The Role of Neuroimaging in the Development & Optimization of Deep Brain Stimulation for Depression

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The last 20 years of neuroscience research has witnessed a fundamental shift in the conceptualization of psychiatric disorders, with the dominant psychological and neurochemical theories of the past now complemented by a growing emphasis on developmental, genetic, molecular, and brain circuit models. Facilitating this evolving paradigm shift has been the growing contribution of functional and structural neuroimaging, with studies of the pathophysiology of major depression increasingly adopting these strategies.

Critical to the development of deep brain stimulation (DBS) as a new treatment approach for intractable major depression has been the evolving understanding of the brain circuits that mediate normal and abnormal mood states and the systematic characterization of changes in these circuits that accompany successful and unsuccessful response to treatment [1]. The rationale for targeting the subcallosal cingulate (SCC/Brodmann Area 25) was provided by converging data showing: (a) significant increased SCC/Brodmann Area (BA) 25 activity during acute negative mood using blood flow PET scanning, (b) post mortem cellular abnormalities in this region in depressed patients, and (c) predictable SCC/BA25 decreases in blood flow and metabolism in patients responding to various established antidepressant treatments [2]. It was hypothesized that chronic stimulation of the SCC and adjacent white matter would reduce chronically elevated SCC/BA25 activity and have downstream effects on brain regions within a putative “depression network” directly connected to the SCC via the targeted white matter tracts.

With a growing number of published research studies demonstrating robust and sustained antidepressant effects of SCC DBS [3,4] and ongoing full scale randomized clinical trials of this and other brain targets, there continues to be a unique opportunity to better characterize brain-system dysfunction maintaining the treatment resistant depressed state as well as the necessary-and-sufficient changes mediating successful antidepressant response. For example, measures of regional blood flow and metabolism have not only provided foundation for the initial selection of the subcallosal cingulate as a plausible antidepressant DBS target, but such methods are also proving useful to quantify regional physiological effects of chronic stimulation at this and other brain targets. Imaging strategies are also being extended to test the utility of the combined use of PET, fMRI, DTI/tractography, and EEG/LFP measurements to further identify baseline as well as stimulation induced change patterns that predict treatment outcome [5-9]. As clinical studies proceed, development of reliable circuit-specific biomarkers that can improve patient recruitment, enhance surgical targeting, and optimize parameter selection will be necessary to fully realize the potential of this new treatment strategy.

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