Mood Congruent Hippocampal Activation Biases: Double Dissociation of Negative and Positive Contexts in Depressed and Healthy Adults

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Introduction: Negatively-biased emotional information processing is a salient feature in depression that has been attributed primarily to dysregulation of the amygdala and other limbic structures [1]. While less is known about the role of the hippocampus in negative attentional bias, it is accepted that the hippocampus is dysfunctional in depression [2], and recent research suggests hippocampal involvement in processing emotionally-valenced stimuli [3]. This study developed a functional magnetic resonance imaging (FMRI) technique suited to explore hippocampal response to standardized positive and negative stimuli [4] in depressed and healthy adults.

Methods: Eight adults diagnosed with depression (DEP; mean QIDS-SR score = 11.1, mean age = 32.1 yrs) and 14 controls (CON; mean QIDS-SR score = 2.3, mean age = 44.6 yrs) were scanned in a Siemens 3T Tim Trio scanner using a 12-channel array receive-only head coil. Written informed consent was obtained from all participants in the protocol approved by the local Institutional Review Board. In the event-related fMRI paradigm subjects were asked to rate (on a six-point scale from "Very Disturbing to Very Pleasant") pictures alternating with simply viewing the pictures arranged into periods of positive (Pos), negative (Neg) and neutral (Neu) valence. Each picture was shown for 6 sec and inter-stimulus intervals between picture ratings varied between 6-34 sec (mean = 13.4 sec). Visual analog subject mood ratings ("How are you feeling right now?") were also interspersed throughout the rating and viewing of the emotional and neutral pictures.

FMRI scans were acquired with a sagittal whole-brain gradient echo EPI (TR/TE = 2000/15 ms, FA = 90 deg, in-plane resolution = 3 mm x 3 mm; 44 slices with thickness 3 mm). A T1-weighted MPRAGE scan was acquired for anatomic reference. The voxel time series data from each run were registered, smoothed with a FWHM = 6 mm isotropic gaussian filter and concatenated. Hemodynamic responses (HDR) to Neg, Pos and Neu picture ratings were estimated with deconvolution analysis conducted under a multiple regression framework. Maps of voxel-wise HDR amplitudes were subsequently spatially normalized to the MNI template. Appropriate 1-way (picture valence) and 2-way (Group X Valence) ANOVA was performed on HDR amplitudes to assess group-level activation and between-group differences in activation to Pos and Neg. Finally, hierarchical regression was employed to assess the linear dependence of FMRI activation on subject-ratings. Statistical parametric maps from different analyses were clustered and significance of cluster-level activation was assessed with Monte-Carlo modeling [5]. Data analysis was conducted using AFNI and FSL software.

Results: There were no significant differences in picture ratings between DEP and CON for the positive, negative and neutral stimuli. CON showed significantly (cluster level $p<0.0001$) greater activation than DEP in the left hippocampus and posterior insula during the Pos condition (Figure 1). DEP demonstrated significantly (cluster level $p<0.02$) greater activation than CON in the left hippocampus and anterior insula for the Neg condition. As depicted in Figure 2, this increased hippocampal activation in DEP during the Neg condition was located slightly more medial and anterior than the CON > DEP activation cluster during the Pos condition. Hierarchical regression modeling revealed that activation in the right hippocampal cortex trended oppositely with picture-rating during the Neg condition in the two subject groups. While DEP exhibited significantly (cluster level $p<0.0001$) increased activation with increasing picture-rating (i.e for less negative pictures), CON significantly (cluster level $p<0.02$) decreased activation with increasing picture-rating. As shown in Figure 3, both clusters of activation were located in the parahippocampal cortex, with DEP activation medial to the CON activation cluster.

Discussion: The neural underpinnings of the negative attentional bias in depression has recently been investigated quite frequently [6-8], although there is no consensus on the functional neuroanatomy of this phenomenon. The results presented here show selective mood-congruent activation in the left hippocampus for both depressed and healthy control subjects. Further, preliminary evidence indicates that the right hippocampus may be activated while processing increasing degrees of mood-incongruent stimuli in both depressed and healthy adults. These data raise the hypotheses for selective roles of the bilateral hippocampi in the processing of the emotional valence of external stimuli within the context of subjects' mood state. Ongoing research with a larger sample size and more rigorous diagnostic classification will be useful to test these hypotheses and to determine how and to what extent the hippocampus participates in mood-biased information processing in depression.

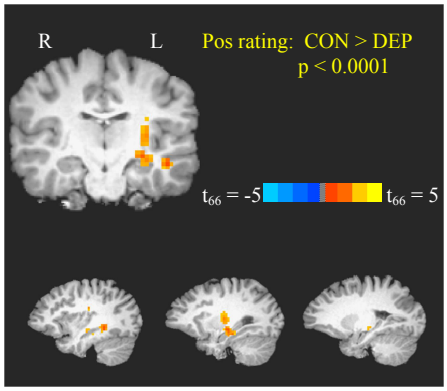

Figure 1: CON - DEP contrast map showing decreased ($p < 0.0001$) DEP activation to Pos rating in left hippocampus

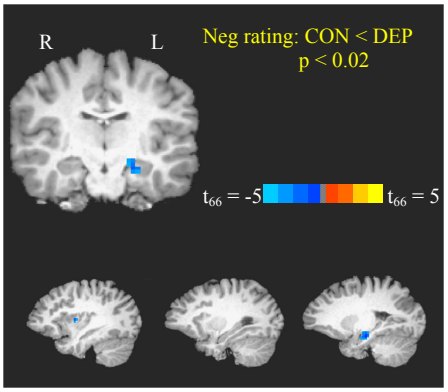

Figure 2: CON - DEP contrast map showing increased ($p < 0.02$) DEP activation to Neg rating in left hippocampus

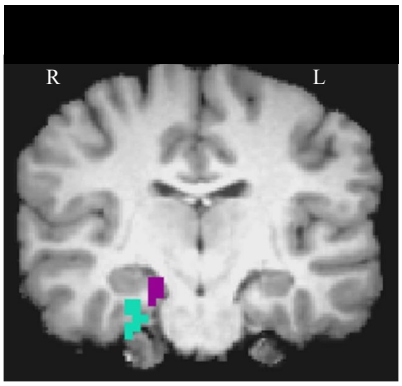

Figure 3: Location of significant clusters from hierarchical regression. DEP cluster (violet) showed increased and CON (cyan) decreased BOLD response with increasing valence scores

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