A novel fMRI task to visualize frontal lobe circuitry associated with transient sadness

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Purpose: We developed a novel functional magnetic resonance imaging (fMRI) method designed to activate the subgenual anterior cingulate cortex (sACC) and other frontal regions during transient sadness. We sought to develop a task that would show sufficient and specific activation in individuals to be useful as a potential target for deep brain stimulation treatment (DBS).

Introduction: Mayberg and others have shown that the sACC is an important region in regulating depressive symptoms[1]. Positron Emission Tomography (PET) is typically used in these studies for diagnosis and treatment efficacy but lacks the spatial precision of fMRI. While some fMRI studies report frontal lobe changes in depression, these are generally group studies of transient sadness or the studies utilize cognitive rather than emotional paradigms, such as the Stroop task.[2,3] Using fMRI, as is done with presurgical mapping of motor or language functioning to accommodate individual differences in functional anatomy, would potentially provide more precise information for mapping activation patterns in depression. We designed a task to exploit the strengths of a block design but still allow individualized attainment of the desired emotional state; a "hybrid" task. Our paradigm also included an "engaging" task to control for nonspecific activation in the cingulate cortex due to general attention/arousal.

Methods:

Task Design**:** Task design was based on previous group studies comparing transient sadness and neutral (euthymic) mood states. We combined pictures (e.g., mothers grieving their dead babies) and auditory (melancholy Celtic music) to elicit sadness against a baseline/neutral condition of outdoor scenes/soothing music. We used the "Ken Burns Effect" to enhance mood change. Participants were instructed to respond via button press when a target mood was elicited by the corresponding pictures. The button press triggers a 30 second block of the same condition, then the program switched to the alternate condition, which runs until the button press which triggers a 30 second block of the same mood state. The task ends after 3 sad and 4 neutral blocks are obtained. Two runs of this task are given. An "engaging" task consists of a similar neutral condition alternating with "engaging" pictures of groups of people typically talking or laughing, with upbeat music. Instructions are similar to those of the "sad" task and this task is also performed twice. Sadness and engaging tasks were counterbalanced across individuals.

Imaging Parameters: All participants were scanned on the same 3.0 Tesla GE Signa HDX system with an 8-channel head coil. Scan parameters for echo planar imaging (EPI): TR = 3000 ms, TE = 25 ms, flip angle = 80°, FOV 24mm, in-plane resolution 64x64, with 4-mm-thick slices covering the entire brain. For each scan, we prescribed a high number of volumes (about 20 minutes) because of the variability across participants and runs; the scans were terminated when the participant finished the last block in the task. A high resolution structural T1 sagittal image was also obtained for coregistration: TR = minimum, TE = 2.5 ms, flip angle = 8°, FOV = 26mm, 256 x 256 matrix, 1.2 mm thick slices.

Task Analysis: All analyses were performed with SPM5. For each task, the volumes from the 30" blocks were extracted, realigned, coregistered to each individual's T1 scan, and minimally smoothed (2mm^3). A region of interest (ROI) was generated using MRIcro software for each participant based on their own anatomy including Brodmann areas 24, 25, 32, and 33, as well as the posterior, medial portions of Brodmann areas 10, 11, and 12. In order to determine the unique activation pattern associated with transient sadness, the sad vs. neutral contrast was masked to exclude activation from the engaging vs. neutral contrast. We also performed psychophysiological interaction (PPI) analyses using the PPI function in SPM5 to determine 1) the connectivity of the sACC and other frontal regions and 2) if the connectivity associated with transient sadness was different from the connectivity pattern during the engaging task, which would provide further evidence for specificity of the sad task.

Results: Data are presented from 6 healthy adults (2M/4F; 20-50 years), with no history of major medical or psychiatric illnesses and no past or present use of psychiatric medications who served as volunteers for task development. Institutional informed consent was obtained from all participants. All participants reported experiencing a feeling of sadness during the sad blocks. Figure 1 shows activation patterns and SPM(T) values and extent sizes for a cluster (circled) in the sACC region. 5/6 participants showed activation in the sACC, with one person showing pregenual cingulate (preACC) rather than sACC activity during transient sadness. All participants also activated other frontal regions; most showed activity in the midcingulate, orbitofrontal or frontal pole, which are all shown to have connections to the sACC in a recent tractography study[4]. Although we masked the sad task with the engaging task to help isolate transient sadness from activity associated with general arousal, we also performed connectivity analyses using PPI for both the sad and engaging tasks to determine whether unique patterns would emerge. The sad task showed a distinct and, in most cases, a more extensive connectivity pattern than the engaging task that included anterior midcingulate and pregenual, medial prefrontal, and orbitofrontal regions.

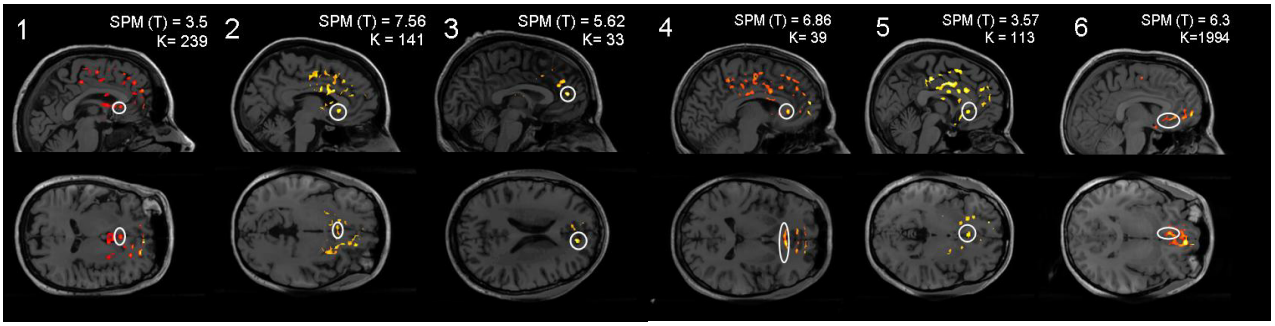

Figure 1. Individual fMRI Activation Patterns During Transient Sadness. Sagittal and axial images from 6 participants depicting the "sad vs. neutral" mood contrast, masked for the engaging condition. The circled region indicates a sACC (or preACC for Subject 3) region consistent with other depression literature. The strength and extent of the circled activation is listed above for each subject.

Conclusion: We have promising evidence that the sACC and other frontal regions associated with transient sadness can be visualized in individuals using a novel "hybrid" fMRI task design. Future studies are planned to determine activation patterns in depressed patients and whether this task will be useful in tracking functional changes in depression.

References : [1]Mayberg et al. Neuron 45:651-660 ; 2005. [2]Anand et al. Biol Psychiatry 57:1079-88; 2005 [3]Schlosser et al. Neuroimage 43:645-655; 2008; [4]Johansen-Berg et al. Cerebral Cortex 18 :1374-83

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