Effects of acute tryptophan depletion on affective processing in first-degree relatives of depressive patients and controls after exposure to uncontrollable stress

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Abstract

Rationale Individuals with a family history of depression may be more likely to develop depression due to an innate vulnerability of their serotonergic system. However, even though serotonergic vulnerability may constitute a risk factor in the development of depression, it does not seem to be sufficient to cause a depressive episode. Based on previous data, it is suggested that stress may be a mediating factor.

Objectives This study examined the role of serotonin (5-HT) in stress coping in individuals with or without a family history of depression.

Materials and methods Nineteen healthy first-degree relatives of depressive patients (FH+) and 19 healthy controls without a family history of depression (FH−) were tested in a double-blind placebo-controlled design for affective processing under acute stress exposure, following acute tryptophan depletion (ATD) or placebo.

Results Significant negative effects were found of stress on affective processing in FH− and FH+. In addition, FH− responded slower to positive words after stress only following ATD, whereas FH+ responded marginally slower under stress already after placebo and before stress following ATD.

Conclusion Acute stress exposure reduces positive affective bias; supporting the role of stress as an important predecessor in the development of depression. Furthermore, FH+ may be more susceptible than FH− to the negative effects of stress as well as to the negative effects of ATD. The results support the assumption that the 5-HT system is involved in stress resilience and may be more vulnerable in first-degree relatives of depression.

Keywords Serotonin · Major depression · Tryptophan depletion · Family history · Stress · Vulnerability

Introduction

First-degree relatives of depressive patients have a two- to threefold increased risk of developing depression (Kelsoe 2005; Sullivan et al. 2000). Although environmental factors play a role, adoption and twin studies indicate that the heritability ranges between 31% and 41% (Sullivan et al. 2000). Although the neurobiological equivalent of this genetic predisposition remains unclear, the brain serotonergic system seems to be involved (Maes and Meltzer 1995; Owens and Nemeroff 1994). Evidence comes from studies reporting lower plasma serotonin (5-HT) precursor availability of tryptophan for the brain, reduced cerebrospinal fluid (CSF) concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and decreased platelet 5-HT uptake in depression, suggesting diminished brain 5-HT function (Maes and Meltzer 1995; Neumeister et al. 2004b).

Acute tryptophan depletion (ATD) is commonly used to study serotonergic vulnerability (for a review, see Fusar-Poli et al. 2006; Young et al. 1985). The intervention reduces brain 5-HT through intake of a tryptophan-free amino acid mixture which reduces tryptophan (TRP) relative to the sum of the other large neutral amino acids (LNAAs) with which TRP competes for brain uptake (i.e. Fernstrom and Wurtman 1971; Gessa et al. 1974; Maes and Meltzer 1995; Moja et al.)
et al. 1987; Heim and Nemeroff 2001; Van Praag 2004) and life events often precede the onset of depression (Brown et al. 2004). Stressful life events are thought to be prone to the negative affective effects of stress exposure following ATD (Firk and Markus 2007).

Depression is associated with reduced attention, memory and executive functioning (Elliott et al. 1996; Paelecke-Habermann et al. 2005; Porter et al. 2003; Tavares et al. 2003); among which attention bias towards negative information has frequently been demonstrated (e.g., Lim and Kim 2005; Rinck and Becker 2005). Depressed patients respond slower to happy words compared to sad words during affective go/no-go tasks (Erickson et al. 2005; Murphy et al. 1999) and this was also observed in healthy individuals following ATD (Murphy et al. 2002).

The present study investigated whether first-degree relatives of depressive patients (FH+), as compared with subjects without a family history of depression (FH−), are more prone to the negative effects of stress exposure and TRP depletion on affective processing. Based on previous data (Murphy et al. 2002), it is hypothesized that stress, particularly after ATD, would slow down responses to positive words and that this is more pronounced in FH+.

Materials and methods

Subjects

Maastricht University students (n=200) completed a questionnaire package concerning personal details. Students reporting having at least one first-degree relative diagnosed with major depression were invited for a personal interview, as well as students reporting no first and second-degree relative with a depressive disorder. To assess FH, all participants were interviewed by a trained psychologist with an abbreviated version of the Family History Research Diagnostic Criteria (FHRDC) (Endicott et al. 1975). In addition, participants meeting the FH+ inclusion criteria were asked whether relatives could be contacted for confirmation.

Nineteen healthy first-degree relatives of depressive patients (FH+) and 19 healthy controls without a family history of depression (FH−) were selected for the experiment. A structured psychiatric interview (MINI) (Sheehan et al. 1991) was carried out to exclude psychiatric disorders. Furthermore, the Symptom Checklist SCL-90 (Arrindell and Ettema 1986) and the Beck Depression Inventory (BDI) (Beck et al. 1961) were filled in to verify the absence of depressive and general psychopathologic symptomatology. The FH− group and the FH+ group did not differ with respect to sex, age, BMI and BDI, and SCL-90 scores (all that even healthy subjects are susceptible to the mood-lowering effects of stress exposure following ATD.

Based on these previous findings, FH+ individuals are thought to be prone to the negative affective effects of stress due to serotonergic vulnerability. In addition, this may even be more profound after ATD (Firk and Markus 2007).

Acute TRP depletion is found to reverse antidepressant-induced remission (Booij et al. 2005; Delgado et al. 1990, 1999) and induces depressive symptoms in remitted depressive patients (Booij and Van der Does 2007; Hayward et al. 2005; Moreno et al. 2000, 2006; Neumeister et al. 2004a), whereas in healthy subjects, no or only modest effects are found (e.g., Benkelfat et al. 1994; Bhatti et al. 1998; Evers et al. 2005; Fusar-Poli et al. 2007; Klaassen et al. 1999; Ruhe et al. 2007). However, depressogenic effects of ATD seem to be mediated by family history for depression. Healthy subjects with a positive family history (FH+) of depression show greater depressed mood after ATD than healthy controls without a family history (FH−) (Benkelfat et al. 1994; Klaassen et al. 1999; Neumeister et al. 2002; Sobczak et al. 2002a; van der Veen et al. 2007). Furthermore, mood lowering effects of ATD may depend on the 5-HT transporter genotype, a gene-linked polymorphic region (5-HTTLPR) with two functional variants (Neumeister et al. 2002, 2006; Roiser et al. 2007; Walderhaug et al. 2007) that has been shown to modulate the vulnerability to depression (Caspi et al. 2003). These findings support the assumption of a 5-HT vulnerability factor for depression in FH+ increasing susceptibility to 5-HT alterations.

Even though serotonergic vulnerability may constitute a likely risk factor in the development of depression, it does not seem to be the sole contributor. Recent studies revealed that stress may be an important mediating factor. Stressful life events often precede the onset of depression (Brown et al. 1987; Heim and Nemeroff 2001; Van Praag 2004) and individuals with a genetic 5-HT vulnerability respond more readily to stressful life events with depressive feelings than individuals without a genetic vulnerability (Caspi et al. 2003). Furthermore, there is considerable evidence for complex interactions between the serotonergic system and neuroendocrine stress mechanisms (Van Praag 2004) and 5-HT is involved in the initiation and termination of the stress response (Dinan 1996; Fuller 1996; Lefebvre et al. 1992). Acute stress increases brain 5-HT turnover (e.g., Davis et al. 1995; De Kloet et al. 1982; De Kloet et al. 1983) as a biological mechanism for stress adaptation (Nuller and Ostroumova 1980; Van Praag et al. 2004), whereas dysfunctional brain 5-HT is found to reduce HPA function and stress adaptation (Maes et al. 1991; Seckl and Fink 1991). In addition, brain 5-HT augmentation is found to reduce the negative effects of stress on cortisol stress-responses and depressive symptoms in healthy but stress-susceptible subjects compared to controls (Markus et al. 2000a, 2002). In accordance, Richell et al. (2005) reported...
Demographic characteristics are presented in Table 1.

Participants were excluded if they reported chronic and current illness; history of psychiatric or medical illness; medication use; metabolic, hormonal, or intestinal diseases; irregular diets; or deviant eating habits and excessive alcohol or drug use. Participants’ health was checked with standardized medical questionnaires that were evaluated by a trained doctoral-level psychologist under the supervision of a medical doctor.

Participants included in the study revealed normal body-mass indexes (BMI, between 19 and 26 kg/m²) were non-smokers and were requested not to use alcohol or any kind of drugs before and during the study. Inclusion criteria for FH+ were the presence of at least one first-degree relative with major depression according to the DSM-IV criteria, whereas inclusion criteria for FH− include absence of a first- or second-degree relative with major depression.

The study was approved by the Medical Ethics Committee of the Academic Hospital Maastricht and complied with the requirements of the European Council of Good Clinical Practice (GCP) adopted by the 52nd World Medical Association General Assembly, Edinburgh, Scotland (October, 2000). All subjects gave their informed consent and were paid 125 Euros for participation.

Design

A placebo-controlled, double-blind, crossover design was used. During two experimental sessions, subjects were monitored for affective processing before and after acute stress exposure either following intake of a TRP-free (ATD) or a TRP-containing placebo (PLC) amino acid mixture. The order of presentation of the ATD and PLC condition was counterbalanced within groups and both experimental sessions were separated by at least 1 week. Female subjects were tested in the follicular phase of their menstrual cycle or when actually taking oral contraceptives.

Table 1 Demographic characteristics of the FH+ group and FH− group

|        | FH+   | FH−   |
|--------|-------|-------|
| Women  | 15    | 14    |
| Men    | 4     | 5     |
| Age    | 20.5 (2.1) | 22.1 (3.6) |
| BMI    | 21.7 (2.2) | 23.1 (2.5) |
| SCL-90 | 19.9 (17.9) | 26.4 (23.6) |
| BDI    | 3.6 (3.6) | 5.4 (4.2) |

Values are mean (SD).

Procedure

Eligible participants attended a briefing at Maastricht University to receive information about the study and to be scheduled for the experiment.

On each experimental morning, two subjects arrived at the laboratory at 08:30 am and 10:00 am, respectively. Subjects fasted overnight; only water or tea without sugar was permitted. After arrival, a first blood sample was taken followed by a first version of the affective go/no-go task to make subjects familiar with the test condition. Then, a first measurement of vegetative side effects was conducted followed by administration of the amino acid mixture (t₀). Four and a half hours later (t₄.₅), a second blood sample was taken followed by a second measure of vegetative side effects. Then (t₅) participants conducted a second version of the affective go/no-go task followed by the stress task. After completion of the stress task, a third version of the affective go/no-go task was administered.

Between intake of the amino acid mixture and exposure to laboratory tasks, the subjects were able to study or to read magazines in a separated private room. They had free access to water and decaffeinated tea. Two hours after administration of the amino acid mixture, they received a standardized protein-poor lunch as previously used in ATD studies (Riedel et al. 1999; Sobczak et al. 2002a, b). At the end of each test day, subjects received a high protein snack and bananas, which are natural sources of L-tryptophan to facilitate a quick recovery from possible negative effects of ATD.

Acute tryptophan depletion

A reduction in brain 5-HT was accomplished by ATD through the use of a tryptophan-free collagen-protein (CP) amino acid drink (Blokland et al. 2004; Evers et al. 2005). To obtain a drinkable mixture, 100 g of the protein powder was mixed with 200 ml of tap water and 20 ml syrup. The placebo mixture was identical in composition but 1.2 g L-TRP (Sigma, Zwijndrecht; The Netherlands) was added. See Table 2 for the amino acid composition of the different conditions (Evers et al. 2005).

This ATD method differs from the classic methodology by including a gelatin-based hydrolyzed CP that contains the entire range of amino acids (except for L-TRP) in the form of peptides. After administration, these peptides are decomposed into amino acids and the mechanism of depletion is identical to the classic ATD method (Blokland et al. 2004; Evers et al. 2005).

Stress exposure

The Markus–Peters computerized mental arithmetic task (MPA) was used as an uncontrollable stress situation.
Subjects were given eight successive 1-min trials during which they had to solve a specific number of multiple choice mental arithmetic problems (the criterion) under time constraints, while exposed to continuous 75, 80, or 85 dB industrial noise presented through headphones. They were led to believe that the intensity of the noise depended on their performance; if they failed the criterion, noise intensity was chosen by the computer during the next trial; if they met the criterion, they could choose the intensity of the noise. In fact, the criterion was always set at one sum above what subjects could manage as calculated from the average time per sum needed on previous trials. This task has been demonstrated to induce psychological and physiological stress (Markus et al. 1998, 2000a, b; Peters et al. 1998).

Affective go/no-go paradigm

A modified version of the affective go/no-go task described by Murphy et al. (1999) was used to detect affective attentional bias. In this task, happy and sad words were presented on the screen one-by-one for 300 ms, followed by an interstimulus interval of 900 ms during which participants must make or withhold a response depending on word valence. The task comprised two practice and 12 experimental blocks; each containing nine happy words and nine sad words. Subjects were instructed to respond either to happy or sad words before each block and to respond as quickly as possible.

Every two blocks, the targets and the distractors changed; words that were previously targets became distractors and vice versa (SSHHSSHHSSHH or HHSSHHSSHHSSHH). Due to this arrangement, shift blocks and non-shift blocks could be studied. The 27 happy words and 27 sad words were derived from previous studies (e.g., Lim and Kim 2005; Rinck and Becker 2005) and were matched on frequency, word length, and valence. Every word was presented twice as target and twice as distractor; once in a shift block and once in a non-shift block.

Vegetative side effects

In order to measure possible side effects of the amino acid mixtures, a list (five-point scales) of 10 vegetative side effects was completed before and 4.5 h after intake. The list contained the following items: feeling cold, feeling hot, dizziness, transpiration, bulled vision, nausea, palpitations, dry mouth, and abdominal complaints.

Biochemical analyses

Blood samples were collected in 5 ml vacutainer tubes containing sodium heparine for amino acids and were centrifuged at 5,000 rpm for 10 min at 4°C. Subsequently, the supernatants were directly stored at −80°C until analysis. Before storage, the supernatant for amino acid determination (100 μl) were mixed with 4 mg sulfasalicylic acid. Analyses were conducted with HPLC, making use of a 2–3 μm Bischof Spherisorb ODS II column. The plasma tryptophan ratio was calculated by dividing the tryptophan concentration by the sum of the other large neutral amino acids, i.e., valine, isoleucine, leucine, tyrosine, and phenylalanine.

Table 2 Composition (grams) of the gelatin-based protein (all values are g per 100 g of each mixture)

|                  | ATD | PLC |
|------------------|-----|-----|
| Phenylalanine    | 1.9 | 1.9 |
| Tyrosine         | 0.4 | 0.4 |
| Valine           | 2.1 | 2.1 |
| Leucine          | 3   | 3   |
| Isoleucine       | 1.4 | 1.4 |
| Tryptophan       | 0.1 | 1.3 |
| Serine           | 3.1 | 3.1 |
| Glycine          | 22.5| 22.5|
| Histidine        | 0.5 | 0.5 |
| Arginine         | 8.8 | 8.8 |
| Threonine        | 1.1 | 1.1 |
| Alanine          | 9.3 | 9.3 |
| Proline          | 13.3| 13.3|
| Methionine       | 0.6 | 0.6 |
| Cystein          | 0.2 | 0.2 |
| Lysine           | 3.6 | 3.6 |
| Hydroxyproline   | 12.1| 12.1|
| Hydroxylysine    | 1.4 | 1.4 |
| Aspartic acid + asparagines | 9.3 | 9.3 |
| Glutamic acid + glutamine | 5.2 | 5.2 |

The main research questions were analyzed by repeated measures analyses of variance (ANOVAs) by using the General Linear Model (GLM: SPSS 12.0 for Windows) with one between-subjects factor family history (FH+ versus FH−) and the within-subjects factors treatment (ATD versus PLC), stress (pre-stress versus post-stress), or time (t0 versus t4.5) on the several dependent measures. Furthermore, in the analyses of the affective go/no go performance target valence (sad versus happy) and shift (shift versus non-shift condition) were added as within-subjects factors. Although we counterbalanced for order and gender, these factors were preliminary taken as covariates. However, since none of these factors contributed to (or changed) any of our findings, order of treatment and gender were left out of the final analyses. All statistics are evaluated at a significance level of 5% (two-tailed).
Results

Plasma amino acids (TRP:LNAA ratio)

Repeated measures analysis of variance with FH (FH− versus FH+) as between-subjects factor and treatment (ATD versus PLC) and time (t₀ versus t₄.₅) as within-subjects factors were carried out for total plasma TRP concentrations and for the TRP:LNAA ratio. For TRP concentrations, a significant treatment × time interaction was found \[ F(1,36)=156.57, p<0.001 \] reflecting a decrease from t₀ to t₄.₅ by 62% after ATD and an increase from t₀ to t₄.₅ by 13% after PLC administration (see Fig. 1). Analysis of the plasma TRP:LNAA ratio revealed a significant treatment × time interaction \[ F(1,36)=158.77, p<0.001 \]. As indicated in Fig. 1, there was a 65% decline in plasma TRP:LNAA after ATD and an increase from t₀ to t₄.₅ by 8% after PLC. No other main or interaction effects were found including FH.

Vegetative side effects

Repeated measures analysis of variance with FH (FH− versus FH+) as between-subjects factor and treatment (ATD versus PLC) and time (t₀ versus t₄.₅) as within-subjects factors on the total score of vegetative side effects did not reveal any significant main or interaction effects.

Affective go/no-go performance

Mean values and standard deviations are presented in Table 3. Repeated measures ANOVAs were carried out with FH (FH− versus FH+) as between-subjects factor and treatment (ATD versus PLC), target valence (sad versus happy), shift (shift versus non-shift condition), and stress (pre-stress versus post-stress) as within-subjects factors on reaction time, errors, and omissions. To investigate changes from baseline to pre-stress (to explore acute effects of treatment), we repeated the statistical analyses and replaced the WS factor stress (pre-stress versus post-stress) with the WS factor time (baseline versus pre-stress). However, as we did not find any effect of treatment, these analyses are not described. Furthermore, no baseline differences were found between test days.

Reaction Time Analysis of reaction time (RT) data revealed a significant valence × stress interaction \[ F(1,36)=5.42, p=0.026 \] reflecting increased RTs for happy words post-stress compared to pre-stress \[ t(37)=2.09, p<0.043 \] but not for sad words \[ t(37)=1.39, p=0.17 \] (Fig. 2). However, this interaction was qualified by a significant 5-way FH × treatment × stress × valence × shift interaction \[ F(1,36)=3.99, p=0.05 \]. Further analysis for the shift and non-shift condition separately revealed a significant FH × treatment × stress × valence interaction for the non-shift condition only \[ F(1,36)=6.36, p=0.016 \]. In the non-shift condition, there was a significant FH × treatment × stress interaction for happy words only \[ F(1,36)=6.69, p=0.014 \]. As visualized in Fig. 3, the FH− group showed slower RTs post-stress compared to pre-stress only following ATD \[ t(18)=2.57, p=0.019 \] but not after PLC \[ t(18)<1 \], whereas the FH+ group showed slower RTs post-stress compared to pre-stress independent of treatment and slower RTs already following ATD (before stress onset). These latter changes in the FH+ group, however, did not approach significance by further post-hoc testing \( P \text{ between } 0.07 \text{ and } 0.11 \).

Errors Analysis of error data revealed a main effect of shift \[ F(1,36)=18.81, p<0.001 \]; indicating significant more errors during shift blocks compared to the non-shift blocks. Analysis also revealed a main effect of stress \[ F(1,36)=8.42, p=0.006 \], indicating a decrease in the number of errors post-stress compared to pre-stress. There were no effects of FH, treatment, or valence.

Omissions Analysis of omission data revealed a significant stress by valence interaction \[ F(1,36)=7.57, p=0.009 \], indicating that significant more omissions were made post-stress compared to post-stress for happy words \[ t(37)=2.31, p=0.027 \] but not for sad words \[ t(37)=1.16, p=0.25 \]. There were no effects of FH or treatment.
Discussion

The goal of the present study was to assess affective processing in individuals with a positive (FH+) or negative (FH−) family history of depression following ATD or placebo under acute stress exposure. Tryptophan depletion lowered the plasma TRP:LNAA ratio by 65%, which is comparable with previous studies using the collagen–protein (Evers et al. 2005) or classic ATD mixture (Van der Does 2001).

Although psychological or physiological stress responses were not measured in the current study, significant stress-induced emotional, cognitive, hormonal, and electrophysiological changes have been reported with the MPA task (e.g., Markus et al. 2002; Peters et al. 1998). Furthermore, reaction times significantly decreased after the stress task, further supporting that stress was successfully induced in the current study.

Analysis of affective processing revealed a stress by valence interaction reflecting reduced responsiveness to happy words after acute stress exposure. Previous findings already demonstrated slowed or diminished responses to happy words in depressed patients compared to healthy controls (Deveney and Deldin 2004; Erickson et al. 2005; Murphy et al. 1999), which may reflect lower mood and subsequent increased interference from sad distractors. Current findings indicate that a positive affective bias normally found in healthy individuals may also be diminished by acute stress exposure, which may be due to a stress-induced lowering of mood (van der Veen et al. 2007). This further supports the hypothesis of stress as an important predecessor in the development of depression (Brown et al. 1987; Heim and Nemeroff 2001; Van Praag 2004). Current data further suggest that the negative effects of stress on (reducing) positive affective bias may depend on family history of depression and may be influenced by ATD and task-shifting. The FH− group showed stress-induced slowed responses to happy words in non-shift blocks only following ATD, whereas the FH+ group roughly seemed to exhibit such reductions already after ATD (which was not found after PLC) as well as after stress following PLC.

The present findings suggest that acute stress induces a negative affective bias and that FH− subjects may be more stress-resilient than FH+ subjects and may become susceptible to stress especially after ATD. Interestingly, although task shifting requires more cognitive flexibility (e.g., Monsell 2003), the negative affective bias (slowed

| Table 3 Affective go/no go data |
|--------------------------------|
| FH+                         |
|                             |
| PLCCFH+FH−  ATD PLC FH+FH−  ATD |
| Happy shift RTs  | 512 (78) | 500 (79) | 487 (98) | 497 (72) | 497 (61) | 514 (55) | 497 (53) | 504 (60) |
| Errors                   | 2.8 (2.4) | 2.2 (1.8) | 3.2 (2.6) | 3.3 (3.8) | 3.1 (2.6) | 2.7 (2.2) | 3.2 (2.6) | 3.3 (3.8) |
| Omissions                | 2.4 (2.8) | 2.4 (2.6) | 3.3 (4.6) | 2.3 (3.0) | 1.3 (1.3) | 1.2 (2.0) | 1.1 (1.2) | 1.3 (2.5) |
| Happy non-shift RTs     | 486 (77) | 522 (69) | 511 (57) | 489 (95) | 496 (61) | 492 (51) | 489 (58) | 520 (59) |
| Errors                   | 2.5 (1.9) | 1.7 (1.2) | 1.8 (1.6) | 2.6 (2.1) | 2.2 (1.8) | 1.9 (2.5) | 2.1 (2.3) | 2.1 (2.0) |
| Omissions                | 3.1 (3.5) | 1.6 (1.7) | 1.7 (1.4) | 1.9 (2.7) | 1.7 (2.1) | 1.6 (1.4) | 1.6 (2.1) | 0.8 (1.1) |
| Sad shift RTs           | 514 (72) | 499 (63) | 511 (57) | 489 (95) | 508 (98) | 506 (46) | 522 (58) | 504 (59) |
| Errors                   | 3.2 (2.7) | 2.2 (2.7) | 3.5 (4.4) | 2.7 (2.9) | 2.4 (2.1) | 1.4 (1.6) | 2.4 (2.5) | 2.4 (1.9) |
| Omissions                | 1.9 (2.9) | 2.1 (2.4) | 1.9 (3.0) | 2.7 (4.0) | 1.4 (2.1) | 1.1 (1.2) | 0.5 (0.8) | 1.4 (2.2) |
| Sad non-shift RTs       | 519 (52) | 510 (65) | 517 (51) | 507 (42) | 512 (48) | 526 (58) | 514 (53) | 515 (57) |
| Errors                   | 2.5 (2.3) | 2.2 (1.6) | 2.0 (1.6) | 2.1 (2.5) | 1.5 (1.7) | 1.6 (1.7) | 2.3 (1.9) | 1.7 (1.9) |
| Omissions                | 1.7 (1.9) | 1.6 (2.1) | 1.7 (1.6) | 2.0 (2.6) | 0.8 (1.1) | 0.8 (1.2) | 1.0 (1.4) | 1.1 (1.2) |

Values represent mean (SD)

Fig. 2 Mean RTs (SE) for happy and sad targets before and after stress exposure collapsed over treatment and family history.
responses to happy words following stress and ATD) could only be seen for the non-shift blocks but not for the shift blocks. Although hypothetical, the increased negative affective bias following stress as well as ATD may be less profound the more attention or alertness is required (shift blocks) and may be increased in situations in which less attention is required (non-shift blocks). Previous ATD studies with healthy subjects revealed mixed results; either reporting negative affective bias following ATD for shift and non-shift blocks (Murphy et al. 2002) or no effects at all (Roiser et al. 2007; Rubinsztein et al. 2001). Current data may explain these inconsistent findings by the mediating influence of stress. Individuals with a family history of depression may already be prone to the negative effects of ATD and may also be more negatively affected by stress in the absence of ATD. These findings should of course be interpreted with caution since they appear to be rather modest (also depending on task-shifting and valence) and do not remain significant after repeated post-hoc testing in the separated small FH+ group. Yet, they nicely comply with—and elaborate on—previous findings and suggestions of an innate 5-HT vulnerability in FH+ (Benkelfat et al. 1994; Klaassen et al. 1999; Sobczak et al. 2002a, b). Hence, serotonin plays an important role in stress coping, and clear interactions appear between 5-HT and the neuroendocrine stress system (Porter et al. 2004). Acute stress increases 5-HT neurotransmission (Davis et al. 1995; De Kloet et al. 1982, 1983), which promotes stress adaptation by mediating negative feedback control of cortisol on the HPA axis (Nuller and Ostroumova 1980; Van Praag 2004). Increased 5-HT under stress will be diminished after ATD and subsequently may increase stress vulnerability. Richell et al. (2005) reported greater negative mood after stress in healthy subjects following ATD that was attributed to reduced function of the 5-HT-mediated resilience system and subsequent enhanced stress susceptibility. In the studies of Markus et al. (2000a, 2002), 5-HT augmentation was found to enhance resilience to stress only in chronically stressed (healthy) subjects probably by compensatory stress-induced 5-HT receptor sensitization. Whereas 5-HT challenge may particularly improve stress coping in 5-HT vulnerable subjects, ATD may lower stress coping also in non-vulnerable subjects due to a drastic depletion in brain TRP and subsequent 5-HT function.

One limitation of the present study is that we did not include mood changes. It has been suggested that ATD-induced changes in affective processing are mediated by reduced mood (van der Veen et al. 2007) which may also hold for stress-induced changes. However, it remains questionable whether ATD- or stress-induced changes in affective processing are necessarily mediated by subjective mood changes. Murphy et al. (2002) reported a negative affective bias in the affective go/no-go following ATD in healthy volunteers but did not find any changes in mood. Therefore, measuring affective processing may be a more sensitive method to measure stress- or ATD-related changes. Yet, in further studies it would, nevertheless, be interesting to include changes in explicit mood experiences as an additional affective measure. A second limitation may be that we did not contact family members to confirm diagnoses; however, participants were interviewed by a trained psychologist and to increase reliability, all participants were asked whether relatives could be contacted to confirm diagnoses.

In conclusion, acute stress exposure reduces positive affective bias supporting the role of stress as an important predecessor in the development of depression. However, these negative effects of stress may depend on family history of depression: FH+ may be more susceptible to the negative effects of stress and ATD on affective processing than FH−. Nevertheless, the tentative explanation that FH+ is more prone to stress and ATD due to an innate serotonergic vulnerability merits further research.

Disclosure/conflicts of interest All authors ensure the integrity of the work and none of them has any direct or indirect financial or personal interests, or conflicts of interest, to the subject matter of the manuscript.
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