Brain-Behavioral Systems in Patients with Comorbid Anxiety - Depression vs. Healthy Individuals

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Abstract

Background: According to the brain-behavioral systems theory, behavioral inhibition and behavioral activation systems contribute to the development of many psychopathological conditions. Given that anxiety and depression are the most common emotional disorders and the fact that they are highly overlapping, the aim of this study was to compare the brain-behavioral systems in the patients with comorbid anxiety-depression and healthy individuals.

Method: This study was cross-sectional. Sample includes Sixty-four patients with comorbid anxiety and depression attending to the community health centers of Jiroft city and 64 healthy individuals. They were selected using purposive sampling and matched for age and gender. After obtaining informed consent, they were asked to fill Jackson-5 scale, Beck Depression Inventory and Beck Anxiety Inventory. Data are analyzed by MANOVA.

Results: The results showed that the two groups had significant differences in behavior inhibition system, fight, flight and freeze. However, there was no difference in behavioral activation system.

Conclusion: Given the observed differences in the brain-behavioral systems between patients with comorbid anxiety-depression and healthy individuals, this theory may explain the comorbidity of anxiety and depression.

Introduction

A large number of studies documented depression and anxiety as highly comorbid disorders. It is reported that 75 percent of those afflicted with depression, also experience anxiety symptoms (1-3). Comorbidity of emotional disorders is linked with the most severe periods of the psychological disease and a weaker response to treatment (4). Several models have been suggested to bring us to the better understanding of phenomenological comorbidity of depression and anxiety (5-9); Yet, Gray’s reinforcement sensitivity theory (10) gained less attention in the comorbidity of depression and anxiety.

Inspired by Eysenck’s theory, Gray (10) developed the Reinforcement Sensitivity Theory and based it on three brain-behavioral systems: Behavioral Activation System (BAS), Behavioral Inhibition System (BIS), and Fight Flight System (FFS). He believed these brain-behavioral systems underlie the individual differences so that, their activations would arouse different emotional responses such as fear and anxiety.
BAS is the first system in the Gray model which responds to the conditioned stimuli of reward and non-punishment conditions. Activated and its sensitivity heightened, this system arouses positive emotions and active avoidance of punishment (11). BAS sensitivity is associated with the increase of positive emotions and the impulsive dimensions of the personality (12). The second system, BIS, is responsive to conditioned stimuli of punishment, non-reward, novel stimuli and also to innate fear stimuli. Activated, this system arouses anxiety, behavioral inhibition, passive avoidance and extinction and also increases attention and arousal. FFFS, which is the third system in Gray’s model, is associated with activations of amygdale and hypothalamus and is sensitive to aversive stimuli. Studies on the role of these systems in clinical psychological disorders showed that the excessive activity of BAS and BIS makes people prone to mental disorders (13).

The results of some studies demonstrated the association between these three systems and a number of mental disorders; FFFS is proved to be linked with phobia and panic disorder (14). BAS is associated with addictive behaviors, social-emotional and psychological adaptation (15), bipolar disorder (16, 17), and attention-deficit and hyperactivity disorder (18, 19). BIS is linked with generalized anxiety disorder (20), obsessive compulsive disorder (14), and also major depressive disorder [MDD] (17, 21).

MDD may occur due to the extremely insensitive BAS that fails to arouse positive emotions or to respond to encouraging environmental stimuli (7). Depressive individuals with lower levels of BAS are more likely to fail to respond to positive incidents and stimuli in their environment. They are less likely to search for positive stimuli and are less engaged in pleasure-giving activities (22). Indeed, low sensitive BAS seems to be common with patients who are suffering from unipolar depression (17). Moreover, BIS that has been confirmed to be associated with anxiety, has revealed strong link with unipolar depression (23). Though BAS low sensitivity is associated with depression, BIS high sensitivity is reported to be linked with a wide range of emotional problems (13).

Johnson, et al. (24) found out that high BIS score is a predictive factor for lifelong anxiety and depression. Examining the relation between brain-behavioral systems and anxiety, Ly and Gomez (25) found out that anxiety is positively related to BIS and punishment sensitivity, but it is negatively related to BAS. In the study of Vervoort et al. (26), the anxious group scores in BIS were higher than nonanxious group. In Kimberl, et al. study (27), higher BIS scores predicted anxiety and depression.

Findings that show relation of BIS high sensitivity to anxiety and depression (21, 28, 29) may explain depression-anxiety comorbidity. Yet, there is relatively little literature supporting this view. High BIS and low BAS may also provide a potential ground for the comorbid relation between anxiety and depression. Besides these, BIS is likely to be a common risk factor for both disorders (30). In general, the study of relationship between personality theories and mental disorders can increase our understanding of the etiology
and comorbidity of these disorders (31, 32) and suggest appropriate ways for preventing and treating them (33).

In addition to the corroborated findings, Gray’s reinforcement sensitivity theory brings us to the understanding that irregularity in brain-behavioral systems is one of the factors leading to comorbidity of anxiety and depression. There has been relatively little research conducted on the activity of brain-behavioral systems in those patients suffering from both the anxiety and depression in other countries and there is no study about this topic in Iran. Therefore, the current study aimed to discern whether the normal cases and the patients with comorbid anxiety-depression differ in their brain-behavioral systems.

Method

In this cross-sectional study, the brain-behavioral systems of normal individuals and patients afflicted with anxiety-depression comorbidity were investigated. The studied population consisted of patients with comorbid anxiety-depression referring to governmental and non-governmental health care centers in Jiroft city. They were selected through purposive sampling method and scored average to high according to Beck Depression Inventory-II [BDI-II] and Beck Anxiety Inventory [BAI]. The diagnostic results were also confirmed in consultation with a psychiatrist and a clinical psychologist. In addition, the normal cases consisted of people referring to health care centers to receive due services. Selected purposively due to their low score in BDI-II and BAI, they were matched to the patient participants based on the age and gender variables. The sample size was estimated by G*Power (34). Split into two groups, the sample yielded an effect size of $f^2=0.25$, a relatively medium effect size, a power of .80 and 64 subjects per group. The results were then analyzed using SPSS version 21 by MANOVA.

Study tools

Beck Depression Inventory-II: This inventory (35) is a revised version of BDI-II that was designed and validated to measure the severity of depression in Iranian samples (36). It is designed for individuals aged 13 and over and its scoring is based on Likert scale. The cut-off points are 0–13 that indicates minimal depression or no depression at all, 14–19 that indicates mild depression, 20–28 that indicates moderate depression, and 29–63 that indicates severe depression (37, 38). Studies on the second version of this inventory have reported that it has desirable validity, reliability and factor structure and also it is a proper substitute for the first version (36). An Iranian study, reported a strong alpha coefficient of 0.91, a 0.89 correlation coefficient between the two halves, a test-retest (1-week interval) coefficient of 0.94 and 0.93 correlations with BDI-I in an Iranian sample (36). In the current study, Cronbach’s alpha was 0.92.

Beck Anxiety Inventory (BAI): Given the importance of the main dimensions of anxiety- that are the cognitive and physiological symptoms- Beck, et al. (39) designed a 21-questions self-report inventory with Likert scale. BAI scores the frequency of the subjects’ anxiety symptoms on a scale value of 0 to 3 during the past week. The suggested cutoff points are 0–7 for minimal anxiety, 8–15 for mild anxiety, 16–25 for moderate anxiety, and 26–63 for severe anxiety. In
studying the internal consistency of the questionnaire in Iranian society, alpha coefficient was 0.92, there was a 0.91 reliability coefficient between the two halves, a test-retest (1-week interval) coefficient of 0.81 and a correlation of 0.62 with BDI-II (36). Cronbach’s alpha for this study was 0.92.

Jackson Five-Scale Inventory: Jackson (40) developed a 30-question inventory to properly measure revised-Reinforcement Sensitivity Theory. The inventory consists of five subscales: BAS, BIS, and Fight, Flight and Freeze system (FFFS). Six questions have been designed for each subscale. Using confirmatory and exploratory factor analysis, Jackson developed and assessed new scales (Jackson Five-Scale). The results showed a satisfactory internal reliability and a desirable validity of the construct. The participant answered a 5-item Likert scale with 1 = strongly agreed (Always) and 5 = strongly disagreed (Never). Using double-translation method, Hasani, et al. (41) employed the Farsi version of Jackson Five-Scale Inventory for 308 participants (174 males & 134 females). The reliability of the inventory was examined by internal consistency, item-total correlations, and test-retest methods. Moreover, the scale’s validity was examined by exploratory factor analysis, subscales’ inter-correlations, and criterion validity. Cronbach’s alpha value range (0.72 to 0.88), test-retest coefficients (0.64 to 0.78), and, item-total correlations (0.28 to 0.68) showed that the Farsi version of Jackson Five-factor Inventory is of a desirable validity. Confirmatory and exploratory factor analysis also supported the five main factors of the inventory. Subscales’ internal consistency (ranged from 0.11 to 0.53) was reported as desirable, too. Finally, the scale’s validity was reported satisfactory since a specific pattern of correlation coefficient was recognized between inventory subscales from one hand and negative emotion, positive emotion, BAS and BIS, Eysenck’s personality dimensions, and Bart’s impulsivity dimensions on the other hand. Cronbach’s alpha calculated for the subscales were: BAS: 0.52, BIS: 0.62, Fight: 0.75, Flight: 0.68 and Freeze: 0.63.

Procedure

The study’s inclusion criteria consisted of literacy for answering the inventory, being in the age range of 18-55 years and willingness to participate in the study. Exclusion criteria included lack of literacy, psychiatric disorders history except for anxiety and depression, bipolar mood disorder, mental retardation, physical diseases or any other conditions attributable to depression. These disorders assessed in the two groups through clinical interviews before the questionnaires were completed. Qualified participants were thus selected and asked to complete the questioners. Participants scored high (≥20) and low (0-12) in BDI-II and high (≥16) and low (0-7) in BAI were allocated to the patients and normal groups, respectively and individually completed the questionnaires. Participants were then thanked.

Results

The demographic information of participants has been summarized in table 1.
Independent samples t-tests showed no significant age differences in the two groups, t(126) = 1.02, p = 0.30. In addition, comparing two groups using chi-square test showed no significant differences in terms of gender (p = 0.34), marital status (p = 0.84), education (p = 0.06), and addiction history (p = 0.09). However, significant group differences are observed in terms of anxiety and depression history (p = 0.001) and psychiatric drugs use (p = 0.001). The groups differed significantly only in psychiatric drug use and anxiety and on depression history whereby those in the patient group reported more history of anxiety, depression disorder and psychiatric drug use.

Means, SDs, skewness, S.E. of skewness, kurtosis and S.E of kurtosis of the variables have been shown in Table 2.

**Table 1. Demographic characteristics of the studied groups**

<table>
<thead>
<tr>
<th>Descriptive Variable</th>
<th>Normal group (n=64)</th>
<th>Patient group (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>frequency</td>
<td>percent</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41</td>
<td>64.1</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>35.9</td>
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<tr>
<td>Marital Status</td>
<td></td>
<td></td>
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<tr>
<td>Single</td>
<td>17</td>
<td>26.6</td>
</tr>
<tr>
<td>Married</td>
<td>47</td>
<td>73.4</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>12</td>
<td>18.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10</td>
<td>15.6</td>
</tr>
<tr>
<td>High school Diploma</td>
<td>23</td>
<td>35.9</td>
</tr>
<tr>
<td>Bachelor</td>
<td>18</td>
<td>28.1</td>
</tr>
<tr>
<td>Master</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Addiction History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>No</td>
<td>63</td>
<td>98.4</td>
</tr>
<tr>
<td>Anxiety and depression History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>7.8</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>92.2</td>
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<tr>
<td>Psychiatric Drugs Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>No</td>
<td>62</td>
<td>96.9</td>
</tr>
</tbody>
</table>

**Table 2. Means, SDs and the other distribution statistics of the studied variables**

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>Age</th>
<th>Depression</th>
<th>Anxiety</th>
<th>BAS</th>
<th>BIS</th>
<th>Fight</th>
<th>Flight</th>
<th>Freeze</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Mean</td>
<td>32.33</td>
<td>4.84</td>
<td>3.52</td>
<td>19.52</td>
<td>20.47</td>
<td>14.05</td>
<td>16.66</td>
<td>15.67</td>
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<tr>
<td></td>
<td>SD</td>
<td>9.26</td>
<td>4.09</td>
<td>2.98</td>
<td>4.54</td>
<td>6.22</td>
<td>4.85</td>
<td>475</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td>Skewness</td>
<td>.431</td>
<td>.477</td>
<td>.953</td>
<td>-645</td>
<td>-535</td>
<td>.489</td>
<td>-194</td>
<td>-001</td>
</tr>
<tr>
<td></td>
<td>S.E. Skewness</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
</tr>
<tr>
<td></td>
<td>Kurtosis</td>
<td>-.471</td>
<td>-899</td>
<td>1.891</td>
<td>1.130</td>
<td>-344</td>
<td>.184</td>
<td>-354</td>
<td>-222</td>
</tr>
<tr>
<td></td>
<td>S.E Kurtosis</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
</tr>
<tr>
<td>Patients</td>
<td>Mean</td>
<td>30.86</td>
<td>30.23</td>
<td>29.45</td>
<td>19.94</td>
<td>22.77</td>
<td>18.59</td>
<td>19.38</td>
<td>19.77</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6.76</td>
<td>8.26</td>
<td>9.39</td>
<td>4.10</td>
<td>4.41</td>
<td>5.44</td>
<td>4.82</td>
<td>4.80</td>
</tr>
<tr>
<td></td>
<td>Skewness</td>
<td>.538</td>
<td>.728</td>
<td>.804</td>
<td>-.301</td>
<td>-.621</td>
<td>-.135</td>
<td>-.722</td>
<td>-.142</td>
</tr>
<tr>
<td></td>
<td>S.E. Skewness</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
<td>.299</td>
</tr>
<tr>
<td></td>
<td>Kurtosis</td>
<td>.356</td>
<td>.210</td>
<td>1.283</td>
<td>-422</td>
<td>-190</td>
<td>.324</td>
<td>.111</td>
<td>-.484</td>
</tr>
<tr>
<td></td>
<td>S.E Kurtosis</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
<td>.590</td>
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</tbody>
</table>

MANOVA analyses confirmed that there was a significant multivariate effect; Pillai’s Trace = 265, F(1,126) = 8.81, p = 0.001, when compared with the normal group, participants in the patient group were significantly higher in the mean scores of BIS, F(1,126) = 5.79, p = 0.018, Fight, F(1,126) = 24.88, p = 0.001, Flight, F(1,126) = 10.30, p = 0.002, and Freeze, F(1,126) = 27.97, p = 0.001. There was no significant difference in BAS, F (1,126) = 30, p = 0.58.
Discussion and Conclusion

The current study aimed to compare brain-behavioral systems in the normal individuals and patients afflicted with comorbid anxiety and depression. Congruent with the previous studies, the results validated the hypothesis that individuals with comorbid anxiety-depression differ in their brain-behavioral systems from healthy cases (23, 24, 42, 43). In the similar way, Gray (44) believed that anxiety and neurotic depression, i.e., comorbid depression-anxiety, is the result of BIS excessive activity. Yusuke, et al. (45) have investigated the personality characteristics and their probable relations to anxiety and depression symptoms. They have reported both anxiety and depression as positively and significantly linked with BIS.

In general, high BIS sensitivity leads to increased attention to threat, increased negative affect and increasing behavioral inhibition which ultimately leads to anxiety (46). In other words, the higher BIS sensitivity increases the response to negative events (47). Hence, this finding suggests that BIS may play a role both in depression and anxiety. In r-RST, BIS is responsible for resolving the conflict, i.e., situations involving both reward and threat (48). This applies to conflicts between competing goals of the FFFS and the BAS (avoiding pain and approaching reward) but can also be between FFFS-FFFS goals or BAS-BAS goals (e.g., making a choice between two potential rewards). According to r-RST, r-BIS operates in either one of two modes. When in “checking” mode, its role is to be a risk-assessor, meaning that it monitors the environment and scans memory of previous aversive events in order to detect potential danger. When in “control” mode, r-BIS becomes activated and attention to the environment increases. In the case of a FFFS-BAS conflict, this is when it would assess the merits of avoiding versus approaching the stimulus in making a decision about the best response (49). As a decision-making system, the corresponding emotions are feelings of anxiety and worry in the face of unfamiliar stimuli or frustration when faced with the absence of reward. Therefore, people with comorbid depression and anxiety are likely to be more in the conflict situations.

In the last decades, researchers paid attention to Reinforcement Sensitivity Theory (RST) in different disorders. Depression is turned out to be one of the disorders gaining considerable attention in those studies. According to RST, depression is characterized with motivational deficiencies or lack of positive reinforcement and as well by an increase in avoidance behaviors such as social withdrawal. In addition, the mentioned theory associates depression with low BAS and high BIS (50). Quilty and collaborators (17), reported a strong link between depression symptoms and higher sensitivity to punishment (BIS). On the other hand, anxiety disorders are characterized by an increase in the vigilance to threat stimuli and they are linked with higher BIS (23). Moreover, it is believed that higher levels of BIS would arouse more anxiety (45).

The neuroanatomical bases of BIS are located in serotonergic and noradrenergic pathways in orbitofrontal cortex, septo-hippocampal system and the Papez circuit (10, 51). Due to the BIS higher sensitivity
in those patients with comorbid anxiety-depression, and given the fact that these individuals respond well to serotonin reuptake inhibitors (52), the findings of the present study supports Gray’s model which assumes that the serotonergic irregularities of septo-hippocampal system form the basis for depression and anxiety. Levita et al. (53) in their study on the BIS, anxiety and hippocampal volume in the nonclinical population found that greater levels of BIS were positively associated with right hippocampal volume.

Pourmohammad-Rezai-Tajrishi and Mirzamani-Bafghi (54) found a significant link between BIS and depression. Mansuri and Bakhshipour-Roudsari (55) showed that BIS is associated with pathological and non-pathological anxiety. Basharpour and Mozafari (56) studied the role of BAS and BIS in predicting students’ state-trait anxiety. They reported a link between high BIS and state-trait anxiety. They also showed that the lower BAS is linked only with trait anxiety. Karsazi and Hashemi (57) examined the structural relations of brain-behavioral systems and the difficulty of emotion-regulation to depression and social anxiety symptoms. Their findings revealed that the brain-behavioral systems can act out as personality-neurobiological basis for depression and social anxiety disorder. These findings show that these neurobiological systems are vulnerable to depression and anxiety.

The present study demonstrated that normal individuals and those with comorbid anxiety-depression did not differ significantly in BAS. According to Gray (44), BAS activity differs in anhedonic depression and anxiety-depression comorbidity. Examining for the BAS and BIS activity in these two subtypes of depression, Kimbrel, et al. (27) found out that low BAS only predicts anhedonic depression; and high BIS is associated with anxiety-depression comorbidity. Thus, anxiety-depression comorbidity might well explain the reason for the finding that the groups in the present study showed no difference in BAS. Likewise, Yusuke, and colleagues (45) found no significant correlation between depression and BAS. Yet, using hierarchical regression to control anxiety symptoms, they found a link between depression and BAS. In their study of brain-behavioral systems and depression/anxiety dimensions, Spielberg, et al. (58) reported anhedonic depression and anxiety dimensions (cognitive and physical arousal) to be linked with high BIS. They also reported that only anhedonic depression is linked with low BAS. Thus, it is likely that high BIS leads to anxiety-depression comorbidity. Yet, more studies needed to be done to uncover the link between BAS and depression subtypes and their due symptoms.

Small sample size and the employment of cross-sectional data gathering method were the limitations of the current study. Yet, the study was an unprecedented one in Iran that contrasted the brain-behavioral systems in normal individuals and those with depression-anxiety comorbidity. So, this theory may explain Iranian patients with comorbidity of anxiety and depression. As we know, human behavior is strongly influenced by cultural differences, and this theory may explain the psychological phenomenon occurred to Iranian patients instead of patients in other cultural contexts.
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