nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-020-01175-8

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 disorder[1] associated with a high level of treatment resistance[2]. Deep brain stimulation (DBS) emerged in 2003 as a highly promising addition to the therapeutic armamentarium[3] for the most refractory patients[2]. 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 needed[7]. 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 psychiatry[10]. 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 epilepsy[13]. 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, anergy 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 stereoelectroencephalography 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 Scale[18]. 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 SGC[3] and the VC/VS[9]—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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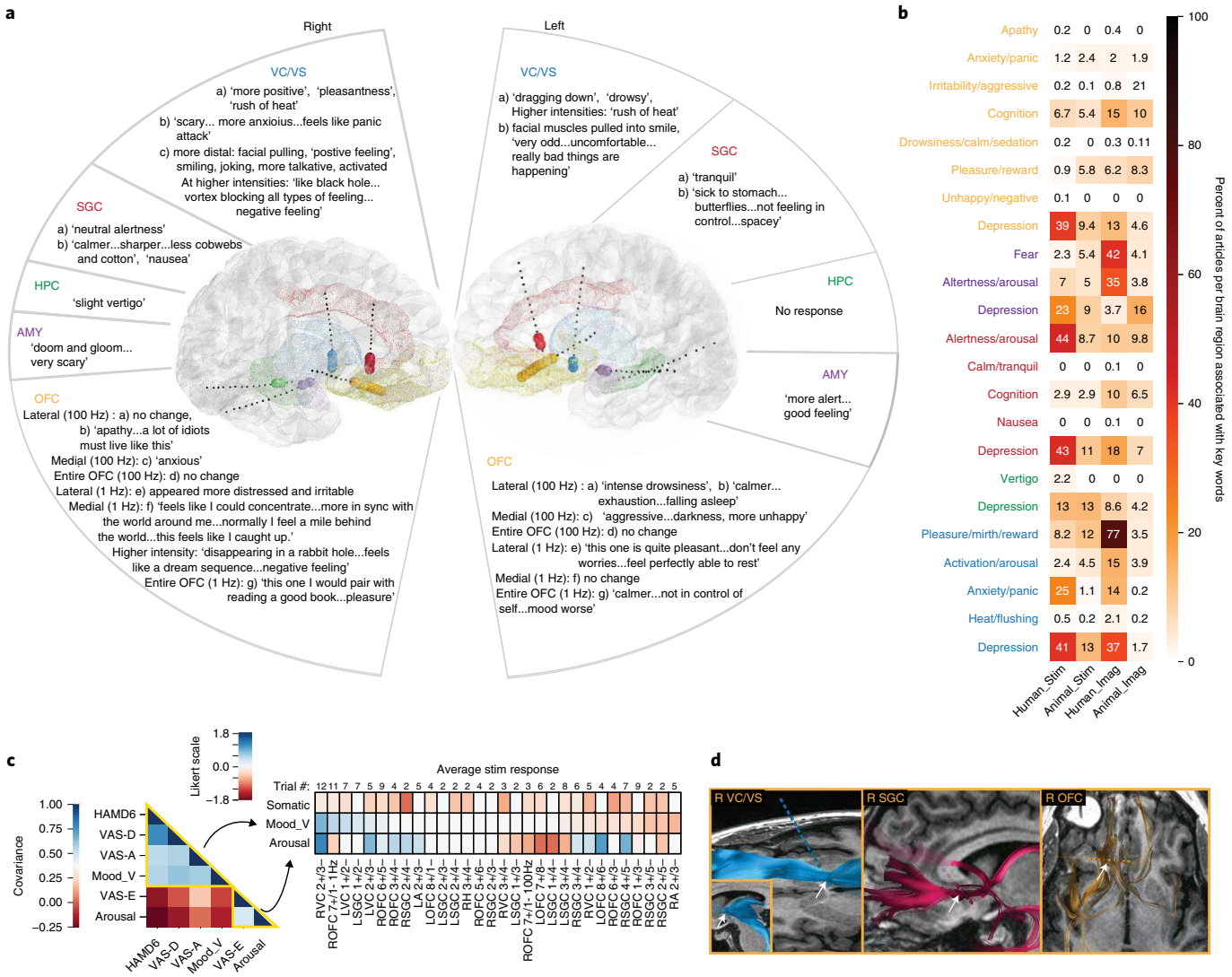

Fig. 1 | Mapping mood across the corticolimbic circuit. a, Examples of the clinical responses to ~90 s of stimulation. Electrodes that demonstrated a positive or negative mood response to stimulation are enlarged for emphasis and shaded with color of respective region. **b**, Relationship of patient 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 simulation 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 effects[12] 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 networks[7]. 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

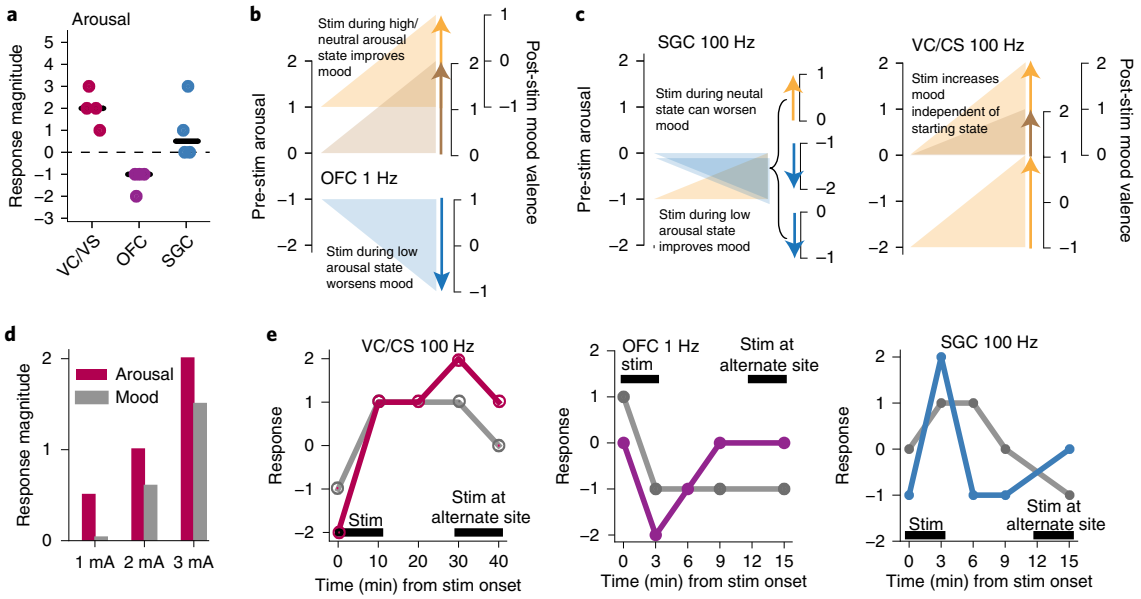

Fig. 2 | Characterization of response properties. a, Effect of stimulation on arousal dimension of depression across four trials of stimulation in each brain region. **b**, State dependence for OFC stimulation. The left axis marks the arousal state before stimulation; the right axis shows mood state (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.

Received: 31 May 2020; Accepted: 12 November 2020;
Published online: 18 January 2021

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Reporting Summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

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.

Acknowledgements

This work was supported by National Institutes of Health award K23NS110962 (to K.W.S.), a NARSAD Young Investigator grant from the Brain and Behavioral Research Foundation (to K.W.S.) and the Ray and Dagmar Dolby Family Fund through the Department of Psychiatry at the University of California, San Francisco (to K.W.S., A.D.K., E.F.C. and L.P.S.). E.F.C. was supported by the National Institutes of Health (U01NS098971, R01MH114860, R01MH111444, R01DC015504, R01DC01237, UH3 NS109556, UH3NS115631 and R01 NS105675), the New York Stem Cell Foundation, the Howard Hughes Medical Institute, the McKnight Foundation, the Shurl and Kay Curci Foundation and the William K. Bowes Foundation. A.D.K. acknowledges support from the National Institutes of Health (P01AG019724, R01 HL142051-01, R01AG059794, R01DK117953, UH3 NS109556-01 and R01AG060477-01A1), PCORI, Janssen, Jazz, Axsome (AXS-05-301) and Reveal Biosensors. L.P.S. receives support from the National Institutes of Health (U24 DA041123).

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

Supplementary information is available for this paper at https://doi.org/10.1038/s41591-020-01175-8.

Correspondence and requests for materials should be addressed to K.W.S.

Peer review information Jerome Staal and Kate Gao were the primary editors on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

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Last updated by author(s): 2020-May-27

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☒	☐	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
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Software and code

Policy information about availability of computer code

Data collection	No software
Data analysis	Data analysis was performed using custom code in python. It will be made available through a GitHub repository.

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Data availability
The source data that support the findings in this report are available within the report itself, in the supplementary materials, and within our publicly available code.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

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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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

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 possiblity 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.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

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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.

Outcomes	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.