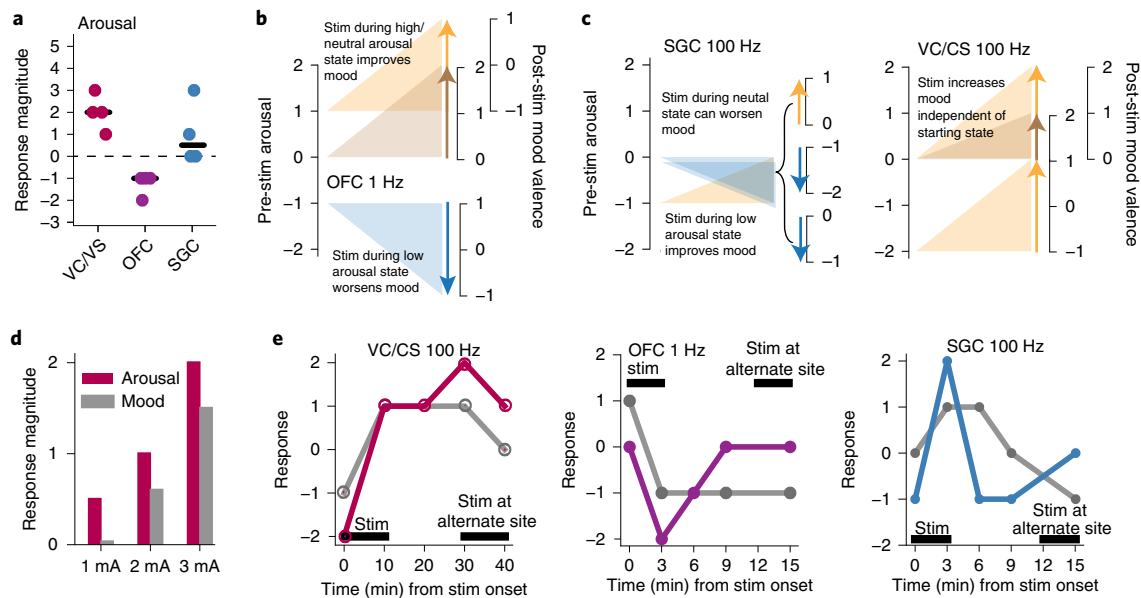


Fig. 2 | Characterization of response properties. **a**, Effect of stimulation on arousal dimension of depression across four trials of stimulation in each brain region. **b**, State dependence for OFC stimulation. The left axis marks the arousal state before stimulation; the right axis shows mood state (Mood_V) measured after stimulation. **c**, State dependence for SGC and VC/CS stimulation. **d**, Dose dependence of stimulation for VC/VS on dimensions of both mood and anxiety. Each bar represents response after one trial of stimulation at 1, 2 or 3 mA. **e**, Response durability for example trials are shown for VC/CS (red), OFC (purple) and SGC (blue) for both arousal (colored line) and Mood_V (gray line). The black bar indicates the duration of stimulation.

depression. Although our results do not contain neurophysiological findings that would be needed to drive closed-loop therapy, our findings that the response to stimulation is rapid in onset, dose dependent, sustained beyond the stimulation itself and context dependent suggest that a closed-loop strategy is of interest for further study in trMDD. Future work will be needed to determine inter-individual variability in stimulus–response relationships. Nonetheless, this case establishes network principles and methodology for implementation of a precision medicine paradigm for circuit-targeted therapy. The principles we established extend to noninvasive modulation of brain circuitry that could allow circuit-targeted personalized therapy to be broadly available to people with MDD.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-020-01175-8>.

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Data availability

The source data that support the findings in this report are available in the report itself, in the Supplementary Information and in our publicly available code. Source data are provided with this paper.

Code availability

The code and data used to produce the figures in this paper are available at <https://github.com/ScangosLab/PR01>.

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Author contributions

K.W.S., A.D.K. and E.F.C. initiated this work and supervised the study. K.W.S. drafted the manuscript, and G.S.M., K.W.S. and L.P.S. collected and analyzed the data. A.D.K. and E.G.C. finalized the manuscript. All authors approved this work and take responsibility for its integrity.

Competing interests

A.D.K. consults for Eisai, Evecxia, Ferring, Galderma, Harmony Biosciences, Idorsia, Jazz, Janssen, Merck, Neurocrine, Pernix, Sage, Takeda, Big Health, Millenium Pharmaceuticals, Otsuka Pharmaceuticals, and Neurawell. All other authors declare no competing interests.

Additional information

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Sample size	The sample size is n=1 in this case report.
Data exclusions	No data relevant to the case report was excluded. Where indicated in the main text, example data is shown to illustrate proof-of-concept.
Replication	This is a case report and findings need to be replicated across a larger population as is indicated in the main text. Where possible, we completed multiple trials of each experiment. The number of trials is reported.
Randomization	The data is not randomized as it is a n=1 case-report.
Blinding	The patient was blinded during the sham controlled stimulation studies. Investigators were not blinded.

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Human research participants

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Population characteristics	The patient was a 36 yo woman with severe treatment resistant depression.
Recruitment	The patient contacted our center about participation in a clinical trial of closed-loop DBS (PRESIDIO trial). The patient's physician had heard about the trial and brought it up to the patient in her clinic appointment. She then contacted us about the possibility of participating.
Ethics oversight	The IRB and FDA approved this study. We also work with a neurologist who specializes in ethics of deep brain stimulation.

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Clinical trial registration	NCT04004169
Study protocol	Please see https://clinicaltrials.gov/ct2/show/NCT04004169 . We can provide the study protocol upon reasonable request.
Data collection	Data was collected for 10 days in October 2019.

Primary and secondary outcome variables were defined for the clinical trial protocol. The presented case report presents findings from the first stage of this trial which was an exploratory stage to identify personalized brain targets.