Toward Patient-Specific Targeting and Parameter Setting of Deep Brain Stimulation for Relief of Depression

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The subcallosal cingulate cortex (SCC) is a target for deep brain stimulation (DBS) in efforts to help alleviate depression in patients for whom other treatments are ineffective. Riva-Posse *et al.* (1) combine preoperative magnetic resonance imaging and diffusion tensor imaging with postoperative imaging and probabilistic cartography in 17 patients who received SCC DBS and evaluate the efficacy of this approach to identify critical and patient-specific sites in the white matter. Responders, defined as patients whose condition improved after DBS, could be divided into two groups: At 6 months, 7 patients responded to stimulation and 10 did not. At 2 years, 6 more patients responded (total of 13 responders) and 2 did not. The authors provide imaging data at 6 months for 6 responders (1 responder did not have diffusion tensor imaging of adequate quality) and 10 nonresponders and at 2 years for 12 responders and 2 nonresponders. Two patients underwent explantation before 2 years.

Probabilistic tractography using the estimated activation volumes of electrode contacts for each patient showed that responders at 6 months had in common pathways leading to the medial prefrontal cortex (Brodmann area 10) through forceps minor on both sides and the medial segment of the uncinate fasciculus; a pathway leading to the dorsal and midcingulate region; and midline pathways leading to subcortical nuclei, including the nucleus accumbens, caudate, putamen, and anterior thalamus (Figure 1). The last-mentioned pathways are likely comparable to descending pathways in monkeys that also involve the amygdala (2). The estimated activation volumes of electrode contacts in the nonresponders at 6 months failed to show this connectivity. This study has significant practical implications and leads to new testable hypotheses, setting the stage for future studies.

The most fascinating data from the study are the connectivity maps showing the conversion of nonresponders at 6 months to responders at 2 years (6 responders at 6 months to 10 responders at 2 years). These late responders showed extension in the connectivity of the pathways characteristic of responders at 6 months or 2 years. This finding raises several questions: Is the conversion of nonresponders to responders due to changes in the parameters of stimulation or the specific loci stimulated or both? These changes were made for ethical considerations in a clinical study in an effort to optimize the efficacy of stimulation.

Several other possibilities must also be considered in view of the special characteristics of the SCC, the region situated above the site of stimulation. The SCC is a limbic region as identified by structural features. However, the SCC is unique even among limbic cortices according to several parameter dimensions (3). One feature that sets this region apart from others is a lopsided architecture, with deep layers being considerably denser than the upper layers. Other notable architectonic features include a very low myelin content even among the generally low-myelinated limbic cortices and a low glia-to-neuron ratio (3). The SCC also has a high concentration of the growth-associated protein GAP-43. This protein is expressed in all areas during development but persists preferentially in high-order association and limbic cortices in adult primates (4). All of these features may be relevant when considering the positive outcome of DBS below the SCC as reported by Riva-Posse *et al.*

The structural features that set the SCC apart from other regions are associated with plasticity, a process that is thought to be impaired in major depressive disorder (MDD) (5). A prominent feature in MDD is reduction in glia and astrocytes in particular. In view of the lower density of glia in the SCC in normal primates, there may not be a big margin for error, so that even a small reduction in MDD may exacerbate the tonic activity in this region. The other striking features of the SCC—very low myelin content and persistent expression of the axon growth protein GAP-43 in adults—are consistent with a role of the SCC in remodeling functions.

The other prominent feature of the SCC region is the emphasis of the deep layers in normal primates. The deep layers give rise to "feedback" pathways to other cortices, and based on its structure as a limbic region, the SCC may be the ultimate "feedback" system and may exercise a tonic influence on other cortices (6). This feature is consistent with the participation of the SCC in the default mode network that is active when one is engaged in inner reflection and not in a specific task. The deep layers (in all areas) project to subcortical structures, including the thalamus and striatum (caudate and putamen). In the SCC region in particular, the deep layers also project robustly to the amygdala, the hypothalamus, and brainstem structures. However, even though the SCC in macaque monkeys has strong bidirectional connections with the amygdala, it can be considered a stronger "sender" of pathways to the amygdala than a receiver of input from the amygdala, based on relative (rather than absolute) input-output relationships with the amygdala (7). Several of the targets of the SCC in the hypothalamus, brainstem, and amygdala innervate structures that have relatively direct output to central autonomic structures associated with emotional arousal. Hyperactivity in the SCC as reported in MDD is likely to increase activity in autonomic structures and feelings of anxiety.

Electrical stimulation of the SCC could help reduce the abnormally high activity of the region, but the mechanism is unclear. There is also no clear explanation for the variability in the time of response or lack thereof. One possibility is that electrical stimulation of the SCC may result in global or local circuit epigenetic modifications that can tip gene expression dynamics toward increased plasticity of neurons and their networks in responders but not in nonresponders. This fundamental relationship through a dynamic equilibrium linking the large-scale organization of gene expression in the brain with cellular/circuit

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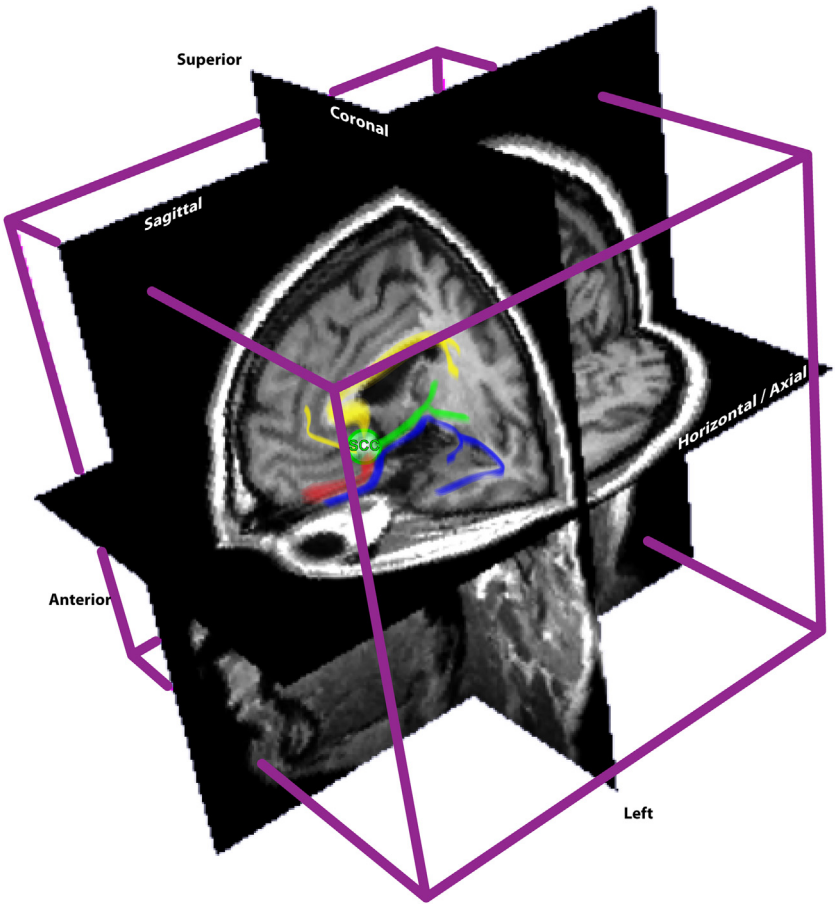

Figure 1. Subcallosal cingulate (SCC) fiber bundles targeted and likely activated by deep brain stimulation, based on whole-brain probabilistic tractography of estimated electrode activation volumes. Red indicates forceps minor, linking anterior and posterior medial cortices bilaterally. Blue indicates uncinate fasciculus, linking ventromedial and orbital cortices with temporal regions, including the amygdala. Yellow indicates cingulate bundle and paracingulate pathways to dorsal anterior cingulate and midcingulate cortices. Green indicates descending subcortical pathways to ventral striatum, hypothalamus, and anterior thalamus.

plasticity and individual variability in behavior can be seen even in genetically identical animals (8).

One of the plastic processes set off by electrical stimulation may be proliferation and restoration of glia that serve many metabolic functions. A key function is reuptake of glutamate from the extracellular space, which may help reduce the abnormally high activity in the SCC in MDD. Glia have several other metabolic functions (5). Reduction of glial markers or astrocytes is also reported for the hippocampus (5), which sends the most robust pathway to the SCC in primates.

Another possibility is that electrical stimulation upregulates various neurotrophic factors (5), including GAP-43, which is sensitive to perturbation under a variety of conditions (4,9). It is an intriguing possibility that initial stimulation may optimize conditions for plastic changes that are manifested only at a later time in a subset of patients with MDD. In normal adult human brains, GAP-43 is also expressed in the hippocampus and amygdala (4), which have particularly strong connectional ties with the SCC.

As the authors note, the region of stimulation below the SCC is at the crossroads of major pathways. Stimulation of the SCC region can drive changes in brain network dynamics, leading not only to surrounding cingulate and medial prefrontal cortices but also to subcortical structures that likely involve the ventral striatum/nucleus accumbens, the amygdala, and other structures. It is not yet possible to disambiguate the unique contribution of each of the activated pathways or determine the extent to which the descending pathways may also engage the reward system, as suggested in other studies (10). The authors suggest that stimulation of SCC Brodmann area 10 pathways may be sufficient for the antidepressant response. If stimulated anteriorly, this site would not likely include all of the pathways reported in the present study. However, if proved to be adequate in future studies, the Brodmann area 10 site may reduce or eliminate side effects and surgical complications that are likely to be more common with implantation in the SCC as well as in other targets used in recent years for stimulation to treat MDD (10).

In conclusion, DBS has shown promising results in initial studies in the most difficult cases of patients with treatment-resistant MDD. In most patients with MDD, DBS of the SCC is associated with positive antidepressant effects, albeit with variable response magnitude and variable time of response. The results of this study can be used as a template for the refinement of interventions, based on the mapping of anatomic targets and their underlying network connectivity. These findings have the potential to improve and optimize electrode implantation and selection of stimulation parameters in individual patients. Based on the differences between responders and nonresponders, it would be of great interest to see whether treatment outcome depends on successful targeting and activation of all three fiber bundles (bilateral forceps minor, cingulum, and medial frontostriatal/subcortical fibers) or a subset of this group. The present study as well as previous work underscores the need for further investigation using primate animal models and larger cohorts of patients to elucidate the underlying mechanisms that mediate

positive clinical outcomes and help evaluate appropriate treatment parameters.

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