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SHORT COMMUNICATION

# Emotional processing as a predictor of symptom change: An acute tryptophan depletion study in depressed patients

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**Abstract**

Acute tryptophan depletion (ATD) in currently depressed patients has no immediate effect on symptoms, but leads to transient symptom improvement or worsening the next day. In view of recent findings concerning the cognitive effects of serotonin manipulations, we used ATD in fourteen depressed patients to investigate whether cognitive effects following ATD predict symptom changes. We found that symptom improvement 24 h after ATD was associated with an improved recall of positive words and with less attentional bias and recall of negative words, 5 h after ATD. These results indicate that serotonergic alterations affect emotional processing which may subsequently lead to symptom changes.


## 1. Introduction

Despite a large improvement in our understanding of antidepressant pharmacodynamics, the precise mechanisms underlying the mood-altering effect remain unknown. Recent studies in healthy volunteers and patients suggest that a psychological mechanism may play a role. These studies have shown that acute or subchronic antidepressant drug administration increases the processing of positive information, without eliciting a mood change (Harmer, 2008; Harmer et al., 2003, 2004). Conversely, decreasing central serotonin (5-HT) function with acute tryptophan depletion (ATD) leads to emotional biases in healthy samples in the absence of symptom changes (Murphy et al., 2002). In remitted depressed patients, participants who do not show an immediate symptom response to ATD do show the emotional bias change (Booij et al., 2005b), These studies suggest that changes in emotional biases may mediate the mood-improving capacities of antidepressants. If this is true,

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these early effects on emotional processing may predict treatment response (Harmer, 2008). However, testing the causal relationship — altered 5-HT function affects emotional processing, which in turn leads to mood alterations — has not been done, and this is the goal of the present study.

The effects of ATD have often been studied in remitted depressed patients. Part of this population experiences transient symptoms of depression when tryptophan (Trp) levels are at their lowest (Booij et al., 2003). In currently depressed patients, however, ATD does not affect symptoms at the time of minimal Trp concentrations but leads to a delayed, bidirectional effect. One day after the ATD session, symptoms improve in some patients but worsen in others, even though Trp concentrations have returned to baseline (Delgado et al., 1994). We have replicated this delayed symptom effect in a small sample of depressed patients who were treated with venlafaxine (Booij et al., 2005a). In this previously published report, we did not include cognitive testing results since the focus of the research was on the effect of current type of treatment. Though the mechanisms of this bimodal mood response 24 h after ATD remain unknown, in view of the recent accumulating findings on the very fast cognitive effects of antidepressants and other 5-HT manipulations (Harmer, 2008; Harmer et al., 2003, 2004), we realized that the delayed and bidirectional symptom response to ATD in currently depressed patients makes this sample suitable to investigate the temporal relationship between low 5-HT, emotional processing and mood, which gets us closer to the question of causality. If changes in emotional processing cause symptom changes, the immediate effects of ATD on emotional processing should correlate with the delayed symptom effect of ATD. If emotional processing and symptom change are independent, no such association would be expected.

## 2. Experimental procedures

Fourteen patients (Table S1) were administered a high-dose and low-dose ATD mixture (100 *vs.* 25 g amino acids) in a double-blind randomized crossover design, preceded by a 24 h low protein diet (Booij et al., 2005a–c). The 100 g and 25 g ATD mixture have previously been shown to lower plasma Trp levels by approximately 90% and 50%, respectively, in this sample (Booij et al., 2005a) as well as in other samples (Booij et al., 2005b, 2006; Merens et al., 2008; Spillmann et al., 2001). The sample has been described in detail previously (Booij et al., 2005a). Inclusion criteria were: age between 18 and 65 years, meeting criteria for current major depressive episode (First et al., 2002) and a HRSD-17 score higher than 15 (cf. (Frank et al., 1991)). Exclusion criteria were: substance abuse within the last 3 months, lifetime psychosis, major physical illness, lactation and pregnancy. The procedures and measurements were similar to those of our study in remitted depressed patients (Booij et al., 2005b). Venous blood (10 ml) was taken in the morning, 6 h after ATD and the next day (t+24) and analyzed for total plasma Trp and the other large neutral amino acids (Fekkes et al., 1995). Mood was assessed 1 h before ATD (t−1), 6.5 h later (t+6.5), and the next morning (t+24) with the MADRS (Montgomery and Asberg, 1979). Emotional processing was assessed with the Emotional Stroop task (EST) (Booij et al., 2005b) approximately 5.5 h after administration of the ATD mixture. The stimuli were positive, neutral or depression-related words, presented consecutively on a computer screen. Participants were asked to name the colors as quickly as possible. Primary outcome measures were the interference values for positive and negative words (Booij et al., 2005b). The Self-Referent Adjective Encoding and Recall Task (SAERT) (Booij et al., 2005c; Dobson and Shaw, 1987) was used to assess processing of information relevant to depression and was completed approximately 4.45 h after ATD. This task consists of a random presentation of 10 positive and 10 negative adjectives and 6 neutral words, preceded by three neutral practice trials. Each word was presented twice. During the first presentation, patients had to decide as quickly as possible whether or not the word was self-descriptive. Immediately thereafter, the same word was presented again, accompanied by a 6-point scale ranging from 'not at all applicable' to 'very applicable.' Response speed was emphasized for the initial ratings, but not for the second presentation. Immediately after the presentations, participants were asked to recall the adjectives presented. We have previously shown that ATD affects the *recall* of personality traits in remitted patients who also had a mood response to ATD. The *rating* of the traits remained unaffected (Booij et al., 2005c). Therefore, we used the percentage of positive and negative traits recalled as the primary outcome variables in the present study. These were expressed as a percentage of the total words recalled, and as the ratio of negative words recalled relative to positive words. Information processing for neutral material was assessed between 5 and 6 h after ATD by the Stroop-Color-Word Test; Tower of London; Left/Right Simon Task; Visual Recognition Test for Abstract Figures; and the Letter Fluency Test (Booij et al., 2005b). The cognitive tasks were practiced one week before the first ATD session except for the SAERT because only two valid versions of this task were available.

Following testing for statistical assumptions and outliers/influential data points, data were analyzed by means of General Linear Models for Repeated Measures and Pearson correlations. The study was approved by an independent medical ethics committee (METIGG, Utrecht), and performed according to their guidelines and regulations. All patients were informed about the study by their clinician and in detail by the investigator (LB), and provided written informed consent.

## 3. Results

Three patients experienced a strong emotional reaction to the EST during the practice session and did not complete this task during the ATD sessions. As reported previously (Booij et al., 2005a), neither high-dose nor low-dose ATD changed mood 6.5 h after administration, nor was there any difference in mood change between the conditions ($p>0.20$). The response 24 h after high-dose ATD was highly variable (mean ± SD: 4.9 ± 10.9, range: −19, +18 points change). In the low-dose condition, the response was also variable though less so than in the high-dose condition (mean ± SD: 0.1 ± 5.3, range: −10, +8 points change). Symptom severity returned to baseline levels within 48 h, except for one patient who reported a mood improvement in the high-dose condition that lasted 72 h.

### 3.1. Effects of ATD on emotional processing

#### 3.1.1. High-dose condition

There were no differences between the high and low-dose ATD conditions on the cognitive tasks, including the emotional processing tasks. (Table S2). However, a mood improvement in the high-dose ATD condition (t−1 minus t+24 h) was associated with lower interference levels for negative words ($r=-0.62$ $p=0.04$) on the EST (Fig. 1). Lower interference is indicative of lower attentional bias for negative information. The correlation between symptoms and interference for positive information was not significant ($r=-0.41$, $p=0.21$). In the high-dose

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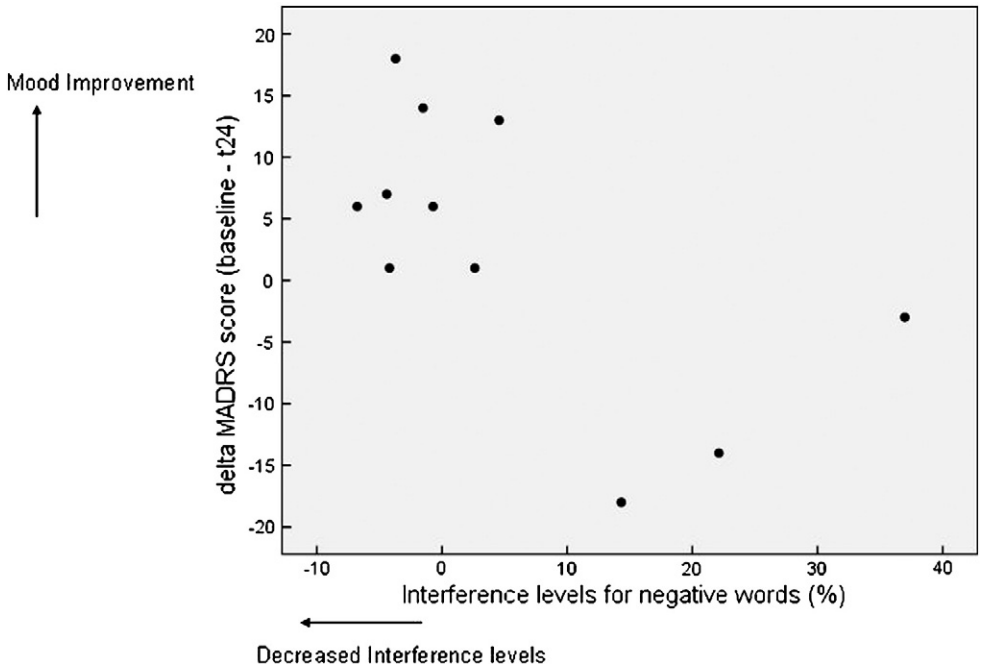


**Figure 1** Relationship between processing for negative information following ATD and symptom change (t−1–t24). Interference levels were defined as the percentage of extra time needed for the negative words relative to the neutral words ((mean reaction time (RT) for negative words−mean RT neutral words)/(mean RT neutral words)*(100)).

condition, symptom improvement at t+24 was also associated with a lower percentage of negative words recalled ($r=-0.79$, $p=0.001$), a higher percentage of positive words recalled ($r=0.70$, $p=0.006$), and a lower percentage of negative words recalled, relative to positive words ($r=-0.85$, $p<0.001$) on the SAERT (Fig. 2). There were no correlations between mood and percentage of neutral words recalled or with the other SAERT outcome measures, nor with any of the outcome measures on the non-emotional information processing tasks.

### 3.1.2. Low-dose condition

There were no significant correlations between symptom change and the EST outcome measures in the low-dose condition (interference levels for positive words: $r=0.03$,

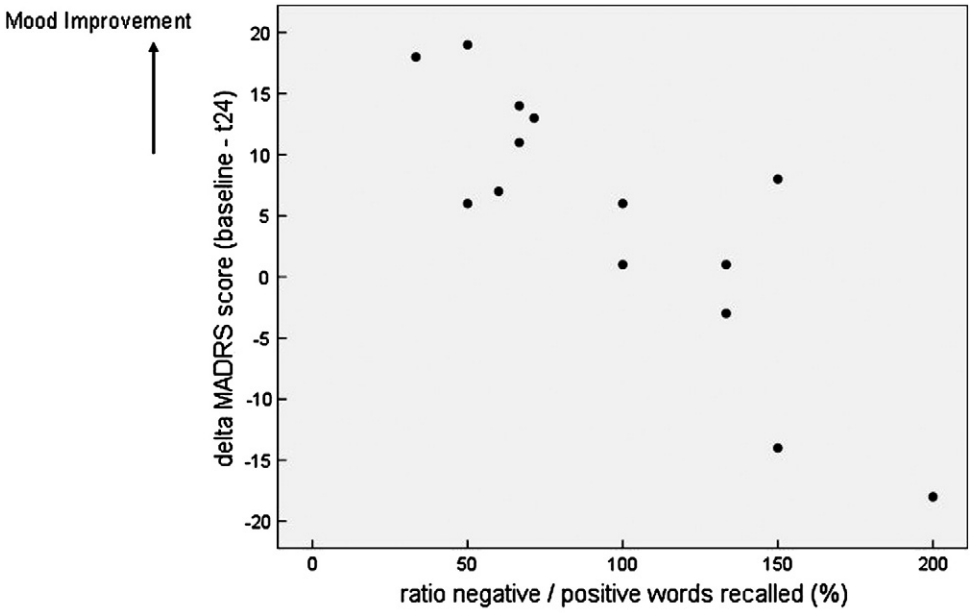


**Figure 2** Relationship between percentage of negative words recalled, relative to positive words (5 h after high-dose ATD), and symptom change (t−1–t24).

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$p=0.93$; interference levels for negative words: $r=-0.31$, $p=0.36$). On the SAERT, mood change in the low-dose condition (t−1 minus t+24 h) correlated with the percentage of negative words recalled ($r=-0.55$, $p=0.04$) in the low-dose condition. When controlling for this association in the low-dose condition, the correlation between mood change and percentage of negative words recalled in the high-dose condition remained significant ($r=-0.85$, $p<0.001$). There were no correlations between mood change and percentage of positive words ($r=0.37$, $p=0.19$) or negative/positive words ratio ($r=-0.40$, $p=0.15$) in the low-dose condition.

#### 3.1.3. Practice session

Mood changes in the high-dose condition were not predicted by interference levels for positive or negative words during the intake session ($r=-0.10$, $p=0.77$; $r=-0.02$, $p=0.94$, respectively), nor did MADRS scores at intake predict interference levels for positive or negative words at intake ($r=0.43$, $p=0.19$; $r=-0.13$, $p=0.70$, respectively).

## 4. Discussion

The present study shows that the bimodal symptom response to ATD in depressed patients is preceded by a bimodal emotional processing bias in the same direction. Patients whose symptoms improved 24 h after ATD had shown a more positive emotional processing bias 5 h after ATD. The reverse was true for patients whose symptoms got worse 24 h after ATD.

The fact that we observed a relation between an emotional processing measure and symptom change following a serotonergic manipulation, indirectly supports the theory that antidepressants exert immediate cognitive changes which may over time translate into symptomatic improvements (Harmer, 2008).

The pros and cons of the low-dose ATD condition (25 g ATD), as an alternative method for the Trp-containing placebo mixture have been discussed previously (Booij et al., 2005b). Overall, studies conducted in the past decade by us and by others suggest that the low-dose condition is an acceptable control for the high-dose condition (Booij et al., 2005b, 2006; Merens et al., 2008; Spillmann et al., 2001). Nevertheless, it would be of interest to investigate whether the results could be replicated using a Trp-containing placebo mixture.

The current study has some limitations. The small sample may have resulted in insufficient power to detect differences between the high and the low-dose condition on the tasks. Secondly, the lack of baseline measures does not allow testing causality. Although the relationship between emotional processing and subsequent symptom change was negligible in the low-dose condition and intake session, further studies including baseline measures are needed to test true causality. Finally, although the delayed mood improvement after ATD is consistent with another study in depressed patients (Delgado et al., 1994), the observed mood effect is still counter-intuitive. A detailed discussion of this point is beyond the scope of this paper, but has been addressed by others (Delgado et al., 1994; Price et al., 1997, 1998).

With these limitations in mind, the present study indicates that alterations in 5-HT neurotransmission may affect emotional processing which leads to subsequent changes in symptoms. Obviously, this psychological mechanism through which ATD, and possibly also antidepressants may exert their effects is in no way incompatible with the known biochemical and neurophysiological pathways. The implementation of emotional processing measures in clinical trials may help to understand the underlying mechanisms of clinical responses to 5-HT antidepressants, and may be a non-intrusive measure to detect responders and non-responders in an early phase of treatment.

Supplementary materials related to this article can be found online at doi:10.1016/j.euroneuro.2010.09.007.

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## Contributors

Both authors designed the study, interpreted the data and wrote the manuscript. Linda Booij collected and analyzed the data. Willem van der Does supervised the study.

## Conflict of interest

Both authors have no conflicts of interest.

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