

Subtypes of nucleus accumbens activations for anticipation of gains and losses in healthy and depressed subjects

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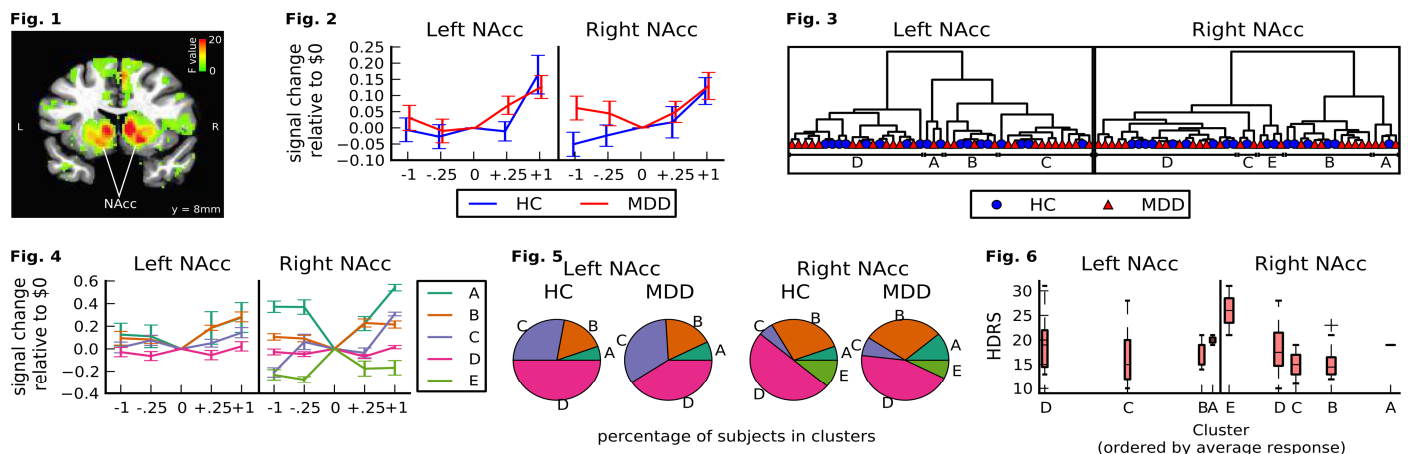
Target audience: Researchers and clinicians interested in the reward- and punishment neural circuitry of healthy and depressed subjects.

Purpose: Abnormal reward- and punishment-related brain BOLD activity in the nucleus accumbens (NAcc) of patients with major depressive disorder (MDD) has been reported^{1,2}. In fMRI studies of healthy subjects the literature is in disagreement regarding the pattern of NAcc activity in anticipation of reward and punishment. Using the monetary incentive delayed-response (MID) task, some studies reported that the NAcc's role is to mediate *only* anticipation of gains, while others reported NAcc activity for anticipation of *both* gains and losses³⁻⁵. These conflicting results may reflect heterogeneity in the response of the neural circuitry connectivity in healthy samples during the neural processing related to reward and punishment. Notably for MDD subjects, both hyper- and hypo-active NAcc response to reward have been reported⁶. We therefore explored subtypes of NAcc activity patterns for anticipation of gains and losses in depressed and healthy control (HC) subjects using the MID task.

Methods: Eighteen HC (ages 20–52 years, mean±SD=29.5±10.3, 10 female) and 27 MDD subjects (ages 21–55 years, 35.1±10.6, 19 female, Hamilton depression rating scales (HDRS 21-items) 10–31, 18.0±5.2) participated in this IRB-approved study. Imaging was conducted on a 3T GE MR750 MRI scanner using a 32ch receive-only head array coil (Nova Medical). The whole-brain EPI-based fMRI scans (TR/TE=2000/30ms, FA=90°, FOV/slice=240/3.2mm x 37 axial slices, matrix=128x128, SENSE acceleration=2) were acquired while subjects performed the MID task. The MID comprised 30 trials of each of five conditions composed of the following win/ loss contingencies: -\$1, -\$0.25, \$0, +\$0.25, +\$1, applied in a rapid event-related design [7s/trial]. Functional images were spatially normalized to the stereotaxic array of Talairach and Tournoux using the Advanced Normalization Tool⁷. The fMRI time courses were standardized to percent signal change. With the general linear model analysis, fitted response amplitudes in the anticipation period were estimated. Changes in BOLD activity during the anticipatory phase of the win or loss trials relative to control trials (\$0) were analyzed with a linear mixed effect model⁸. Task condition, diagnosis, condition-by-diagnosis interaction, age and sex covariates were entered into the model. To explore subtypes of NAcc responses, hierarchical clustering analysis was performed. Mean responses within the left and right NAcc masked with the condition effect (FDR-corrected p<0.05) were used in the cluster analysis. Cluster tree was cut by the automatic cluster cut algorithm⁹ to extract clusters.

Results: The MDD and HC groups did not differ significantly in mean age or sex composition. A significant condition effect (FDR-corrected p<0.05) was seen in reward-related regions including the NAcc, striatum, ventral tegmental area, and substantia nigra, as well as in the anterior and middle cingulate cortex. Fig. 1 shows F-values of condition effect within the striatum. No significant diagnosis effect or interaction between condition and diagnosis was seen in any region. Fig. 2 shows average and standard error of NAcc response for HC and MDD groups. The left NAcc was more active to gains than losses in both groups, while the right NAcc was active to both gains and losses in the MDD group. Using the clustering analysis, four and five clusters were identified for the left and right NAcc, respectively (Fig. 3). Fig. 4 shows average responses for each cluster. Cluster A showed hyper-activity to both gains and losses. Cluster D of the left NAcc and E of the right NAcc showed hypo-activity to both gains and losses. Both HC and MDD groups had similar percentages of subject distribution in each cluster (Fig. 5). A nonsignificant trend toward an interaction between condition and symptom severity (HDRS) was found in the right NAcc (p=0.072). This interaction indicated that MDD subjects with more severe symptoms had a hypo-active (cluster F) NAcc BOLD response (Fig. 6; only MDD subjects are shown).

Discussion and Conclusion: We classified multiple subtypes of NAcc activity for anticipation of gains and losses. Individual variability was seen in both HC and MDD groups. Since the hypo-active subtype was seen in both groups, NAcc hypo-activity may not simply reflect a pathological pattern related to MDD. For the MDD group, however, symptom severity was related to hypo-activity within the NAcc, which suggests that subject's trait of hypo-active NAcc might worsen symptoms in depression.



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