Cognitive and genetic aspects of emotional reactions in depression

Thesis

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Introduction

The central issue of contemporary psychiatry is to integrate and synthesize traditionally distinct approaches. In this work, we attempted to achieve this aim using the methods of psychiatry genetics, cognitive psychology, and neophenomenology. These approaches were implemented in the framework of emotion regulation to gain insight into the nature of mood disorders, genetic bases of affective appraisal, recognition of complex social emotions, and psychosis vulnerability associated with mood disorders.

Aims

The general aim of the studies was to extend and refine recent clinical nosological systems with new tools of behavioral characterization and psychopathology. Therefore, we amalgamated molecular genetics (serotonin transporter [5-HTT] polymorphism), cognitive psychology (Scherer's emotion appraisal questionnaire), and Jasper's phenomenology (Huber's basic symptoms of psychotic experience). We investigated two aspects of emotion regulation dysfunctions of mood disorders and vulnerability. First, we addressed the relationship between the polymorphism of the 5-HTT and emotion appraisal in healthy volunteers. In the second study, we investigated the recognition of complex social emotions in patients with major depressive disorder, taking into consideration the presence or absence of basic symptoms of psychotic experiences.

1. Aims of the first study

The aim of this study was to investigate the effect of the allelic variation of the 5-HTTLPR gene on emotion appraisal. Various lines of evidence suggest that an allelic variation of the upstream regulatory region of the serotonin transporter gene *(5-HTTLPR)* is related to anxiety- and depression-related traits, which may indicate dysfunctional emotion regulation. One of the most important aspects of emotion regulation is how we interpret and reflect to the experience of an emotion. In this respect, there is a considerable variance in the population. For example, one may appraise sadness more unpleasant, less controllable, and excessively demanding than others. Despite its importance, to date, no studies have been investigated the effect of the allelic variation of the 5-HTTLPR gene on emotion appraisal. In this study, we genotyped the 5-HTTLPR gene of 114 healthy individuals recruited from the community and compared emotion appraisal profiles in the case of negative (fear and sadness) and positive (joy) emotions as a function of serotonin transporter gene allelic variations.

2. Aims of the second study

In this study we focused on the ability of young depressed patients with or without psychosis risk to recognize complex social emotions and mental states by viewing the eye region of faces (Reading the Mind in the Eyes test). Our hypothesis was that young depressed patients with psychosis risk show more severe anomalous subjective experiences, such as self-disorder and perplexity, and are less able to recognize complex social emotions.

Häfner and Maurer (2006) concluded that early signs and symptoms of schizophrenia and major depression are often similar, and both produce marked functional and social impairment. Recent prospective studies in young adults who later developed psychosis ('ultra high-risk' mental state) indicate social decline, unspecific symptoms (anxiety, depression, personality changes, abuse of psychoactive substances), basic symptoms (disturbances in thinking, perception, self-representation, and reality testing) in early initial prodromal state.

In this study, we used three levels of assessment to determine psychosis risk-associated alterations. Besides the evaluation of symptoms of the late prodromal phase (attenuated and brief limited psychotic symptoms), we assessed subjective experiences of patients (basic symptoms) such as overstrain, increased reactivity to environmental stimuli, disturbances of thought, anomalous perceptual experiences, motor disturbances, and estrangement. Finally, we focused on the ability of patients to recognize complex social emotions and mental states by viewing the eye region of faces (Baron-Cohen et al, 2001) . The most important early signs of depression and schizophrenia are social isolation and disturbances in interpersonal contact (Häfner and Maurer, 2006) . The cognitive bases of these disturbances may include altered perception of social signals, such as facial expressions, and abnormal attribution of complex mental states of others (social emotions, thoughts, and intentions), also called mentalization or 'theory of mind' .

Methods

1. Emotion appraisal and the genetic polymorphism of the serotonin transporter

Subjects

In this study, we genotyped the *SLC64A* gene of 114 healthy individuals (s-carriers: 79, non-carriers: 35). Participants were recruited at the Semmelweis University (Budapest, Hungary) and at the University of Szeged (Szeged, Hungary). The two study groups demonstrated no significant difference in sex distribution, age, education and socioeconomic status. The Mini-International Neuropsychiatric Interview was used to exclude psychiatric disorders. Genotyping was performed according to the methods of Lesch et al (1996). Emotion appraisal was assessed using Scherer's appraisal questionnaire. The participant was asked to recall a situation in which he/she had recently experienced a strong emotion. The questionnaire for fear, sadness, and joy consisted of four parts: (1) situation description, (2) subjective feeling state, (3) physiological symptoms and expressive reactions, and (4) appraisal.

Statistical analysis

Ratings for each emotion appraisal were converted to z-scores. Z-scores were the deviation of a value for a specific emotion from the mean over all emotions investigated, as described by Scherer. The group mean of these z-scores was calculated for fear, sadness, and joy. The general linear models panel of the STATISTICA 7.0 software (StatSoft Inc., Tulsa) was used to conduct repeated measures analyses of variance (ANOVAs) and post-hoc Tukey HSD tests.

2. Recognition of complex social emotions in major depresive disorder – the role of the psychosis risk

Subjects

Patients (n = 68) were recruited at the Semmelweis University (Budapest, Hungary) and at the University of Szeged (Szeged, Hungary). All patients met the following criteria: (1) the DSM-IV diagnosis of major depressive disorder as revealed by the Mini-International Neuropsychiatric Interview and the Structured Clinical Interview for DSM-IV Axis I

Disorders, (2) no history of previous psychiatric illness or substance dependence and no treatment with psychotropic medication, and (3) no evidence for general medical conditions Socioeconomic status was evaluated using the Hollingshead Four Factor Index.

The young depressed patients referred to crisis intervention units were assessed with the Comprehensive Assessment of At Risk Mental States (CAARMS) instrument, which evaluates psychosis risk by focusing on subthreshold psychotic symptoms appearing during the late prodromal phase. The CAARMS instrument allows the formulation of diagnostic categories such as Attenuated Psychotic Symptoms (APS) and Brief Limited Intermittent Psychotic Symptoms (BLIPS). Twenty six patients fulfilled the criteria of APS (n = 19) and/or BLIPS (n = 7). The healthy control group included 50 volunteers who were acquaintances and relatives of the university staff. The controls were screened for psychopathology using the SCID-CV. The three study groups demonstrated no significant difference in sex distribution, age, education and socioeconomic status.

Statistical analysis

The STATISTICA 7.0. software (StatSoft, Inc., Tulsa, Okla., USA) was used for data analysis. The BSABS scores were first analyzed with Kruskall-Wallis tests, followed by Mann-Whitney U tests. Forward stepwise regression analysis was used to determine the BSABS and RME test scores that significantly predicted diagnostic group membership (patients with and without psychosis risk). The regression analysis was followed by a discriminant analysis. The scores from the RME test were entered into a repeated measures analysis of variance (ANOVA). Fisher's LSD tests were used for post-hoc comparisons. Demographic data were compared with two-tailed t-tests. Cohen's effect size values *(d)* were calculated between depressed patients with and without psychosis risk. Spearman's correlation coefficients were calculated between BSABS and RME test scores. The level of significance was alpha < 0.05. In the case of multiple comparisons, Bonferroni-corrections were used.

Results

1. Emotion appraisal and the genetic polymorphism of the serotonin transporter

First, we investigated the effect of gender. This ANOVA revealed no significant main effect of gender ($F<1$, $p>0.1$), and therefore data from male and female participants were collapsed in the further analysis. The genotype (s-carriers vs. non-carriers) by emotion by appraisal type three-way ANOVA revealed significant main effects of emotion ($F(2,224)=365.21$, $p<0.0001$) and appraisal ($F(7,784)=126.61$, $p<0.0001$). There was a two-way interaction between emotion and appraisal ($F(14,1586)=446.92$, $p<0.0001$). Most critically, there also was a two-way interactions between genotype and appraisal ($F(7,784)=7.32$, $p<0.0001$) and a three-way interaction between genotype, emotion, and appraisal ($F(14,1568)=2.69$, $p<0.001$).

In the case of fear, there was a significant two-way interaction between genotype and appraisal ($F(7,784)=11.41$, $p<0.0001$). The post-hoc tests revealed that s-carriers achieved higher scores than non-carriers for unpleasantness ($p<0.0001$) and goal-hindrance ($p<0.01$). In contrast, s-carriers achieved lower scores than non-carriers for coping ($p<0.0001$).

In the case of sadness, a similar two-way interaction was found between genotype and appraisal ($F(7,784)=6.68$, $p<0.0001$). The post-hoc tests revealed that s-carriers achieved higher scores than non-carriers for unpleasantness ($p<0.05$) and goal-hindrance ($p<0.01$). S-carriers achieved lower scores than non-carriers for coping ($p<0.05$).

Finally, in the case of joy, there was no interaction between genotype and appraisal ($F<1$, $p>0.1$).

2. Recognition of complex social emotions in major depresive disorder – the role of the psychosis risk

Recognition of Complex Emotions

The ANOVA revealed significant main effects of group ($F(2,115) = 10.30$, $p < 0.001$), expression type ($F(2,230) = 19.43$, $p < 0.001$), and a significant two-way interaction between these measures ($F(4,230) = 3.44$, $p = 0.01$). Depressed patients without psychosis risk were able to recognize less negative social emotions ($p = 0.02$), whereas there were no significant

differences for positive social and cognitive expressions ($p > 0.1$) as compared with the controls. Patients with psychosis risk were also impaired on the recognition of negative social emotions ($p = 0.004$), and they displayed additional deficits in the case of cognitive expressions ($p = 0.009$). There were no significant differences between the patients with and without psychosis risk (p 1 0.1).

Subjective Experiences

Kruskall-Wallis tests indicated a significant main effect of group for each item. When healthy controls were compared with depressed patients without psychosis risk, Mann-Whitney tests revealed significant differences for the diminished affectivity ($Z = –6.8$, d.f. = 1, $p < 0.0001$) and the cognitive disorder components ($Z = –3.8$, d.f. = 1, $p = 0.0001$) of the BSABS. In contrast, patients with psychosis risk displayed higher BSABS scores for all components as compared with the controls ($Z < –5$, d.f. = 1, $p < 0.0001$). Patients with psychosis risk displayed significantly higher scores for perplexity ($Z = –5.9$, d.f. = 1, $p < 0.0001$), cognitive disorder ($Z = –3.6$, d.f. = 1, $p = 0.0003$), self-disorder ($Z = –5.8$, d.f. = 1, $p < 0.0001$), perceptual disorder ($Z = –4.0$, d.f. = 1, $p < 0.0001$), and cenesthesias ($Z = –3.4$, d.f. = 1, $p = 0.0007$) as compared with patients without psychosis risk.

The forward stepwise regression analysis revealed that the first predictor of group membership (depressed with and without psychosis risk) was perplexity ($F(1,116) = 87.88$, $p < 0.0001$, $R 2 = 0.57$, beta = 0.76), the second was self disorder ($F(2,65) = 76.54$, $p < 0.0001$, $R 2 = 0.70$, beta [perplexity] = 0.48, beta [self disorder] = 0.46), and the third was diminished affectivity ($F(3,64) = 57.76$, $p < 0.0001$, $R 2 = 0.73$, beta [perplexity] = 0.52, beta [self disorder] = 0.46, beta [diminished affectivity] = –0.17). The other BSABS items and the RME test scores were not significant predictors. The discriminant analysis revealed that perplexity ($F(1,57) = 24.41$, p ! 0.0001, Wilk's lambda = 0.34), self disorder ($F(1,57) = 17.75$, $p < 0.0001$, Wilk's lambda = 0.31), and diminished affectivity ($F(1,57) = 5.15$, $p = 0.03$, Wilk's lambda = 0.26) were the significant discriminators. The other BSABS items and RME scores were not significant discriminators. In the non-risk group, 95.2% of cases were correctly classified, whereas this value was 92.3% in the risk group.

Correlation between Subjective Experiences and Emotion Recognition

In the healthy control group and in patients without psychosis risk, there was no significant correlation between BSABS and RME scores ($R < 0.2$, $p > 0.1$). In the high-risk group, only self-disorder showed a significant correlation with RME scores.

Conclusions

1. The s-variant of the serotonin transporter gene is associated with the alterations of emotional appraisal. It was remarkable that the effect of serotonin transporter polymorphism was confined to negative emotions (fear and sadness) and to specific appraisal types (unpleasantness, goal-hindrance, and coping).
2. Our data further clarifies these findings, demonstrating that participants with the s-variant experience negative emotions more unpleasant, more influential and disruptive on personal goals, and feel less ability to cope with these emotions.
3. The 38 percent of young depresed patients met the criteria of Attenuated Psychotic Symptomps (APS) or Brief Limited Intermittent Psychotic Symptomps (BLPS).
4. The results revealed that subjective experiences, with a special reference to perplexity and self-disorder, significantly predicted whether young depressed patients were at ultra high-risk for psychosis or not.
5. Compared to healthy controls, depressed patients showed impaired recgnition of negative social expresions. The high risk patients also showed impaired recognition of cognitive expressions, which was not observed in depressed patients without psychosis risk.
6. In the high-risk group, self-disorder, such as depersonalization and experience of discontinuity in own action, was associated with less effective recognition of the mental states from eye expressions.

In our first study, the results are consistent with previous findings suggesting that the s-variant of the serotonin transporter gene is associated with anxiety- and depression-related traits. Our data further clarifies these findings, demonstrating that participants with the s-variant experience negative emotions more unpleasant, more influential and disruptive on personal goals, and feel less ability to cope with these emotions. It was remarkable that the effect of serotonin transporter polymorphism was confined to negative emotions (fear and sadness) and to specific appraisal types (unpleasantness, goal-hindrance, and coping). This is consistent with the results of Wilhelm et al. (2007) who found that the s-variant of the serotonin transporter gene is associated with the use of fewer problem-solving strategies and less efficient coping with stressful situations.

The results of our second study revealed that subjective experiences, with a special reference to perplexity and self-disorder, significantly predicted whether young depressed patients were at ultra high-risk for psychosis or not. These high risk patients also showed impaired recognition of cognitive expressions, which was not observed in patients without psychosis risk. This is especially interesting, because it has been suggested that depressed patients show social perception and 'theory of mind' disabilities. Our data indicate that theory of mind impairments are confined to negative social expressions in depression.

Publications

Publications related to the thesis

1. **Szily E**, Kéri S. Anomalous subjective experience and psychosis risk in young depressed patients. Psychopathology. 2009;42(4):229-35.

2. **Szily E**, Bowen J, Unoka Z, Simon L, Kéri S. Emotion appraisal is modulated by the genetic polymorphism of the serotonin transporter. J Neural Transm. 2008 Jun;115(6):819-22.

3. **Szily E**, Kéri S. Emotion-related brain regions**.** Ideggyogy Sz. 2008 Mar 30;61(3-4):77-86.

4. **Szily E**, Unoka Zs, Simon L. A harag kognitív értékelésprofiljának vizsgálata depressziós betegek és egészséges kontroll személyek körében. Psychiatria Hungarica 2002. XVII. 5. 489-498.

5. Csukly G, Czobor P, **Szily E**, Takács B, Simon L. Facial expression recognition in depressed subjects: the impact of intensity level and arousal dimension. J Nerv Ment Dis. 2009 Feb;197(2):98-103.

6. Unoka Zs, Simon L, Berán E, **Szily E**. Érzelem előzmény értékelésprofilok szerepe az érzelmek kialakulásában és differenciálódásában: az inger értékelés ellenőrzések modellvizsgálata magyar mintán. Psychiatria Hungarica 2002. XVII. 5. 464-488.

Other publications

1. Murai Z, Baran B, Tolna J, **Szily E**, Gazdag G. Neuropsychiatric symptoms caused by mefloquine (report of several cases). Orv Hetil. 2005 Jan 16;146(3):133-6.