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The Neural Correlates of Anomalous Habituation to Negative Emotional Pictures in Borderline and Avoidant Personality Disorder Patients

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Abstract

Objective—Extreme emotional reactivity is a defining feature of borderline personality disorder, yet the neural-behavioral mechanisms underlying this affective instability are poorly understood. One possible contributor would be diminished ability to engage the mechanism of emotional habituation. We tested this hypothesis by examining behavioral and neural correlates of habituation in borderline patients, healthy controls, and a psychopathological control group of avoidant personality disorder patients.

Method—During fMRI scan acquisition, borderline patients, healthy controls and avoidant personality disorder patients viewed novel and repeated pictures, providing valence ratings at each presentation. Statistical parametric maps of the contrasts of activation during repeat versus novel negative picture viewing were compared between groups. Psychophysiological interaction analysis was employed to examine functional connectivity differences between groups.

Results—Unlike healthy controls, neither borderline nor avoidant personality disorder participants showed increased activity in dorsal anterior cingulate cortex when viewing repeat versus novel pictures. This failure to increase dorsal anterior cingulate activity was associated with greater affective instability in borderline participants. In addition, borderline and avoidant participants showed smaller insula-amygdala connectivity increases than healthy participants and did not show habituation in ratings of the emotional intensity of the images as did healthy participants. Borderline patients differed from avoidant patients in insula-ventral anterior cingulate connectivity during habituation.

Conclusions—Borderline patients fail to habituate to negative pictures as do healthy participants and differ from both healthy controls and avoidant patients in neural activity during habituation. A failure to effectively engage emotional habituation processes may contribute to affective instability in borderline patients.

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Keywords

borderline personality disorder; avoidant personality disorder; affective instability; fMRI; functional connectivity

Borderline personality disorder, an enduring condition, present in an estimated 2.7 % of the population (1), is characterized by severe affective instability, turbulent interpersonal relationships, and impulsive aggression (2). Approximately 10% of borderline patients commit suicide (2), and suicidality in borderline patients is associated with affective instability (3). Despite its clinical significance, we do not understand the processes underlying affective instability in this population (4). One factor that could contribute would be an impaired ability to engage the adaptive emotional regulatory processes commonly used by healthy individuals. These include voluntary emotion regulation strategies such as cognitive reappraisal (5) and implicit processes such as habituation, whereby multiple exposures to a stimulus yield diminished responsiveness (6). Anomalous neural activity has been identified in borderline patients during cognitive reappraisal (7, 8). The present study extends this work to examine whether emotional habituation mechanisms are impaired as well.

Habituation of affect, which entails the reduction in subjective distress upon repeated exposure to an aversive stimulus, is a well-established and highly adaptive psychophysiological phenomenon. Habituation plays a critical role, as well, in psychotherapeutic interventions such as desensitization (9). Neuroimaging studies in healthy individuals have demonstrated that habituation is associated with decreases in blood-oxygen-level-dependent (BOLD) signal in limbic regions such as the amygdala, the hippocampus, the insula, and the anterior cingulate cortex (ACC), as well as cortical regions such as left dorsolateral prefrontal cortex and temporal cortex (10–13). We have found that insula-amygdala connectivity increases in healthy individuals as they habituate to negative pictures (Denny et al, submitted). However in borderline patients little is known about limbic and cortical network response to repeated exposure to negative stimuli.

Functional neuroimaging studies of borderline patients engaged in emotion processing tasks have identified increased amygdala activity when viewing faces (14, 15), and increased amygdala, fusiform (16, 17), primary visual, anterior cingulate and superior temporal gyrus activity (17) when viewing negative compared to neutral emotional pictures, as well as increased amygdala activity when viewing repeated images (18). During cognitive reappraisal by distancing, borderline patients do not activate the dorsal anterior cingulate cortex and intraparietal sulci and do not downregulate amygdala activity to the extent that healthy controls do (7). Moreover, studies of functional connectivity in borderline patients during viewing of fear faces (19) and during pain processing (20) have shown anomalous connectivity patterns involving the insula, amygdala and prefrontal regions. However, there have been no studies of the relationship between functional connectivity and habituation in borderline patients.

We hypothesized that borderline patients would not be able to use habituation as effectively as healthy controls and that this would be reflected in decreased behavioral habituation and anomalous activity in emotion regulatory networks when they viewed repeated vs. novel aversive pictures. Specifically, we predicted that borderline patients would not activate the dorsal anterior cingulate, a region implicated in emotion regulation, and would not increase insula-amygdala connectivity to the degree that healthy controls do when confronting repeated negative pictures. Furthermore, we hypothesized that impairment in the implicit regulatory mechanism of habituation would contribute to the affective instability of

borderline patients and thus we predicted that affective instability in borderline patients would correlate with a deficit in dorsal anterior cingulate activity and insula-amygdala connectivity during habituation.

To examine the possibility that any differences between borderline and healthy control participants identified in this study could be the result of a low threshold for affective response, not specific to borderline personality disorder, we included avoidant personality disorder patients as a psychopathological control group. Avoidant personality disorder, which occurs in 1–2% of the population, is characterized by hypersensitivity to negative evaluation, excessive fear of rejection and avoidance of social relationships (21). To date no functional imaging studies of avoidant personality disorder have been reported in the literature, however studies of generalized social anxiety disorder, a disorder thought to be related to avoidant personality disorder, have identified decreased insula-dorsal anterior cingulate functional connectivity relative to controls when viewing fearful faces (22). Hence, we predicted decreased insula-dorsal anterior cingulate connectivity in avoidant participants relative to healthy controls during habituation.

To accomplish these objectives, we examined changes in subjective affect self-reports and in the functional neural architecture of habituation when negative pictures were viewed a second compared to a first time in borderline patients, avoidant patients, and healthy controls.

METHODS AND MATERIALS

Participants

A total of 23 borderline patients, 27 avoidant patients, and 28 healthy controls were recruited from outpatient clinics at the Mount Sinai Medical Center and the James J Peters VA Medical Center in New York City and from newspaper and on-line advertisements. Written informed consent was obtained after procedures were fully explained. Four borderline patients, 4 avoidant patients, and 3 healthy controls were excluded because of excessive head motion or inadequate response rates (see supplement for details). Participants in the borderline group met criteria for DSM-IV borderline personality disorder, including the DSM-IV criteria for affective instability (DSM-IV borderline criterion 6) and not meet criteria for schizotypal or avoidant personality disorder. Participants in the avoidant group met DSM-IV criteria for avoidant personality disorder and but not criteria for borderline or schizotypal personality disorder. Participants with potentially confounding Axis I diagnoses and medical conditions, as described in detail in the supplement, were excluded. Participants were required to be free of psychotropic medications for 2 weeks (6 weeks in the case of fluoxetine). Healthy participants did not meet criteria for any DSM-IV Axis I or Axis II disorder. Diagnostic assessments were obtained using the Structured Interview for Personality Disorders for Axis II and Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition for Axis I. Our group has achieved an interrater reliability of 0.81 (kappa) for diagnosing borderline personality disorder. All participants were rated for affective instability by means of the Affective Lability Scale (23), and for depression using the Hamilton Depression Rating Scale (HAMD).

Sample characteristics are presented in Table 1. The borderline and avoidant groups did not significantly differ in age from the control group. The avoidant participants were slightly younger than the borderline participants ($p < .05$). The female to male ratio did not differ between groups. As expected, the borderline patients demonstrated greater affective instability as measured by the Affective Lability Scale than either comparison group. Depression as rated by the HAMD was low for all groups, but as expected the HAMD score was highest for the borderline group (7.2 ± 2.9), intermediate for the avoidant group ($4.9 \pm$

2.9) and lowest for the healthy control group (1.1 ± 1.1). Present and past Axis I and Axis II comorbidities are presented in the supplemental material.

Event-related Task Design

BOLD signals were acquired as participants viewed a series of 48 negative and 48 neutral pictures drawn from the International Affective Pictures System (24) and the Empathy Picture System (25). The picture set is described in detail in the supplement. Two-thirds of pictures were presented twice. The picture-repeat pairs were distributed uniformly throughout the 27 minutes of the task to control for potential confounds of practice, fatigue, or scanner drift. Pictures that were repeated versus shown only once were counterbalanced across participants. The task design is shown in Figure 1. Neutral pictures were interspersed among the negative pictures so that participants would not become inured to viewing negative pictures; no specific hypotheses were made regarding neutral pictures, which were not the focus of the current analyses. Negative pictures showed scenes reflecting conflict, abuse, or loss and neutral pictures showed people at work or in street scenes. Participants were instructed to allow themselves to fully experience the emotion evoked by the picture, and to indicate their emotional response to the picture they had just viewed on a scale of 1 (most negative) to 5 (most positive).

Image Acquisition and Analysis

BOLD images were obtained with a Siemens 3.0T Allegra scanner using a gradient echoplanar (GE-EPI) sequence employing parameters described in the supplemental material. Preprocessing and statistical analyses were carried out using SPM8 (Wellcome Department of Cognitive Neurology, London) and general linear modeling for each participant was carried out with Neuroelf software (neuroelf.net). Preprocessing parameters and general linear model modeling are described in the supplemental material. For the trial-by-trial affect analyses, parametric weights corresponding to each participant's affect rating per trial were specified. Contrast images for all participants were entered into a second-level random effects group analysis carried out using Neuroelf software. The principal contrast of interest was $\text{Repeat}_{\text{Neg}} - \text{Novel}_{\text{Neg}}$. Whole-brain family-wise error multiple comparison correction thresholds were determined using Alphasim (26). In *a priori* regions-of-interest including amygdala, family-wise error extent thresholds were small-volume corrected using a bilateral Brodmann-atlas based anatomical amygdala mask. Reported coordinates refer to Montreal Neurological Institute (MNI) space.

Functional Connectivity Analyses

Psychophysiological interaction (27) analyses were carried out using a seed region in the left middle-posterior insula, chosen as an affect-related (28, 29) region-of-interest whose activity correlated with trial-by-trial affect ratings as determined in the parametric analyses. The seed region was determined independent of the task-related connectivity changes for $\text{Repeat}_{\text{Neg}}$ vs. $\text{Novel}_{\text{Neg}}$ conditions. To protect against bias by group, we defined this region to be the conjunction of the $\text{Novel}_{\text{Neg}}$ and $\text{Repeat}_{\text{Neg}}$ parametric maps for all three groups. A general linear model was then computed including regressors for the coupling between this seed region and other brain areas, as well as a psychophysiological interaction term reflecting the coupling of the seed region and other brain regions modulated by the psychological context of interest, in this case the change between $\text{Repeat}_{\text{Neg}}$ and $\text{Novel}_{\text{Neg}}$ conditions. Six motion parameters were also included and data were high-pass filtered using a Fourier transform (cut-off=130 s). Following general linear model estimation, random effect analyses were performed as above, with contrasts in this case representing areas showing a significant psychophysiological interaction effect. Results were then statistically thresholded as described above.

RESULTS

Behavioral Results

Figure 2 displays participants' ratings of emotional valence for novel and repeat negative pictures. A repeated measures ANOVA of ratings of picture valence with novelty (novel vs. repeat) as repeated measure and group (borderline, avoidant, healthy) as the between-subjects measure showed a main effect of novelty ($F(2,64) = 7.38, p = .008$), but no group by novelty interaction ($F(92,64) = 0.314, n.s.$). Planned comparisons examining our prediction that only healthy participants would behaviorally habituate showed that healthy controls did habituate to the negative pictures, rating repeat pictures less negatively than novel pictures ($t(24) = 2.71, p < 0.01$, one-tailed), and that borderline and avoidant participants did not ($t(18) = 0.84, ns$ and $t(22) = 1.52, ns$, respectively). Neutral picture behavioral findings are presented in Supplemental Results.

Imaging Results

BOLD Activation in Borderline and Avoidant Participants Compared to Healthy Controls During Repeated Exposure to Negative Pictures—When viewing repeat vs. novel negative pictures, borderline patients in comparison to healthy participants showed a relative decrease in activation in the dorsal anterior cingulate cortex (156 voxel cluster, $p < 0.05$, $k = 150$, family-wise error-corrected; Figures 3A and 3B), and the left superior, left middle and right transverse temporal gyri (Figure S1 and Table S1). In each region this was accounted for by a relative increase in activity in healthy controls. Avoidant patients also showed decreased dorsal anterior cingulate activity relative to healthy participants (162 voxel cluster, $p < 0.05$, $k = 150$, family-wise error-corrected; Figures 3C and 3D), as well as in right transverse temporal gyrus, right thalamus, the left parahippocampal gyrus, left inferior frontal gyrus, left precuneus and right cerebellar culmen (Figure S1 and Table S1). Borderline and avoidant participants did not differ from each other in activation when viewing repeat vs. novel negative pictures at the whole-brain corrected threshold (family-wise errorcorrected, $p < 0.05$). Repeat vs. novel contrasts within the groups are provided in the supplemental material (Figure S2 and Table S2). Collapsing across novelty, we found that borderline patients showed greater amygdala and insula activity in response to negative pictures than either healthy controls or avoidant participants (Figure S3).

Association Between Decreased Engagement of the Dorsal Anterior Cingulate During Habituation and Affective Instability—To determine whether the degree to which deficits in engaging the dorsal anterior cingulate during repeat vs. novel viewing was associated with participants' affective instability, we determined correlations between Affective Lability Scale scores and BOLD signal change in dorsal anterior cingulate for each subject group. An unbiased 65 voxel dorsal anterior cingulate region-of-interest (peak at $[-3, -3, 42]$; Figure 3E) was defined by the conjunction of the repeat – novel contrasts for the (borderline vs. healthy) and (avoidant vs. healthy) comparisons. For both healthy and borderline participants there was a negative correlation ($r = -.038, p < 0.04$ and $r = 0.56, p < 0.01$, one-tailed, respectively) between affective instability and BOLD signal change in this region-of-interest (Figure 3F). For avoidant patients this association was not significant ($r = 0.02, p = 0.47, n.s.$).

Association Between Neural Activity and Subjective Affect Reports—To identify the seed region for subsequent functional connectivity analyses we examined the neural representation of the subjective experience of negative affect by conducting parametric analyses, examining the relationship between regional activation and trial-by-trial affect ratings of the negative pictures. For each of the 3 groups, and for both novel and repeat picture viewings, the degree to which pictures were rated as negative was correlated

with middle-posterior insula activity, with greater activity predicting greater subjective reports of negative affect in all 6 maps, a finding we previously reported using this dataset in healthy participants alone (Denny et al, submitted). Conjunction analysis of the 6 maps yielded a 27 voxel left mid-posterior insula cluster ($p < 0.05$, two-tailed, peak at $[-42, 0, 6]$; see axial inset in Figure 4), which became our insula seed region for subsequent functional connectivity analyses.

Functional Connectivity—Montages showing significant changes in functional connectivity to the left insula seed region for repeat vs. novel viewings within each group are provided in the supplemental material (Figure S4). Significant change in functional connectivity between the left insula seed and amygdala was only observed in healthy controls, where it was observed bilaterally. Group comparisons demonstrated that, when viewing repeat vs. novel pictures, borderline patients increased connectivity between the insula and bilateral amygdalae significantly less than healthy controls (Figure 4, $p < 0.05$, two-tailed, masked with a Brodmann atlas-based anatomical amygdala boundary). Figure 4 shows significant differences between borderline and healthy controls in the change in amygdala-insula connectivity in left amygdala (19 voxels; peak at $[-18, -9, -18]$; family-wise error small-volume corrected, $p < 0.05$, two-tailed) and right amygdala (21 voxels; peak at $[24, -6, -30]$; family-wise error small-volume corrected, $p < 0.05$, two-tailed). Avoidant patients did not show significant differences in insula-amygdala connectivity compared to either healthy or borderline participants. Examination of the correlation between insula-amygdala connectivity change and behavioral habituation suggested a positive association in borderline and healthy participants (such that greater connectivity increases predict greater behavioral habituation) and a negative association in avoidant patients, though these results should be considered preliminary because of the relaxed extent thresholds applied for borderline and healthy participants (Figure S5). There was no significant correlation between insula-amygdala connectivity change and Affective Lability Scale score in any group.

Borderline patients also did not increase connectivity between the insula and the superior frontal gyrus (220 voxels, peak at $[8, 45, 39]$, $p = 0.05$, $k=150$, family-wise error-corrected) to the degree that healthy participants did (Figure S6 and Table S3). Avoidant patients showed less of an increase in connectivity between the insula and a broad region of middle frontal gyrus (including dorsolateral and medial prefrontal cortices) and posterior cingulate (BA 30) than healthy controls and more of an increase to the cerebellum than healthy controls ($p = 0.05$, $k=150$, family-wise error-corrected) (Figures S6 and Table S3).

Directly examining whether borderline differed from avoidant patients, we found that borderline patients demonstrated greater increases in insula connectivity to the ventral anterior cingulate cortex and smaller increases to the cerebellum than avoidant patients ($p=0.05$, $k=150$, family-wise error-corrected; Figures S6-S7 and Table S3).

DISCUSSION

The present study was motivated by the effort to determine whether borderline patients, who are emotionally dysregulated, show anomalous neural activity during the implicit emotion regulatory process of habituation, and whether patients with a different personality disorder characterized by high emotional reactivity to interpersonal situations, avoidant personality disorder, could be distinguished from borderline patients when presented with the same task. Behaviorally, we found that whereas healthy participants habituated to the negative pictures, neither borderline nor avoidant participants did. We also found that during repeat viewing borderline and avoidant participants showed no significant change in dorsal anterior cingulate activity, while healthy participants increased activity in this region. Importantly,

the capacity to increase activation in this region upon repeat viewing was associated with less affective instability in borderline and healthy participants. Taken together, these findings support the hypothesis that anomalies in habituation are associated with affective instability in borderline patients.

Further, when viewing repeated negative emotional pictures, neither borderline nor avoidant patients showed the increased insula-amygdala functional connectivity that healthy participants did. Since increasing insula-amygdala connectivity was associated with increasing behavioral habituation in healthy and borderline participants, failure to adequately increase this connectivity could additionally contribute to impaired behavioral habituation and consequent faulty emotion regulation in borderline patients.

In examining the subjective experience of negative emotion, this study demonstrated that left middle-posterior insula activity correlated with ratings of negative affect in borderline, avoidant and healthy participants during both novel and repeated negative picture viewing. This finding is consistent with the proposal that the insula broadly participates in self-awareness of feeling state and affective integration (30, 31), with a particular role for mid and posterior insula in visceral awareness (29, 32, 33). In addition to these novel findings, we replicated the observation that borderline participants show greater amygdala activation than healthy participants when viewing negative social pictures (7, 14–16), and we extended these observations to show that the increased amygdala activation in borderline patients was also greater than that seen in avoidant participants. In addition, we demonstrated greater insula activation to negative pictures in borderline patients compared to healthy and avoidant participants.

A strength of this study is its inclusion of avoidant participants as a psychopathological control group to explore whether differences in functional patterns identified in borderline patients could be distinguished from those of other personality disorders. Although displaying a number of features in common with borderline patients, the avoidant group differed from borderline in several respects. Borderline differed from avoidant patients in showing a greater increase in insula-ventral anterior cingulate connectivity with repeated viewing of negative pictures. The insula and anterior cingulate have been posited as key nodes in a network dedicated to assessing the salience of external and internal stimuli, allocating attentional and control resources and preparing for action (34). Thus decreased connectivity to this region in avoidant patients suggests the possibility of a distinct mechanism accounting for the affective dysregulation in these patients. The two personality disorder groups also differed from each other in the degree to which increased activation of the dorsal anterior cingulate to repeat vs. novel pictures predicts less affective instability.

Avoidant participants did not activate the thalamus, parahippocampal gyrus, ventrolateral prefrontal cortex, or dorsal anterior cingulate as strongly as healthy controls when viewing repeat vs. novel negative pictures. In addition, they did not increase insula connectivity to extensive cortical regions including the rostral anterior cingulate, the medial and dorsolateral prefrontal cortex and posterior cingulate to the extent that healthy participants did. Decreased insula connectivity to the rostral anterior cingulate when viewing threat pictures has been reported in generalized social anxiety disorder (22), suggesting the possibility of some functional similarities between these disorders.

Although the healthy participants showed significant behavioral habituation and the borderline and avoidant participants did not, the magnitude of the habituation effect in the healthy participants was not large and in the absence of a group by novelty interaction we cannot conclude that there are group differences in behavioral habituation. The small behavioral effect and consequent absence of the interaction effect may be a consequence of

the fact that pictures were repeated only once, and this is a limitation of the present study. Nevertheless, rather robust group differences in activation and functional connectivity were present. The finding of significant neural group differences alongside blunted behavioral differences is common to a number of neurophysiological studies comparing borderline patients to healthy controls (8, 16, 17, 35, 36). New and colleagues have suggested that this may be a consequence of borderline patients' alexithymia and difficulty self-identifying emotion (37).

The present study demonstrates that, when presented with repeated negative pictures, borderline patients show anomalies in limbic-cortical functional connectivity and in engagement of cortical regulatory regions that are associated with affective instability. This suggests that impairment in the implicit emotion regulatory mechanism of habituation may contribute to the affective instability that characterizes borderline patients. The anomalous patterns of activity and connectivity in borderline patients are distinct from those in avoidant patients, indicating that the neural features of habituation in borderline patients are not simply characteristics of personality disorders in general. Understanding the processing deficits underlying anomalous habituation in borderline and avoidant personality disorders may help to guide the development of novel psychotherapeutic or pharmacologic interventions to enhance adaptive habituation in these disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Schematic Depiction of Picture Presentation Design

Each picture is presented for 4 s and is followed by a 3 s rating interval when the subject rates the picture on a 1 (most negative) to 5 (least negative) scale using a response button box. This is followed by a 3 s interstimulus interval. Pictures are shown in 5 consecutive runs of 16 negative and 16 neutral pictures. Two-thirds of the pictures are shown a second time. The repeat pictures are always shown 5.3 min after the first showing of that picture and pictures and repeats are distributed uniformly throughout the 27 min of the task. Novel and repeat pictures are counterbalanced among participants.

Figure 2.
Behavioral Ratings of Picture Valence During the Scan. ** p < 0.01, one-tailed

Figure 3.

Engagement of the dorsal anterior cingulate when viewing repeat vs. novel negative pictures. A.) The map shows a 156 voxel dorsal anterior cingulate cluster indicating a significant difference between healthy control and borderline groups for Repeat_{Neg} vs. Novel_{Neg} activity ($p < 0.05$, $k = 150$, family-wise-corrected), B.) Extracted beta-weights for each group when viewing novel and repeat negative pictures, C.) 162 voxel dorsal anterior cingulate cluster indicating a significant difference between healthy control and avoidant groups for Repeat_{Neg} vs. Novel_{Neg} activity ($p < 0.05$, $k = 150$, family-wise error-corrected), D.) Extracted beta-weights for each group when viewing novel and repeat negative pictures, E.) Unbiased 65 voxel dorsal anterior cingulate region-of-interest derived from conjunction of

voxels showing significant between-group differences for repeat vs. novel negative picture viewing for borderline patients vs. healthy control and avoidant vs. healthy control contrasts ($p < 0.05$, F.) Correlation of repeat vs. novel activation differences in the independently-defined dorsal anterior cingulate region-of-interest with affective instability for each group.

* indicates a significant within-group difference, $p < 0.05$, two-tailed.

Figure 4.
Insula-amygdala functional connectivity in borderline patients and healthy controls.
* $p < 0.05$, two-tailed

Table 1

Sample Characteristics

	Borderline	Healthy Control	Avoidant	Statistic		
				Borderline versus Healthy Control	Avoidant versus Healthy Control	Borderline versus Avoidant
N	19	25	23			
Mean Age (SD)	31.9 (9.9)	28.1 (6.9)	26.3 (4.8)	t(42) = 1.53 $\chi^2 = 0.15$	t(46) = 1.05 $\chi^2 = 0.10$	t(40) = 2.44* $\chi^2 = 0.01$
Gender (F/M)	11/8	13/12	13/10			
ALS Score	71.3 (30.6)	27.3 (20.5)	48.8 (21.5)	t(41) = 5.65*** $\chi^2 = 0.15$	t(46) = 3.55*** $\chi^2 = 0.10$	t(39) = 2.76* $\chi^2 = 0.01$
HAMD Score	7.2 (2.9)	1.1 (1.1)	4.9 (2.9)	t(30) = 7.32*** $\chi^2 = 0.15$	t(34) = 4.60*** $\chi^2 = 0.10$	t(38) = 2.55* $\chi^2 = 0.01$

ALS – Affective Liability Scale; HAMD- Hamilton Depression Scale

* p < .05;

** p < .01;

*** p < .001