Tryptophan depletion affects heart rate variability and impulsivity in remitted depressed patients with a history of suicidal ideation.

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Tryptophan Depletion Affects Heart Rate Variability and Impulsivity in Remitted Depressed Patients with a History of Suicidal Ideation

Linda Booij, Cees A. Swenne, Jos F. Brosschot, P.M. Judith Haffmans, Julian F. Thayer, and A.J. Willem Van der Does

Background: *Depression is a major risk factor for cardiovascular disease. An important risk factor for cardiovascular disease, low heart rate variability, often has been found in depressed patients and has been associated with impulsivity. The present study investigated whether experimental lowering of serotonin would decrease heart rate variability and increase impulsivity in remitted depressed patients, in particular in those patients with disturbed impulse control.*

Methods: *Nineteen patients in remission from depression received high-dose and low-dose acute tryptophan depletion in a randomized, counterbalanced, double-blind crossover design. Heart rate variability and impulsivity were assessed during each acute tryptophan depletion session and during a baseline session. Suicidal ideation during past depression was used as an index for individual differences in impulse control.*

Results: *High-dose acute tryptophan depletion led to a larger increase in depressive symptoms than did low-dose acute tryptophan depletion. High-dose acute tryptophan depletion decreased heart rate variability and increased impulsivity and anxiety, but only in patients with a history of suicidal ideation. Symptom effects of high-dose acute tryptophan depletion correlated with low heart rate variability at baseline.*

Conclusions: *Depressed patients who have problems with controlling impulsivity might be more at risk for developing cardiovascular disease, possibly related to increased vulnerability to impaired 5-hydroxytryptamine function.*

Key Words: Cardiovascular disease, cognition, depression, heart rate, serotonin, tryptophan depletion

The serotonin (5-hydroxytryptamine; 5-HT) system is involved in depression (Maes and Meltzer, 1995) and in impulsive behavior (Soubrié, 1986). Acute tryptophan depletion (ATD), which involves depleting the 5-HT precursor L-tryptophan (Trp), is a powerful technique to investigate lowered serotonin function in an experimental design (Booij et al 2003). The rationale is to lower 5-HT levels and then examine any symptoms provoked by the procedure, thereby allowing the investigator to establish causal relationships between serotonin levels and behavior (Young et al 1985).

It frequently has been demonstrated that ATD leads to a transient symptom exacerbation in a subsample of remitted depressed patients (Booij et al 2003; Delgado et al 1990). Acute tryptophan depletion also has been studied for its effect on impulsivity in a laboratory setting (LeMarquand et al 1999). Subjects were asked to respond to certain stimuli presented on a computer screen and to withhold responding to other stimuli. After ATD, more commission errors (false alarms) were observed in healthy subjects with a family history of alcoholism, but not in healthy males without such family history. The effects of ATD on impulsivity in remitted depressed patients have not been studied. However, fully remitted depressed patients with a history of impulsive behavior (suicidal behavior or ideation) had a larger depressive response to ATD than did patients who had no history of suicidal ideation (SI; Booij et al 2002). This finding is in line with research using other markers of 5-HT function in depressed suicidal patients (e.g., Asberg, 1997) and suggests that abnormalities of the 5-HT system may be limited to a subtype of depression in which anxiety and aggression dysregulation are prominent (Van Praag, 2001).

Depression is a major risk factor for cardiovascular disease (CVD). The prevalence of depression among cardiovascular patients is 5–20 times higher than that in the general population, and depression doubles the probability of a new myocardial infarct within 12 months (Joynt et al 2003) Low heart rate variability (HRV) is a biological risk factor for CVD and may explain the association between depression and CVD (Grippo and Johnson 2002). Low HRV repeatedly has been found in depressed patients (Agelink et al 2002; Rechlin et al 1994); however, the results are not consistent (e.g., Gehi et al 2005). Reduced HRV also has been observed in anxiety disorders (Friedman and Thayer, 1998; Thayer et al 1996) and in impulse-control disorders, including attention-deficit/hyperactivity disorder (Beauchaine et al 2001), substance abuse (Ingjaldsson et al 2003), and psychosis (Valkonen-Korhonen et al 2003), and in healthy highly hostile individuals (Demaree and Everhart, 2004; Sloan et al 2001). These studies suggest that HRV may not be related to a specific diagnosis but rather to symptoms or other characteristics common to various psychiatric conditions, in particular inhibitory neural processes and impulse control (Hansen et al 2003; Ingjaldsson et al 2003).

Several researchers have identified a set of neural structures associated with emotion regulation that includes the prefrontal cortex (Davidson, 2000; Thayer and Lane, 2000). Similarly, the prefrontal cortex has been implicated in inhibitory neural processes, including those necessary for working memory, delayed responding, and impulse control (Garavan et al 1999). It is important to note that HRV has been associated both structurally and functionally with activity of the prefrontal

From the Department of Psychology (LB, JFB, AJWVdD), Leiden University, Leiden; Department of Cardiology (CAS) and Department of Psychiatry (AJWVdD), Leiden University Medical Center, Leiden; Psychomedical Center Parnassia (PMJH), the Hague, the Netherlands; and Department of Psychology (JFT), Ohio State University, Columbus, Ohio.

Address reprint requests to A.J.W. Van der Does, Ph.D., Department of Psychology, Leiden University, Wassenaarseweg 52, 2333 AK, Leiden, the Netherlands; E-mail: vanderdoes@fsw.leidenuniv.nl.

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cortex. Structurally, both pharmacological blockade and neuroimaging studies have shown HRV to be associated with activity in the prefrontal cortex (Ahern et al 2001; Gianaros et al 2004; Lane et al 2001). Functionally, HRV has been associated with emotional regulation as well as with working memory and delayed responding, including measures of impulsivity (Allen et al 2000; Hansen et al 2003, 2004; Ruiz-Padial et al 2003). Overall, these studies suggest a link between HRV and emotion regulation, in particular impulsivity. Regarding depression, the inconsistent findings may be caused by the fact that reduced HRV may be limited to patients with disturbed impulse control.

The mechanism for the association between various negative mental and emotional conditions and reduced HRV may be found in lowered 5-HT function. Although it is widely accepted that lowered 5-HT levels negatively influence mood and behavior, it has become evident only recently that 5-HT depletion or 5-HT receptor blocking attenuate baroreflex gain (Kellett et al 2005a, 2005b). The arterial baroreflex is the main mediator of HRV because this reflex reacts to any blood pressure increase or decrease by a heart rate (HR) decrease or increase. Beat-to-beat blood pressure changes are present in any person, even in a stable hemodynamic situation, because of the modulating effect of respiration on cardiac filling and stroke volume. Thus, respiration causes blood pressure variability, which is transferred by the baroreflex into HRV (Frederiks et al 2000). Hence, serotonin depletion leads to diminished baroreflex function which in turn leads to diminished HRV.

The aim of this study was to investigate whether experimental lowering of 5-HT induces a decrease of HRV and an increase of impulsive behavior in remitted depressed patients. We previously reported that ATD leads to a significantly greater symptom exacerbation in remitted depressed patients with a history of SI, as compared with in patients without such history (Booij et al 2002). These results are in line with a genetic study showing an allelic association of the 5-HT2A receptor gene with SI among depressed patients (Du et al 2000). To further test our hypothesis that serotonergic dysfunction and reduced HRV are more pronounced in a subtype of depression that is characterized by impulsive and aggressive behavior, history of SI was used as an index for individual differences in impulse control. Although other conditions also would imply underlying impulsivity, for example, a history of substance abuse or a cluster B personality disorder, such markers would interfere with our aim to study ATD in patients who have remitted and in whom the primary diagnosis is major depressive disorder.

We assessed HRV on three occasions and, on each occasion, during rest (baseline) and during cognitive testing, in particular the Continuous Performance Test (CPT). Changes in impulsivity after ATD were measured by the CPT (Cornblatt et al 1989; Keshaven et al 2003; Nuechterlein, 1991). As in our previous studies, two different dosages of ATD were used (25.7 g vs. 102.5 g of amino acids), which was aimed at reducing plasma Trp levels by 40%–50% and by 80%–90%, respectively (Van der Does, 2001). Although the 25% strength mixture initially was developed as a placebo procedure by Krahn et al (1996), it has been shown that it reliably leads to moderate reductions of Trp levels in combination with a 1-day low-Trp diet and that this low-dose condition produces some cognitive effects (Booij et al 2005a) but generally no symptoms (Booij et al 2005b; Spillmann et al 2001).

On the basis of results of previous ATD studies and the reported association between depression and CVD, the following hypotheses were tested:

i. High-dose ATD will cause a larger increase in depressive symptoms than low-dose ATD;
ii. High-dose ATD will reduce HRV at rest and during the CPT; and
iii. High-dose ATD will increase impulsivity (indicated by decreased beta levels on the CPT).

The effects on symptoms, HRV, and impulsivity will be more pronounced in patients with a history of SI. Furthermore, we explored the effects of low-dose ATD on HRV and impulsivity and the relation between depressive response to ATD and baseline HRV.

Methods and Materials

Participants

Eligible patients were outpatients of a mood disorders clinic. Inclusion criteria were the following: age between 18 and 65 years; ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin–noradrenalin reuptake inhibitor (SSNRI) for at least 4 weeks; meeting DSM-IV criteria for a primary diagnosis of Major Depressive Disorders in remission; and Hamilton Depression Rating Scale (17 items, HRSD-17; Hamilton 1960) score of lower than 15 (Frank et al 1991). Exclusion criteria were the following: substance abuse within last 3 months, psychosis (lifetime), major physical illness, lactation, and pregnancy. Diagnoses and demographic and clinical background variables, including history of SI during past depression, were assessed with the Structured Clinical Interview for DSM-IV (First et al 1995), given by a psychologist, and were checked in medical records.

Twenty participants entered the study. One female patient dropped out before the afternoon assessments of the first session (high-dose ATD) because of nausea that started 2 hours after depletion. Nausea persisted until late afternoon but had disappeared in the evening. The clinical and demographic characteristics of the remaining 19 patients are presented separately in Table 1 for groups with and without SI during past depression (SI+ vs. SI−).

High-dose and Low-dose ATD

At each depletion session, patients received a 102.5-g (high-dose ATD) or a 25.7-g (low-dose ATD) amino acid mixture in a counterbalanced, randomized, double-blind, crossover design. The composition of the 102.5-g mixture was similar to that in previous ATD studies (e.g., Delgado et al 1990). The 25.7-g mixture consisted of the same amino acids (AAs) but in one quarter amount (Krahn et al 1996). Patients were kept on a 24-hour low-Trp diet (160 mg/d) before both sessions.

Instruments

Symptoms. Symptoms were assessed by using the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979), the HRSD-17 (Hamilton 1960), the Brief Anxiety Scale (BAS; Tyrer et al 1984), the Beck Depression Inventory (BDI-II; Beck et al 1996), and the Positive and Negative Affectivity Scale (PANAS; Watson et al 1988). The latter question-

Table 1. Characteristics of the Sample as a Function of Suicidal Ideation During Past Depression ($N = 19$)

Variable	SI+ ($n = 8$)	SI− ($n = 11$)	Statistics
Males/Females	3/5	5/6	$p = .55^a$
Mean Age, y (SD)	47.5 (10.7)	41.2 (10.6)	$F(1,17) = 1.64$; $p = .22$
Number of Smokers	2	5	$p = .34^a$
Type of Medication: SSRI/SSNRI	5/3	10/1	$p = .18^a$
Mean Number of Past Episodes (SD)	7.0 (8.8)	1.6 (0.7)	$F(1,17) = 4.14$; $p = .06$
Single/Recurrent Episodes	3/5	5/6	$p = .55^a$
Partial/Full Remission	7/1	9/2	$p = .62^a$
Mean Duration of Remission, mo (SD)	35.5 (37.7)	13.7 (25.3)	$F(1,17) = 2.28$; $p = .15$

SSNRI, serotonin noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Fisher's exact test, one tailed. The relatively large number of episodes in the SI+ group was a result of two patients who had more than 10 episodes. The relatively long duration of remission for the SI+ group was a result of two other patients who had been in partial remission for about 7 years.

naire consists of positive- (low score indicative of depression) and negative-affectivity subscales (high score indicative of both depression and anxiety).

Continuous Performance Test. Two hundred sixty-four letters were presented one by one for 150 ms in random order, at 600-ms intervals. Participants were instructed to push the spacebar each time the letter *X* appeared, but only when it had been preceded by the letter *A*. Reaction times (RTs) and errors were registered. The task took 8 minutes to complete. The primary outcome measure was β. Beta is a measure of impulsivity; individuals with high β have the tendency to underrespond and are assumed to be cautious; low β is associated with overresponding and risk-taking behavior (Conners et al 2003; Nuechterlein 1991). Secondary outcome measures were as follows: d' (a measure of accuracy, corrected by response tendency), correct responses to target stimuli (% of hits), responses to nontargets (% of false alarms), and median RTs (ms) to target stimuli. Beta and d' are based on signal detection theory and were calculated as described elsewhere (Nuechterlein, 1991).

Biochemical Analyses. Venous blood was obtained with ethylenediaminetetraacetic acid tubes to determine total plasma Trp and the ratio of Trp to large neutral amino acids (LNAAs). Immediately after sampling, the blood was processed by centrifuge for 20 minutes at 2650 g_{max}, and the plasma was stored at −65°C. Quantitative amino acid analysis was performed by high-performance liquid chromatography as described elsewhere (Fekkes et al 1995).

Cardiac Activity. Cardiac activity was measured with an ambulatory monitoring system (AMS) developed by the Department of Psychophysiology, VU University, Amsterdam, the Netherlands. Six disposable electrodes were placed on the body of the patient (between the collar bones, under the left breast, between the two lower ribs, over the xiphoid process of the sternum, and at the base of the neck and below the line connecting the tips of the shoulder blades) and were connected to the AMS device.

In addition to HR, time domain measures of HRV variables included the standard deviation of the interbeat intervals and the coefficient of variation CV_r (SD/interbeat intervals) as estimates of overall HRV and included the root mean square of successive differences (RMSSD), which is the square root of the mean of the sum of the squared differences between adjacent intervals, and the PNN50, which is the percentage of adjacent intervals that varied by more than 50 ms, as measures of vagally mediated HRV. Frequency domain measures included high-frequency power (HF; 0.14–0.40 Hz; a marker of vagal cardiac control) and low-frequency power (LF; 0.07–0.14 Hz; an index of both sympathetic and vagal cardiac control), calculated according to the procedure as described elsewhere (Bootsma et al 1994).

Procedure

The study was approved by an independent, nationally certified medical ethics committee (METIGG, Utrecht, The Netherlands). After participants received oral and written information about the study, written informed consent was obtained from all participants.

Before the ATD Sessions. Participants were invited to a screening session to verify inclusion and exclusion criteria. If all criteria were met, the CPT was administered. The time between the screening session and the first ATD session was approximately 1 week.

ATD Sessions. During day 1 of each session, patients consumed the low-Trp meal. Patients came to the laboratory at 8 or 9 AM of day 2, after an overnight fast. Mood ratings were obtained, followed by a blood sample (−1 h) and the ATD drink (0 h). For the next 4.5 hours, patients remained in a private research room. The AMS system was placed on the participants 4.5 hours after the ATD drink. After a break of about 10 minutes, cardiac activity was assessed during a 5-minute period, during which participants performed a neutral distraction task to focus their attention away from depressive thoughts or bodily sensations ("resting period"). During this task, participants were given an incomprehensible text (Swedish or Italian) and were asked to strike out one letter (*a* or *e*) each time that these letters appeared in the text (cf: Van der Does et al 1997). At each assessment, the experimenter emphasized that the reason for this task was to engage all participants in the same neutral activity and that speed or accuracy was not important. Recordings were restarted 5 hours after ingestion of the ATD drink. The CPT, completed at +5.5 h, was part of a larger cognitive test battery that is not described further here. After removal of the electrocardiogram electrodes and the AMS device, a blood sample was taken at +6 h. Symptoms were assessed at +6.5 h. Mood ratings were taken the next morning (+24 h). This procedure was repeated at least 1 week later; those who had received high-dose ATD in the first session received low-dose ATD in the second session and vice versa.

Postintervention Session. The day after the second session, participants also completed the CPT. Cardiac activity was recorded during a resting period and during the CPT. Assessments started about 10 minutes after the mood assessments and took place before blood sampling. The procedure was identical to that during the ATD sessions. This postintervention session lasted about 2.5 hours.

Statistical Analyses

Clinical and demographic variables were investigated by means of chi-square tests, and univariate analysis of variance, by using the general linear model (GLM).

The effects of the different doses of ATD on biochemical outcome measures, symptoms, cardiac activity, and CPT were analyzed by separate double repeated-measures multivariate analysis of variance. For the symptom scales and biochemical measures, ATD (low-dose vs. high-dose) and time (−1 h, +6.5 h, and +24 h) were the within-subjects factors. For the CPT, ATD (baseline vs. low-dose vs. high-dose ATD) was used as the within-subject factor. For the cardiovascular measures, ATD (baseline vs. low-dose vs. high-dose ATD) and period (rest vs. CPT) were the within-subjects factors. History of SI (serious suicidal thoughts or attempt vs. no serious suicidal thoughts) was used as a between-subjects factor in the analyses. Relationships between depressive response and impulsivity and between depressive response and HRV were investigated in separate GLM analysis, including response to ATD as the only between-subjects factor, defined as at least a six-point increase on the MADRS scale during the high-dose ATD session (Booij et al 2005b). Contrast tests were used to investigate differences between specific interventions and specific time-points. The Greenhouse-Geisser correction was used to control for violations of sphericity (Vasey and Thayer 1987).

The present study used multiple outcome measures for HRV, and therefore a more stringent level of α might have been needed to keep the probability of a type II error under control. This could have caused a power problem, although the sample size of the present study is comparable with those of some other ATD studies. Thus, to correct for multiple comparisons and to still have reasonable power, we set α at .15 (Stevens 1996), implicating that cardiovascular measures were tested at the .02 level of significance (.15/7; there were seven outcome measures for HRV). There was no need to correct for multiple comparisons for the analysis of symptoms and impulsivity, because both the direction and timing of these effects have been studied extensively in healthy samples and patients (see Booij et al 2003).

Baseline CPT performance was defined as the mean of a postintervention session and the screening session (Booij et al 2005a). This definition was used to control for any learning effects that might occur with repeated administration of the CPT. The suitability of taking the mean of the screening and the postintervention sessions as a baseline measure was checked by comparing CPT performance on the screening and post-ATD sessions and was further checked by a repeated-measures analysis, with session (screening vs. post-ATD session) as a within-subjects factor and order (high vs. low-dose ATD first) as a between-subjects factor. Physiological recordings throughout the afternoon of the ATD sessions were compared with the recordings conducted at the postintervention session.

Results

Data Screening

One patient in the SI+ group had an extremely high false-alarm rate on the CPT in the low-dose condition (22.7%). The mean false-alarm rate of the remaining patients was 0.6% (range: 0, 4.2%). This patient was considered an outlier (Cook's D = 1.17; z residual = |3.78|; Mahalanobis distance = 16.36). This patient pressed the button not only when target stimuli were presented (47/48 trials) but also when the letter X was preceded by the letter D (48/48 trials), with one false positive on the other nontarget stimuli. This patient was left out of the analyses involving β, d', and percentage of false alarms. A blood sample for one patient in the SI+ group was missed at +24 h in the high-dose condition, and blood samples for another patient were missing for all measurements during the low-dose condition because of logistic problems.

Before GLM analysis, RTs for the CPT and HF were log10 transformed, and PNN50 was square root transformed to achieve a normal distribution of the data (Stevens 1996). Scores on the BDI-II and PANAS were analyzed by means of nonparametric tests, because transformations were unsuccessful.

Effects of ATD on Amino Acids

The reduction in total Trp (the difference between −1 h and +6 h) was larger in the high-dose than in the low-dose condition (mean reduction ± SE: 86.44% ± 0.85% vs. 51.54% ± 3.56%) [$F(2,32) = 14.85$; $p < .001$]. For the Trp–LNAA ratio, the reductions were 93.97% ± 0.67% in the high-dose condition and 50.65% ± 3.97% in the low-dose condition, and the intervention by time interaction was significant [$F(2,32) = 36.00$; $p < .001$]. There were no significant differences between SI+ and SI− groups on biochemical measures.

Symptoms

As expected, high-dose ATD led to larger increases in symptoms relative to low-dose ATD (Table 2). Significant ATD by time interactions were found for the MADRS [$F(2,34) = 4.29$; $p = .02$], HRSD [$F(2,34) = 4.11$; $p = .02$], and BAS [$F(2,34) = 5.01$; $p = .01$]. For these scales, the increase in symptoms from −1 h to +6.5 h in the high-dose condition was larger than the increase in the low-dose condition ($p < .01$). Eight of the 19 patients had an increase in MADRS of at least six points. Scores on the PANAS positive-affectivity subscale decreased from −1 h to +6.5 h after high-dose ATD compared with the low-dose ATD ($Z = -2,40$; $p = .02$), whereas BDI-II scores increased at the same time points ($Z = -2,28$; $p = .02$). Significant group (defined by history of SI) by ATD by time interactions were found for the BAS [$F(2,34) = 4.01$; $p = .03$], with the largest increase from −1 h to +6.5 h in the high-dose condition for the SI+ group [$F(1,17) = 7.21$; $p = .016$].

Changes in scores on the PANAS negative-affectivity subscales in the high-dose condition were larger in the SI+ than in the SI−group ($Z = -2.34$; $p = .02$). There were no other group differences on any of the symptom scales, although the univariate contrast test for the HRSD tended toward significance [$F(1,17) = 4.46$; $p = .05$].

Each patient scored zero on the HRSD and MADRS suicidality items, both before and after ATD. Thus, ATD did not increase

Table 2. Means (SE) of the Questionnaires 1 h Before and 6.5 h After High-dose ATD as a Function of Group

	SI+ Group (n = 8)		SI− Group (n = 11)	
Variable	−1 h	+6.5 h	−1 h	+6.5 h
MADRS	5.0 (1.2)	12.0 (2.4)	5.4 (1.3)	9.3 (1.7)
BAS	4.4 (1.7)	7.7 (2.3)	3.6 (1.1)	3.0 (0.7)
HRSD	2.5 (0.8)	7.6 (2.0)	2.9 (0.7)	3.4 (0.6)
BDI-II	7.0 (2.0)	12.2 (2.6)	5.0 (1.5)	6.2 (1.3)
PANAS				
Positive	24.6 (3.1)	19.5 (1.9)	26.4 (2.4)	23.4 (2.3)
Negative	13.4 (1.1)	15.7 (2.1)	12.5 (0.8)	11.0 (0.4)

BAS, Brief Anxiety Scale; BDI-II, Beck Depression Inventory–2nd edition; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery Asberg Depression Rating Scale; PANAS, Positive and Negative Affectivity Scale.

Table 3. Means (SE) of the Cardiac Measures as a Function of Intervention and Group

	SI+ Group (n = 8)		SI− Group (n = 11)	
Variable	Baseline	High-dose	Baseline	High-dose
HR (Beats/min)				
Rest	72.87 (2.63)	83.61 (3.26)	74.28 (3.25)	77.74 (4.52)
CPT	72.02 (1.97)	78.70 (1.83)	70.66 (3.20)	75.23 (4.48)
SD IBI (ms)				
Rest	43.8 (6.36)	32.3 (3.07)	38.5 (4.58)	45.5 (7.77)
CPT	35.3 (2.85)	38.9 (3.65)	44.0 (5.26)	45.6 (5.87)
CV				
Rest	5.25 (0.71)	4.45 (0.40)	4.73 (0.55)	5.52 (0.74)
CPT	4.24 (0.37)	5.09 (0.46)	5.15 (0.61)	5.44 (0.58)
RMSSD (ms)				
Rest	31.25 (6.30)	20.13 (3.78)	25.91 (4.17)	32.64 (5.61)
CPT	22.75 (3.37)	24.88 (4.41)	28.45 (2.68)	30.55 (4.80)
PNN50				
Rest	7.50 (4.37)	1.25 (0.49)	5.82 (2.10)	13.36 (5.12)
CPT	4.00 (2.10)	5.00 (2.60)	7.45 (2.61)	12.55 (4.31)
HF				
Rest	259.8 (26.1)	243.7 (22.1)	253.4 (13.8)	269.3 (10.1)
CPT	246.7 (16.9)	270.1 (13.4)	259.8 (26.1)	243.7 (22.1)
LF				
Rest	255.5 (15.8)	240.3 (16.6)	267.6 (9.8)	275.7 (12.2)
CPT	254.0 (14.8)	254.1 (16.1)	269.4 (12.2)	276.6 (9.2)
LF–HF Ratio				
Rest	1.20 (0.40)	1.34 (0.33)	1.91 (0.56)	1.48 (0.25)
CPT	1.45 (0.34)	1.12 (0.29)	1.88 (0.73)	1.41 (0.21)

Statistics of the low-dose condition are not shown, available upon request.

CV, coefficient of variation; HF, high-frequency power (0.14–0.40 Hz); HR, heart rate; LF, low-frequency power (0.07–0.14 Hz); PNN50, percentage of adjacent intervals that varied more than 50 ms; RMSSD, root mean square of successive differences; SD IBI, SD of interbeat intervals.

suicidality. Overall, symptoms had returned to baseline levels 24 hours after ATD (data not shown).

Effects of ATD on Cardiac Activity

General linear model analyses revealed a main effect of ATD on HR [$F(2,34) = 10.53$; $p < .001$]. High-dose ATD increased HR during rest and during the CPT, as compared with both baseline [$F(1,17) = 14.24$; $p = 002$] and low-dose ATD [$F(1,17) = 11.71$; $p = .003$]. There was no ATD or ATD by period (rest, CPT) effect on any HRV outcome measure. Significant group (SI+, SI−) by ATD by period interactions were found for HR [$F(2,34) = 4.10$; $p = .02$], SD [$F(2,34) = 6.79$; $p = .003$], CVr [$F(2,34) = 6.44$; $p = .004$], RMSSD [$F(2,34) = 5.90$; $p = .006$], PNN50 [$F(2,34) = 6.56$; $p = .004$], and HF [$F(2,34) = 4.30$; $p = .02$] but were not found for LF [$F(2,34) = 0.24$; $p = .78$] or LF–HF ratio [$F(2,34) = 0.81$; $p = 45$]. As shown in Table 3, in the SI+ group, high-dose ATD increased HR [$F(1,17) = 6.62$; $p = .02$] and reduced SD [$F(1,17) = 9.49$; $p = .007$], CVr [$F(1,17) = 9.10$; $p = .008$], RMSSD [$F(1,17) = 13.12$; $p = .002$], PNN50 [$F(1,17) = 7.28$; $p = 015$], and HF [$F(1,17) = 11.30$; $p = .004$] compared with the no-depletion session during the rest period. These effects did not appear during the CPT period. Low-dose ATD in the SI+ group reduced CVr [$F(1,17) = 6.01$; $p = .02$] and tended to reduce SD [$F(1,17) = 5.80$; $p = .03$] compared with the baseline session. Results were very similar when the SI+ group and the SI−group were analyzed separately, with significant decreases in HRV measures in the SI+ group and no effects of ATD on any of the HRV measures in the SI− group. There were no group differences on cardiac measures during the baseline session.

Continuous Performance Test

Practice Effects. There were no significant differences in CPT performance between the post-ATD session and the screening sessions, nor were there any order by session interactions on any outcome measure, indicating that the average score of these two sessions can be used reliably as a baseline score.

Effects of ATD. There was no main effect of ATD on any outcome measure of the CPT. However, the group by ATD interaction for the impulsivity measure β was significant [$F(2,32) = 3.93$; $p = .03$], with differences between high-dose ATD and baseline [$F(1,16) = 4.68$; $p = .046$] and between low-dose and high-dose ATD [$F(1,16) = 6.54$; $p = .02$]. Significant group (SI+, SI−) by intervention interactions also were found for CPT d' [$F(2,32) = 3.98$; $p = .03$], percentage hits [$F(2,34) = 6.83$; $p = .003$], and RT [$F(2,34) = 3.50$; $p = .04$]. Univariate contrast tests for high-dose versus baseline revealed differential effects on d' [$F(1,16) = 7.99$; $p = .01$], percentage hits [$F(1,17) = 7.90$; $p = .01$], and RT [$F(1,17) = 7.63$; $p = .01$] for the SI+ and SI− groups. Compared with baseline, high-dose ATD increased percentage of hits in patients with suicidal ideation, whereas it increased RT and decreased d' (accuracy) and percentage of hits in SI− patients. There were also significant group by intervention effects for high dose versus low dose for percentage of hits [$F(1,17) = 8.37$; $p = .01$] and RT [$F(1,17) = 4.66$; $p = .05$]. There were no differences between baseline versus low-dose, nor were any ATD effects found, on percentage of false alarms (Table 4).

Relation Between Baseline HRV and ATD Response

A significant correlation was found between change in MADRS during high-dose ATD (the difference between +6.5 h

Table 4. Means (SE) of the Continuous Performance Test as a Function of Intervention and Group

	SI+ Group (n = 8)		SI− Group (n = 11)	
Variable	Baseline	High-dose	Baseline	High-dose
Beta (LN)[a]	1.94 (0.32)	1.21 (0.37)	1.83 (0.21)	2.02 (0.29)
d'[a]	4.05 (0.23)	4.33 (0.28)	4.37 (0.23)	3.89 (0.27)
% Hits	91.93 (3.2)	95.83 (2.5)	93.28 (2.5)	86.74 (4.4)
RT Hits (ms)	413.1 (13)	399 (16)	391.8 (9)	408 (14)
% False Alarms[a]	1.32 (0.88)	0.79 (0.25)	0.46 (0.22)	0.67 (0.21)

Statistics of the low-dose condition are not shown, available upon request. LN, natural logarithm; RT, reaction time.

[a]SI+ group based on n = 7.

and −1 h) and baseline PNN50 assessed during rest (r = −.48; p = .04; Figure 1), indicating that a low PNN50 at baseline was associated with a stronger response to ATD. Other correlations between ATD response and HRV parameters were in the same direction but not significant.

Patients with relatively low (below median) levels of SD, RMSSD, or PNN50 more often had a depressive response to ATD (increase of at least six points on the MADRS) as compared with patients with relatively high SD, RMSSD, and PNN50 levels at baseline (6/9 vs. 2/10 patients) [χ^2 = 4.23; p = .04; dt = 1; Fisher's exact test: p = .07 (two tailed); p = .05 (one tailed)]. There were no differences in clinical or demographic measures between these two groups.

Relationship Between Reduction in Tryptophan Levels and Changes in HRV

Analyses of the cardiac measures and CPT were rerun, using symptom response to ATD as a between-subjects variable instead of suicidal tendencies. No significant interaction effects involving symptom response were found.

There were also no significant correlations between plasma Trp or the ratio of Trp to LNAA and ATD-induced changes in any of the cardiovascular outcome measures.

Discussion

The present study confirmed that high-dose ATD induced more depressive symptoms in remitted depressed patients than did the low-dose condition (Booij et al 2005b; Spillmann et al 2001). The main new findings are that in remitted patients with a history of suicidal tendencies, high-dose ATD had the following effects: (1) reduced HRV during rest, (2) increased impulsivity (β; decreased RT), and (3) increased anxiety. Furthermore, low HRV at baseline correlated with the ATD-induced depressive response.

A number of studies have found reduced HRV levels in depressed patients compared with controls (Agelink et al 2002; Rechlin et al 1994), but studies also have reported negative results (Grippo and Johnson 2002; Yeragani et al 1992). It has been suggested that low HRV is limited to patients with severe depression (Agelink et al 2002), to male patients (Thayer et al 1998), or to medicated patients (Bär et al 2004; Lehofer et al 1997). The results of the present study expand the existing literature on HRV, 5-HT function, impulsivity, and depression and suggest that reduced HRV in depression may be limited to patients who are prone to display impulsive or aggressive behavior. This notion is in line with the findings that patients suffering from carcinoid syndrome—a tumor in the gastrointestinal tract that is assumed to induce a prolonged state of low Trp concentrations—often fulfill the DSM-IV criteria for impulse control disorders (Russo et al 2004) and also have a reduced HRV (Meijer et al 2002). Also, respiratory sinus arrhythmia (indicative of the extent of parasympathetic cardiac control) in depressed patients has been found to be negatively associated with suicidal tendencies 6 months later (Rottenberg et al 2002).

The present findings also have implications for models that suggest a role for the prefrontal cortex in a set of neural structures involved in emotion regulation. Previous studies have found that HRV is related both structurally and functionally to activity of the prefrontal cortex (Thayer and Brosschot, 2005). The present findings expand on the previous pharmacological blockade, neuroimaging, and functional work by further illuminating the possible neurochemical basis of the relationship between cortical function and HRV. Given the role that 5-HT is thought to play in inhibitory neural processes, future studies exploring the relationships among 5-HT, cortical function, and HRV appear justified (Manuck et al 2005).

Our findings also have potential relevance for the search for CVD risk markers. Hostility has been shown to be a major risk factor for depression (Krantz and McCeney 2002). It is possible that especially those depressive individuals who have problems controlling aggression or impulsivity are at risk for CVD, because their low 5HT-function in particular may lead to low HRV, which is a direct physiological risk factor for CVD. As far as we know, these features of depression have not yet been addressed in epidemiological studies of depression and CVD.

Contrary to the effects of ATD during the rest period in the SI+ group and contrary to hypotheses, there were no effects on HRV during the CPT. One might speculate that because ATD increased impulsivity in the SI+ group, the CPT elicited risk-taking behavior, which in turn may decrease anxiety and increase HRV during the CPT relative to the rest period.

In contrast with previous findings (Booij et al 2002), the increase in depressive symptoms after ATD was not larger in patients with previous suicidal ideation than in those without. However, because the sample size in the former study was much larger than in the

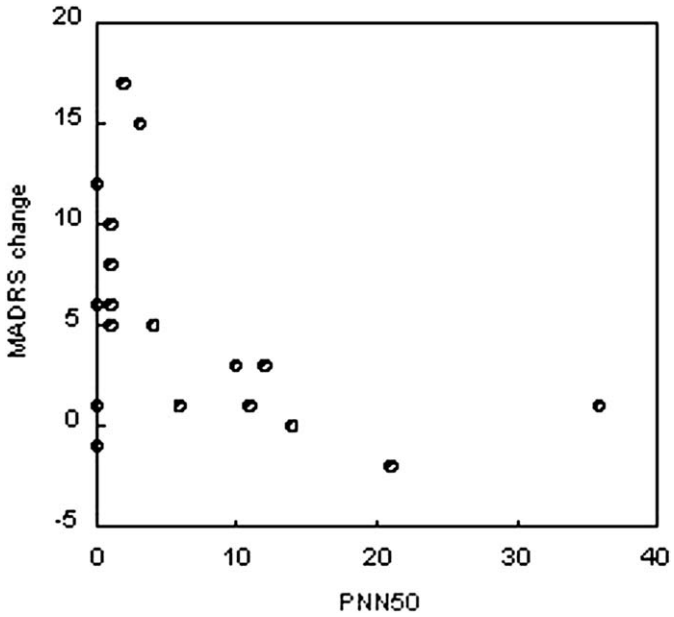

Figure 1. Change in depressive symptoms during high-dose ATD versus percentage of adjacent intervals that varied by more than 50 ms (PNN50) during rest at baseline.

present study, the difference may be a result of a lack of statistical power. Neither low-dose nor high-dose ATD increased suicidal ideation in any of the patients; supporting the notion that the method is ethically appropriate (Booij et al 2005b).

The strengths and limitations of the present design have been discussed elsewhere (Booij et al 2005a). The most important limitation of the present study was that the sample size was relatively small. Furthermore, suicidality was assessed retrospectively and largely on the basis of self-reported information. However, information was obtained by standardized clinical interviews and checked in the medical records. Furthermore, the fact that only one patient with an actual suicide attempt was included rules out the possibility that the observed differences are a result of any neurological damage caused by the suicide attempt. Also, we did not include a control group that received ATD. Finally, several other clinical variables that were not included may have mediated the difference between the SI+ and SI− group on HRV levels, for example, physical fitness, dietary habits, time on medications, and other types of previous treatments. However, the lack of baseline HR and HRV differences between the groups makes such an explanation unlikely. In conclusion, differences in impulse control should be taken into account as a possible mediating factor in future HRV research in depression.

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