Individualized Mapping of the Subgenual Cingulate in Individual Unipolar Depressed Patients Using FMRI

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Introduction:

Currently, at least 20% of patients with severe depression do not respond to treatment and are considered treatment-resistant (TRD). Novel therapies such as deep brain stimulation to targeted brain regions (DBS) could offer hope to an otherwise bleak future for TRD patients. DBS is targeted to the subgenual cingulate gyrus (SGC), an area dysregulated in depression. However, there are individual differences in SGC anatomy, and the relatively poor spatial resolution obtained by the PET hypermetabolic studies of SGC do not provide the exact location(s) within the general SGC region that may respond to DBS treatment. Functional MRI (fMRI) is widely used in presurgical mapping of eloquent cortex because of its good spatial resolution with regard to standard neuronavigational methods, and may be helpful in distinguishing individual differences in SGC functionality. Almost all studies examine SGC-related fMRI activation on a group level, potentially missing neuroanatomical variations among individuals. We recently developed a task which may functionally define the hypothesized dysregulated area for presurgical mapping in individuals, possibly improving DBS targeting[1]. The goal of the current study is to investigate the ability for this task to map the SGC region in patients with Unipolar Major Depression.

Methods Used:

Participants: Participants were outpatients in the Phoenix area. All patients met criteria for Unipolar Major Depression Disorder based on the Structural Clinical Interview for DSM Disorders; the diagnosis was confirmed by the study psychiatrist (GG).

Task Development

This task was designed to compare a sad to a neutral state; however, we recognized that the time to achieve a sad state in individuals is likely to vary. The on-off block design paradigm was altered to account for differences in individual responsivity to sad stimuli by making the task a "hybrid" block design that can ultimately be of variable length among individuals but from which standardized blocks of sad and baseline conditions can be obtained. (**Fig 1**) Only the standardized blocks are analyzed in the post-processing steps. **Imaging Parameters:** On the same 3.0 Tesla GE Signa HDX system with an 8-channel head coil: gradient echo echo-planar imaging (EPI) with TR = 3000 ms, TE = 25 ms, flip angle = 80°, FOV 24mm, in-plane resolution 64x64, with 4-mm-thick slices covering the entire brain. A high resolution structural T1 sagittal image was also obtained.
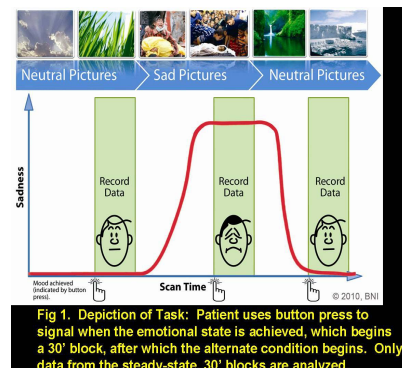

Fig 1. Depiction of Task: Patient uses button press to signal when the emotional state is achieved, which begins a 30' block, after which the alternate condition begins. Only data from the steady-state, 30' blocks are analyzed.

Statistical Analyses:

SPM5 was used for standard post-processing, with a minimal Gaussian kernel of 2-mm^3 used for smoothing in order to maintain good spatial resolution within the SGC. All data were analyzed in native space. A frontal lobe region of interest (ROI) was defined for each individual. The contrast maps from the engaging versus neutral condition ($p \leq .05$, voxel extent threshold = 10) were used to explicitly mask the analysis of the sad versus neutral condition.

Results

Patients (2F/2M) were 29-59 years old, right handed and had Beck Depression Inventory-II scores of 24-50 on the day of scanning, indicating a moderate-severe level of depression. Compared to the 9 control participants previously scanned, the depressed patients took a more variable, and generally longer, time to transition from a neutral to a sad state (from 6-78 sec in patients compared to 6 to 18 sec in controls). All patients tolerated the task and returned to their pre-scan level of depression.
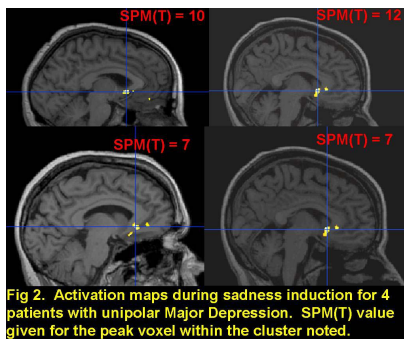

Fig 2. Activation maps during sadness induction for 4 patients with unipolar Major Depression. SPM(T) value given for the peak voxel within the cluster noted.

fMRI maps (**Fig 2)** highlighting the SGC of each patient show that SGC activation value (upper right corner) was generally greater than those obtained on the control subjects (SPM(T) range 3-6).

Discussion and Conclusion: We have developed an fMRI task using a sadness-induction paradigm with a flexible block design that shows good activation within the general SGC region. This task capitalizes on adjusting for the individual variability in attaining a sad state while maintaining a robust block design. Preliminary results show a greater SGC responsivity in depressed patients compared to controls, consistent with prior PET imaging studies[2].

References: 1. Smith et al. *Brain Imaging and Behavior, in press.* 2. Mayberg et al. *Journal Clinical Investigation,* 119; 717- 725