Symptom-based subtypes of major depressive disorder manifest distinct nucleus accumbens hemodynamic responses to reward and punishment

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Target audience: Researchers and clinicians interested in the reward- and punishment neural circuitry and related depressed symptoms.

Purpose: Heterogeneous reward- and punishment-related brain activity in the nucleus accumbens (NAcc) has been reported for healthy controls (HC) and major depressive disorder (MDD) subjects[1-3]. In our previous report[3], we have found hyper- and hypo-active NAcc response subtypes to gains and losses as well as intermediate subtypes between them in the monetary incentive delayed-response (MID) task[4]. Although these subtypes were observed in both HC and MDD subjects, less NAcc activity to both gains and losses were seen in MDD subjects on group average. This suggested that abnormality of NAcc activity could be related to some symptoms of depression in MDD patients. In this study, we investigated NAcc activity in MID task to examine the relationship between the NAcc subtypes and depression symptoms with more number of subjects than the previous report. While sum score of the Hamilton Depression Rating Scales (HAM-D) has been used in the previous study, this scale includes multidimensional factors[5] so that the sum score might not be able to elucidate symptom differences between NAcc subtypes. Here we used scores of each item in HAM-D, Hamilton Anxiety Rating Scale (HAM-A) and Montgomery-Asberg Depression Scale (MADRS) to perform linear discriminant analysis[6] (LDA), and to extract a set of symptoms corresponding to the NAcc response subtypes.

Methods: Forty-six HC (ages 19–55 years, mean±SD=31±10, 27 female) and 38 MDD subjects (ages 19–55 years, 35±11, 25 females, HDRS 21-items 8-30, 17.4±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 an event-related design. Functional images were spatially normalized to the stereotaxic array of Talairach and Tournoux using the Advanced Normalization Tool[7]. With the general linear model analysis, fitted response amplitudes in the anticipation period were estimated. Mean response changes of BOLD activity during the anticipatory phase of the win or loss trials relative to control trials ($0) within the left and right NAcc were used for hierarchical clustering analysis. The automatic cluster cut algorithm[8] and the bayesian information criterion[9] were used to extract clusters. Extracted subtypes of NAcc activity were used for the LDA, which classified MDD subjects into the NAcc subtypes from itemized symptom scores. At the initial step, LDA was done with all items of HAM-D (21 items and 8 atypical symptoms), HAM-A (14 items) and MADRS (10 items). Then low-weighted items for the classification were eliminated recursively. A set of items achieving the best classification performance in cross-validation was taken as the symptom set corresponding to the NAcc response subtypes.

Results: The MDD and HC groups did not differ significantly in mean age or sex composition. Four clusters were extracted for both left and right NAcc responses. Fig. 1 shows average responses (with standard error) of subjects in each cluster. Subjects in cluster A showed hyper-activity to both gains and losses. Subjects in cluster B showed higher activity to gains than losses. Subjects in cluster C were insensitive to both gains and losses. Subjects in cluster D showed hypo-activity (less than $0 condition) to both gains and losses. More hypo-active subjects were observed in MDD group while the composition difference between HC and MDD was not significant (Fig. 2). These results were consistent with the previous report[3]. No significant effect of NAcc subtypes was found for the sum scores of HAM-D, HAM-A, and MADRS respectively. LDA with recursive elimination extracted 22 items for the left NAcc and 27 items for the right NAcc subtypes. Cross-validated classification accuracies were 76.2% and 81.5% for the left and right NAcc respectively. Fig. 3 shows the plot of discriminant scores of LD1 and LD2 of MDD subjects for the left NAcc subtypes. Table 1 shows the items having the highest correlations with LD1, LD2, and LD3 respectively. LD1 and LD3 reflected similar items suggesting that two symptom factors were suffice to characterize the NAcc subtypes. Subtype A had low LD1 and high LD2 scores. Subtype B had low LD1 and low LD2 scores. Subtype C had mild LD1 and low LD2 scores. Subtype D had high LD1 score.

Discussion and Conclusion: Patients with hypo-active NAcc (subtype D) had severe symptoms in 'Depersonalization and Derealization', 'Suicidal thoughts', and 'Anxiety Somatic'. Patients with insensitive NAcc (subtype C) also had these symptoms but less severe than subtype D. Patients with hyper-active NAcc had less symptoms in these items while they had severe symptoms in 'Depressed mood' and 'Inability to feel'. Patients with normal NAcc response (subtype B, majority of healthy subjects showed this response) had no or mild symptoms in these items of discriminating NAcc subtypes. These results indicated that subtypes of reward- and punishment-related responses in NAcc are reflected in a specific set of symptoms in depression.

Fig. 1

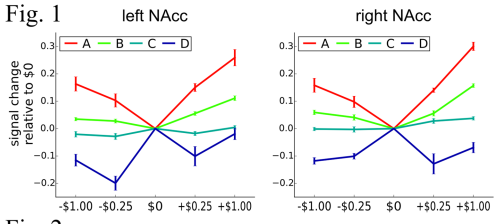
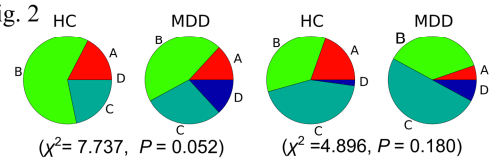


Fig. 2



(χ^2= 7.737, P = 0.052) (χ^2 =4.896, P = 0.180)

Fig. 3

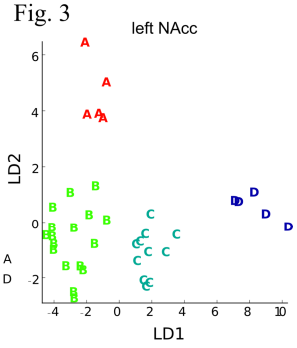


Table 1

LD1	LD2	LD3
Depersonalization and Derealization (HAM-D19, r=0.411*)	Depressed Mood (HAM-A6, r=0.401*)	Depersonalization and Derealization (HAM-D19, r=0.443**)
Suicidal thoughts (MADRS10, r=0.400*)	Inability to feel (MADRS8, r=0.350*)	Suicidal thoughts (MADRS10, r=0.354*)
Anxiety Somatic (HAM-D13, r=0.363*)	Behavior at Interview (HAM-A14, r=-0.316)	Somatic (Muscular) (HAM-A7, r=0.342*)
Somatic (Muscular) (HAM-A7, r=0.318)	Loss of Weight (HAM-D5, r=-0.261)	Depressed Mood (HAM-D1, r=0.309)
Inner tension (MADRS3, r=0.310)	Somatic Symptoms General (HAM-D9, r=0.255)	Depressed Mood (HAM-A6, r=0.263)

r: correlation coefficient, *: P<0.05, **: P<0.01

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