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# Probing the happy place

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**Commentary**

A variety of neurological procedures, including deep brain stimulation and craniotomies that require tissue removal near elegant cortices, require patients to remain awake and responsive in order to monitor function. Such procedures can produce anxiety and are poorly tolerated in some subjects. In this issue of the *JCI*, Bijanki and colleagues demonstrate that electrical stimulation of the left dorsal anterior cingulum bundle promoted a positive (mirthful) effect and reduced anxiety, without sedation, in three patients with epilepsy undergoing intracranial electrode monitoring. The results of this study highlight the need for further evaluation of anterior cingulum stimulation to reduce anxiety during awake surgery and as a possible approach for treating anxiety disorders.



# Probing the happy place

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## Surgical options for neurological conditions and their limitations

The limits of oral pharmacotherapy for treating neuropsychiatric conditions are being increasingly recognized. However, functional neurosurgery is now acknowledged as a safe and efficacious option. As such, an increasing number of patients are being referred for surgery to treat conditions related to disrupted brain network activity, including essential tremor, dystonia, Parkinson's disease, and Tourette syndrome, or to treat epilepsy when focal lesions are symptomatic. When the nodes in dysfunctional brain networks are identified (1, 2), neurosurgical techniques can improve symptoms of various disease states by normalizing information processing through those networks with neuromodulation (3, 4) or correct aberrant neural activity through ablation or resection (5, 6). While attempts have been made to address depression with deep brain stimulation (DBS) (7), anxiety disorders remain a disabling group of disorders of negative valence that may be poorly treated with existing therapies and could be a target for neuromodulation (8).

As a more specific issue, neuromodulation for movement disorders and resective surgery for medication-refractory epilepsy remains underutilized (9), in part because of the stigma and/or anxiety regarding the need for awake surgery, which is sometimes required to evaluate brain electrophysiology and test stimulation effects in the absence of anxiolytics that might alter neural function or patient participation. Advances in imaging techniques and hardware now allow some of these cases to be performed under anesthesia without intraoperative electrophysiology (10, 11). However, awake electrophysiology and/or test stimulation is required when anatomic landmarks are poorly visualized on conventional imaging or when resection targets are adjacent to so-called "eloquent cortex" such as language or motor control areas. Especially in the case of language or motor function, patients may require intraoperative testing during a resective surgery, even in patients in whom the epileptic focus has been identified with extraoperative intracranial monitoring. Patients with epilepsy have a high incidence of depression (12) and anxiety (13), the latter of which potentially complicates the yield from intraoperative testing if the patient does not tolerate and participate in the procedure.

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In this issue, Bijanki et al. (14) provide two important contributions to the fields of neuroscience and functional neurosurgery. First, their study demonstrates the role of a specific region in the dorsal anterior cingulum bundle in the experience of positive emotional content and enactment of mirthful behavior, suggesting a discrete target for neuromodulation to treat anxiety disorders. Second, stimulation of this structure during awake stereotactic functional neurosurgery has potential as an approach for managing intraoperative anxiety without the use of pharmacotherapy.

## Eliciting mirth

Prior work has suggested an association between anterior cingulate stimulation and mirthful behavior (smiling) and/or a positive emotional experience; however, the localization of these effects varied between subjects and studies. In a retrospective report of 57 cases of epilepsy surgery in which clinical responses were elicited from stimulation of the cingulate cortex (15), stimulation of the pregenual anterior cingulate cortex or anterior midcingulate cortex elicited laughter and mirth in five patients, but the stimulation location varied considerably across patients. Laughter or smiling without mirth was more likely to occur with stimulation in the ventral pregenual anterior cingulate cortex. A larger analysis by the same group showed that laughter in 25 patients, stimulated in either the right or left dorsal pregenual anterior cingulate cortex, was associated with a sensation of mirth perceived prior to laughter in most cases (16). While these and other studies offer strong evidence that the experience of mirth and laughter behavior is localized to this general structure, they combine stimulation positions and outcomes across all patients, without describing behavioral responses from adjacent simulation locations relative to one another, within patients.

Bijanki et al. report behavioral responses to stimulation in several locations along the sagittal axis of the cingulate cortex and cingulum bundle, thanks to the

unique placement of a depth electrode in this orientation for three patients with epilepsy. The longitudinal orientation of the electrodes allows the description of behavioral responses of adjacent contacts. The authors show that stimulation of the dorsal anterior cingulum bundle elicited mood elevation and mirthful behavior, while stimulation of the dorsal anterior cingulate cortex did not elicit this response in the same patient. This finding was consistent across the three patients, even when compared with sham or off-target stimulation.

While prior reports do not necessarily differentiate between the ventral anterior cingulate cortex and the dorsal anterior cingulum bundle, the study by Bijanki and colleagues incorporates tractography to differentiate between these two adjacent structures. Neurophysiologic recordings are also provided and show stimulation-related changes in oscillatory power across distributed networks that are generally accepted as having connectivity with the anterior cingulate. The authors even compared physiology between stimulated smiles and unstimulated, natural smiles to control for the effect of smiling itself. Together, the clinical responses and neurophysiological data support prior work from members of this group that emphasizes the importance of targeting networks, not just coordinates, to predict clinical response with neuromodulation (2).

## Future applications and considerations

Bijanki et al. suggest that this target could be explored for treating severe anxiety. While this application seems like a good prospect, we must acknowledge the caveat that their study was not a systematic approach to sampling all regions of the anterior cingulate cortex or the cingulum. Moreover, it is possible that an even more appropriate target could be elucidated with more complete surveillance of these or other structures. In fact, animal studies also suggest that multiple limbic structures might be targets for neuromodulation to treat anxiety disorders (17). Also, the key brain networks that must be targeted for a clinical response should be well defined in preclinical or imaging research to avoid response heterogeneity that may dilute a clinical benefit (7). Furthermore, the study by Bijanki et al. does not report the effect of stimulation on cognitive functions that are localized to nearby areas in the anterior cingulate, even though the authors report results on a full neuropsychological battery. Future studies are warranted to make sure that stimulation parameters effective for anxiety do not negatively impact emotional conflict monitoring performance (18) or more robust, precise measures of decision making (19). Such determinations will be essential to weigh the potential risks and benefits of cingulum stimulation for the treatment of anxiety. Also, long-term studies on the duration of this effect will be needed, given the known plasticity that exists in certain networks and that can allow adaptation and tolerance of neuromodulation (20).

## Application in awake surgery

Bijanki and colleagues also suggest applying this technique in anxious patients undergoing awake functional neurosurgery for intraoperative testing without anesthesia. While their data and videos are quite compelling, several considerations should be made regarding this idea. The most pertinent consideration is whether the added benefit to the patient outweighs any potential risk of complication from an additional depth electrode if it was not already needed for seizure localization. While the risk of intracranial hemorrhage during DBS for movement disorders is low, it is not zero (21), and there may be an association between depth electrodes for epilepsy monitoring and cognitive changes (22). Unless a depth electrode is needed for seizure focus evaluation, it seems at least controversial to suggest electrode placement solely for the anxiolytic effect during surgery. Yet, as hardware, targeting software, imaging quality, and expertise in functional neurosurgery advance, this balance will be continuously reassessed.

Despite the small sample size, this case series offers important insight into the specific localization of mirthful behavior and anxiety reduction with stimulation of the dorsal anterior cingulum bundle. The detailed localization using tractography, adjacent electrode testing in the cingulum, and neurophysiology from various cortical regions will allow future studies of the requisite target networks that must be affected for an anxiolytic effect and takes us one step closer to having a neuromodulation target for anxiety. The findings of Bijanki et al. should serve as a reminder of what a privilege it is to have direct access to the human brain for stimulation and local field potential recording experiments during surgery for routine clinical indications, and that even small numbers of such cases can allow for significant therapeutic advances for disorders, even those unrelated to that being treated at the time of surgery (23).

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